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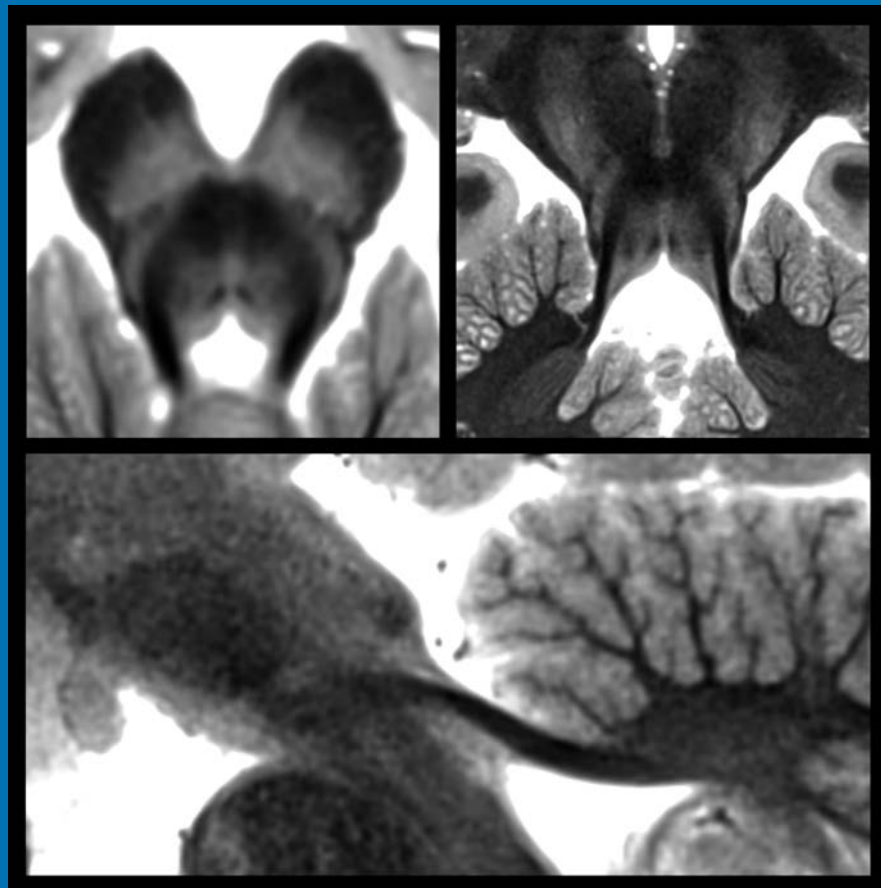
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THE JOURNAL OF DIAGNOSTIC AND
INTERVENTIONAL NEURORADIOLOGY

Whole-brain microscopy discrimination of subcortical anatomy
Imaging of patients with suspected large-vessel occlusion at
primary stroke centers
Endovascular treatment of unruptured MCA bifurcation
aneurysms regardless of aneurysm morphology

Official Journal ASNR • ASFNR • ASHNR • ASPNR • ASSR



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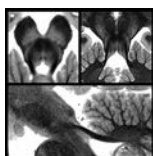
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Demonstration of the dentatorubrothalamic tract within the superior cerebellar peduncle and rostral brain stem. Top left, Axial caudal midbrain image angled 10° anterosuperior to posteroinferior relative to the ACPC plane demonstrates the tract traveling the midbrain to reach the decussation. Top right, Coronal oblique image that is perpendicular to the long axis of the hippocampus at the level of the ventral superior cerebellar decussation shows a component of the dentatorubrothalamic tract arising from the cerebellar dentate nucleus, ascending via the superior cerebellar peduncle to the decussation, and then enveloping the contralateral red nucleus. Bottom, Parasagittal image shows the relatively long anteroposterior dimension of this tract, which becomes less compact and distinct as it ascends toward the thalamus.



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Evidence-Based Medicine Level 1



Evidence-Based Medicine Level 2

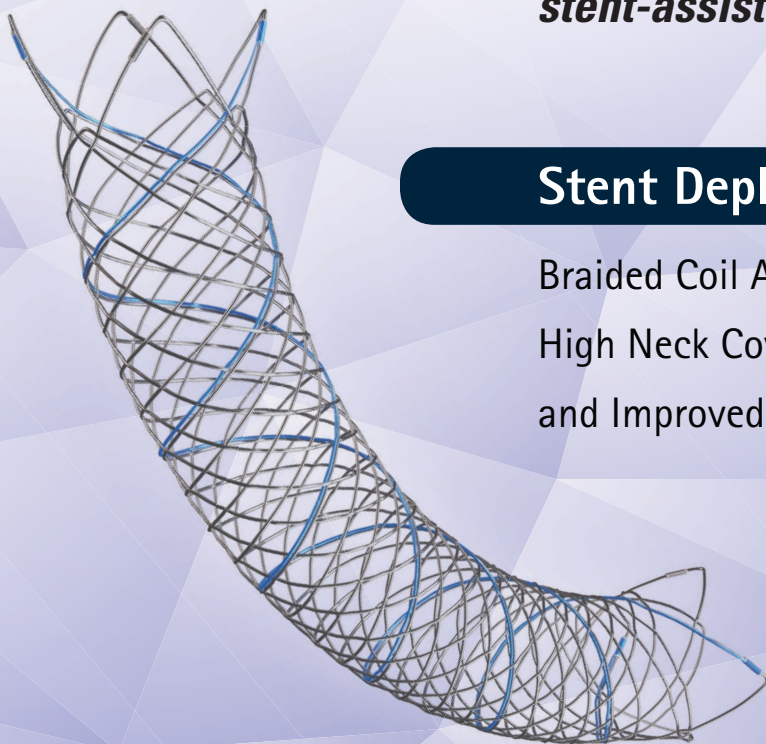


Aneurysm
Therapy
Solutions

LVIS[®]

Intraluminal Support Device

***The first and only stent with
Premarket Approval (PMA) for use in
stent-assisted coil embolization***



Stent Deployment. Refined.

Braided Coil Assist Stents with
High Neck Coverage, Excellent Visibility
and Improved Conformability*

Low-profile Visualized Intرالuminal Support



INDICATIONS FOR USE:

The LVIS[®] and LVIS[®] Jr. devices are indicated for use with neurovascular embolization coils in patients ≥ 18 years of age for the treatment of wide-neck (neck width ≥ 4 mm or dome to neck ratio < 2) saccular intracranial aneurysms arising from a parent vessel with a diameter ≥ 2.0 mm and ≤ 4.5 mm.

Rx Only: Federal (USA) law restricts this device to sale by or on the order of a physician.

The HydroCoil[®] Embolic System (HES) and MicroPlex[®] Coil System (MCS) are intended for the endovascular embolization of intracranial aneurysms and other neurovascular abnormalities such as arteriovenous malformations and arteriovenous fistulae. The HES and MCS are also intended for vascular occlusion of blood vessels within the neurovascular system to permanently obstruct blood flow to an aneurysm or other vascular malformation and for arterial and venous embolizations in the peripheral vasculature.

The device should only be used by physicians who have undergone pre-clinical training in all aspects of HES/MCS procedures as prescribed by MicroVention.

AXS Infinity LS™ Plus Long Sheath

See package insert for complete indications, contraindications, warnings and instructions for use.

INDICATIONS FOR USE

The AXS Infinity LS Plus Long Sheath is indicated for the introduction of interventional devices into the peripheral, coronary, and neuro vasculature.

RX ONLY

CONTRAINDICATIONS

There are no known contraindications.

POTENTIAL ADVERSE EVENTS

- Acute vessel occlusion
- Air embolism
- Death
- Distal embolization
- Emboli
- False aneurysm formation
- Hematoma or hemorrhage at the puncture site
- Infection
- Intracranial hemorrhage
- Ischemia
- Neurological deficit including stroke
- Vessel spasm, thrombosis, dissection or perforation

WARNINGS

Contents supplied STERILE using an ethylene oxide (EO) process. Do not use if sterile barrier is damaged. If damage is found, call your Stryker Neurovascular representative.

For single use only. Do not reuse, reprocess or resterilize. Reuse, reprocessing or resterilization may compromise the structural integrity of the device and/or lead to device failure which, in turn, may result in patient injury, illness or death. Reuse, reprocessing or resterilization may also create a risk of contamination of the device and/or cause patient infection or cross-infection, including, but not limited to, the transmission of infectious disease(s) from one patient to another. Contamination of the device may lead to injury, illness or death of the patient.

After use, dispose of product and packaging in accordance with hospital, administrative and/or local government policy.

1. Do not re-sterilize or reuse, intended for single use only. Re-sterilization and/or reuse may result in cross contamination and/or reduced performance.
2. When the long sheath is exposed to the vascular system, it should be manipulated while under high-quality fluoroscopic observation. Do not advance or retract the long sheath if resistance is met during manipulation; determine the cause of the resistance before proceeding.

PRECAUTIONS

1. Store in a cool, dry, dark place.
2. Do not use kinked, damaged, or opened devices.
3. Use the device prior to the "Use By" date specified on the package.
4. Exposure to temperatures above 54°C (130°F) may damage device. Do not autoclave.
5. Torquing or moving the device against resistance may result in damage to the vessel or device.
6. Maintain a constant infusion of appropriate flush solution.
7. If flow through the device becomes restricted, do not attempt to clear the lumen by infusion. Remove and replace the device.
8. Examine the device to verify functionality and to ensure that its size and shape are suitable for the specific procedure for which it is to be used.
9. The AXS Infinity LS Plus Long Sheath should be used only by physicians trained in percutaneous procedures and/or interventional techniques.
10. Do not use if labeling is incomplete or illegible.

AXS Vecta™ 71 Aspiration Catheter

See package insert for complete indications, contraindications, warnings and instructions for use.

INDICATIONS FOR USE

The AXS Vecta™ Aspiration System, including the AXS Vecta 71 Aspiration Catheter, Aspiration Tubing Set, and VC-701 Cliq Aspirator Pump, is indicated in the revascularization of patients with acute ischemic stroke secondary to intracranial large vessel occlusive disease (within the internal carotid, middle cerebral – M1 and M2 segments, basilar, and vertebral arteries) within 8 hours of symptom onset. Patients who are ineligible for intravenous tissue plasminogen activator (IV t-PA) or who failed IV t-PA therapy are candidates for treatment.

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Scout is a trademark of InNeuroCo, Inc.

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Trevo® XP ProVue Retrievers

See package insert for complete indications, complications, warnings, and instructions for use.

INDICATIONS FOR USE

1. The Trevo Retriever is indicated for use to restore blood flow in the neurovasculature by removing thrombus for the treatment of acute ischemic stroke to reduce disability in patients with a persistent, proximal anterior circulation, large vessel occlusion, and smaller core infarcts who have first received intravenous tissue plasminogen activator (IV t-PA). Endovascular therapy with the device should start within 6 hours of symptom onset.
2. The Trevo Retriever is intended to restore blood flow in the neurovasculature by removing thrombus in patients experiencing ischemic stroke within 8 hours of symptom onset. Patients who are ineligible for intravenous tissue plasminogen activator (IV t-PA) or who fail IV t-PA therapy are candidates for treatment.
3. The Trevo Retriever is indicated for use to restore blood flow in the neurovasculature by removing thrombus for the treatment of acute ischemic stroke to reduce disability in patients with a persistent, proximal anterior circulation, large vessel occlusion of the internal carotid artery (ICA) or middle cerebral artery (MCA)-M1 segments with smaller core infarcts (0-50cc for age < 80 years, 0-20cc for age ≥ 80 years). Endovascular therapy with the device should start within 6-24 hours of time last seen well in patients who are ineligible for intravenous tissue plasminogen activator (IV t-PA) or who fail IV t-PA therapy.

COMPLICATIONS

Procedures requiring percutaneous catheter introduction should not be attempted by physicians unfamiliar with possible complications which may occur during or after the procedure. Possible complications include, but are not limited to, the following: air embolism; hematoma or hemorrhage at puncture site; infection; distal embolization; pain/headache; vessel spasm, thrombosis, dissection, or perforation; emboli; acute occlusion; ischemia; intracranial hemorrhage; false aneurysm formation; neurological deficits including stroke; and death.

COMPATIBILITY

3x20mm retrievers are compatible with Trevo® Pro 14 Microcatheters (REF 90231) and Trevo® Pro 18 Microcatheters (REF 90238). 4x20mm retrievers are compatible with Trevo® Pro 18 Microcatheters (REF 90238). 4x30mm retrievers are compatible with Excelsior® XT-27™ Microcatheters (150cm x 6cm straight REF 275081) and Trevo® Pro 18 Microcatheters (REF 90238). 6x25mm Retrievers are compatible with Excelsior® XT-27™ Microcatheters (150cm x 6cm straight REF 275081). Recommended minimum vessel ID for all Retriever sizes is 2.5mm. Compatibility of the Retriever with other microcatheters has not been established. Performance of the Retriever device may be impacted if a different microcatheter is used.

Balloon Guide Catheters (such as Merci® Balloon Guide Catheter and FlowGate® Balloon Guide Catheter) are recommended for use during thrombus removal procedures.

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RX ONLY

DEVICE DESCRIPTION

The AXS Vecta Aspiration System consists of the **AXS Vecta 71** Aspiration Catheter, the Aspiration Tubing Set, and the VC 701 Cliq Aspirator Pump. The AXS Vecta 71 Aspiration Catheter is a single lumen, flexible, variable stiffness catheter. It has a radiopaque marker band on the distal end and a Luer hub at the proximal end. The AXS Vecta 71 Aspiration Catheter shaft has a lubricious coating at the distal end to reduce friction during use. The Scout Introducer may be used in conjunction with the AXS Vecta 71 Aspiration Catheter to facilitate in the introduction of the AXS Vecta 71 Aspiration Catheter into distal vasculature and aid in navigation to distal anatomy. The Scout Introducer has a lubricious coating at the distal end to reduce friction during use. The inner lumen of the AXS Vecta 71 Aspiration Catheters is compatible with the Scout Introducer, guide wires and micro catheters. The inner lumen of the Scout Introducer is compatible with guide wires and micro catheters of an outer diameter of less than 0.044in. Each package includes one AXS Vecta 71 Aspiration Catheter, one Scout Introducer, one hemostasis valve, and two peel-away introducers. Dimensions of the AXS Vecta 71 Aspiration Catheter and Scout Introducer are included on the individual device label. The AXS Vecta 71 Aspiration Catheters are available in 3 different lengths, the device configurations including the length of the Scout packaged with each catheter and the recommended microcatheter length is presented in the table below.

Catheter part number	INC-11129-115	INC-11129-125	INC-11129-132
Catheter inner diameter (in)	0.071	0.071	0.071
Distal catheter outer diameter (in)	0.082	0.082	0.082
Catheter working length (cm)	115	125	132
Scout Introducer length (cm)	133	143	150
Recommended compatible microcatheter length (cm)	150	160	160
Recommended compatible microcatheter outer diameter (in)	0.044 max	0.044 max	0.044 max
Recommended compatible guidewire outer diameter (in)	0.038 max	0.038 max	0.038 max

The AXS Vecta Aspiration System is recommended for use in the following vessel size ranges based on non-clinical testing:

AXS Vecta 71 Aspiration Catheter	Vessel size (mm)
INC-11129-115	2-4
INC-11129-125	2-4
INC-11129-132	2-4

CONTRAINDICATIONS

The AXS Vecta 71 Aspiration Catheter has not been evaluated for use in the coronary vasculature. Do not use automated high-pressure contrast injection equipment with the AXS Vecta 71 Aspiration Catheter because it may damage the device.

POTENTIAL ADVERSE EVENTS

- Acute vessel occlusion
- Air embolism
- Allergic reaction and anaphylaxis from contrast media
- Arteriovenous fistula
- Death
- Device malfunction
- Distal embolization
- Emboli
- False aneurysm formation
- Hematoma or hemorrhage at the puncture site
- Inability to completely remove thrombus
- Infection
- Intracranial hemorrhage
- Ischemia
- Kidney damage from contrast media
- Neurological deficit including stroke
- Risks associated with angiographic and fluoroscopic radiation including but not limited to: alopecia, burns ranging in severity from skin reddening to ulcers, cataracts, and delayed neoplasia
- Vessel spasm, thrombosis, dissection or perforation

Retrievers are compatible with the Abbott Vascular DOC® Guide Wire Extension (REF 22260). Retrievers are compatible with Boston Scientific Rotating Hemostatic Valve (REF 421242).

SPECIFIC WARNINGS FOR INDICATION 1

- The safety and effectiveness of the Trevo Retrievers in reducing disability has not been established in patients with large core infarcts (i.e. ASPECTS ≤ 7). There may be increased risks, such as intracerebral hemorrhage, in these patients.
- The safety and effectiveness of the Trevo Retrievers in reducing disability has not been established or evaluated in patients with occlusions in the posterior circulation (e.g., basilar or vertebral arteries) or for more distal occlusions in the anterior circulation.

SPECIFIC WARNINGS FOR INDICATION 2

- To reduce risk of vessel damage, take care to appropriately size Retriever to vessel diameter at intended site of deployment.

SPECIFIC WARNINGS FOR INDICATION 3

- The safety and effectiveness of the Trevo Retrievers in reducing disability has not been established in patients with large core infarcts (i.e. ASPECTS ≤ 7). There may be increased risks, such as intracerebral hemorrhage, in these patients.
- The safety and effectiveness of the Trevo Retrievers in reducing disability has not been established or evaluated in patients with occlusions in the posterior circulation (e.g., basilar or vertebral arteries) or for more distal occlusions in the anterior circulation.
- Users should validate their imaging software analysis techniques to ensure robust and consistent results for assessing core infarct size.

WARNINGS APPLIED TO ALL INDICATIONS

- Administration of IV t-PA should be within the FDA-approved window (within 3 hours of stroke symptom onset).
 - Do to reduce risk of vessel damage, adhere to the following recommendations:
 - Do not perform more than six (6) retrieval attempts in same vessel using Retriever devices.
 - Maintain Retriever position in vessel when removing or exchanging Microcatheter.
- To reduce risk of kinking/fracture, adhere to the following recommendations:
 - Immediately after unsheathing Retriever, position Microcatheter tip marker just proximal to shaped section. Maintain Microcatheter tip marker just proximal to shaped section of Retriever during manipulation and withdrawal.
 - Do not rotate or torque Retriever.
 - Use caution when passing Retriever through stented arteries.
- The Retriever is a delicate instrument and should be handled carefully. Before use and when possible during procedure, inspect device carefully for damage. Do not use a device that shows signs of damage. Damage may prevent device from functioning and may cause complications.
- Do not advance or withdraw Retriever against resistance or significant vasospasm. Moving or torquing device against resistance or significant vasospasm may result in damage to vessel or device. Assess cause of resistance using fluoroscopy and if needed resheath the device to withdraw.

WARNINGS

Contents supplied STERILE using an ethylene oxide (EO) process. Do not use if sterile barrier is damaged. If damage is found, call your Stryker representative.

For single use only. Do not reuse, reprocess or resterilize. Reuse, reprocessing or resterilization may compromise the structural integrity of the device and/or lead to device failure which, in turn, may result in patient injury, illness or death. Reuse, reprocessing or resterilization may also create a risk of contamination of the device and/or cause patient infection or cross-infection, including, but not limited to, the transmission of infectious disease(s) from one patient to another. Contamination of the device may lead to injury, illness or death of the patient.

After use, dispose of product and packaging in accordance with hospital, administrative and/or local government policy.

1. The AXS Vecta 71 Aspiration Catheter has not been evaluated for more than one (1) clot retrieval attempt.
2. The AXS Vecta 71 Aspiration Catheter was evaluated for an average duration of direct aspiration of 4 minutes.
3. This product is intended for single use only, do not re-sterilize or reuse. Re-sterilization and/or reuse may result in cross contamination and/or reduced performance.
4. When the catheter is exposed to the vascular system, it should be manipulated while under high-quality fluoroscopic observation. Do not advance or retract the catheter if resistance is met during manipulation; determine the cause of the resistance before proceeding.
5. Operators should take all necessary precautions to limit x-radiation doses to patients and themselves by using sufficient shielding, reducing fluoroscopy times, and modifying x-ray technical factors where possible.

PRECAUTIONS

1. Store in a cool, dry, dark place.
2. Do not use kinked, damaged, or opened devices.
3. Use the device prior to the "Use By" date specified on the package.
4. Exposure to temperatures above 54°C (130°F) may damage device. Do not autoclave.
5. Torquing or moving the device against resistance may result in damage to the vessel or device.
6. Maintain a constant infusion of appropriate flush solution.
7. If flow through the device becomes restricted, do not attempt to clear the lumen by infusion. Remove and replace the device.
8. Examine the device to verify functionality and to ensure that its size and shape are suitable for the specific procedure for which it is to be used.
9. The AXS Vecta Aspiration System should be used only by physicians trained in percutaneous procedures and/or interventional techniques.
10. The Scout Introducer should be used with a guidewire and microcatheter inserted when in vasculature.
11. If using the AXS Vecta Aspiration System for thrombectomy, monitor the canister fluid level and replace the canister if the fill level reaches 75% of the canister volume.
12. Administration of anticoagulants and antiplatelets should be suspended until 24 hours post-treatment. Medical management and acute post stroke care should follow the American Stroke Association (ASA) guidelines.
13. Any neurological determination should be evaluated by urgent CT scan and other evaluations as indicated according to investigator/hospital best practice.
14. As in all surgical interventions, monitoring of intra-procedural blood loss is recommended so that appropriate management may be instituted.
15. Limit the usage of the AXS Vecta 71 Aspiration Catheter to arteries greater than the catheter's outer diameter.
16. Excessive aspiration with the distal tip of the AXS Vecta 71 Aspiration Catheter covered by the vessel wall may cause vessel injury. Carefully investigate location of the distal tip under fluoroscopy prior to aspiration.
17. There is an inherent risk with the use of angiography and fluoroscopy.
18. When transporting the VC-701 Cliq pump, utilize the pump handle.
19. Do not use if labeling is incomplete or illegible.



Stryker Neurovascular
47900 Bayside Parkway
Fremont, CA 94538

strykerneurovascular.com

Date of Release: SEP/2018

EX_EN_US

- If Retriever is difficult to withdraw from the vessel, do not torque Retriever. Advance Microcatheter distally, gently pull Retriever back into Microcatheter, and remove Retriever and Microcatheter as a unit. If undue resistance is met when withdrawing the Retriever into the Microcatheter, consider extending the Retriever using the Abbott Vascular DOC guidewire extension (REF 22260) so that the Microcatheter can be exchanged for a larger diameter catheter such as a DAC® Catheter. Gently withdraw the Retriever into the larger diameter catheter.
- Administer anti-coagulation and anti-platelet medications per standard institutional guidelines.
- Users should take all necessary precautions to limit x-radiation doses to patients and themselves by using sufficient shielding, reducing fluoroscopy times, and modifying X-ray technical factors where possible.

PRECAUTIONS

- Prescription only – device restricted to use by or on order of a physician.
- Store in cool, dry, dark place.
- Do not use open or damaged packages.
- Use by "Use By" date.
- Exposure to temperatures above 54°C (130°F) may damage device and accessories. Do not autoclave.
- Do not expose Retriever to solvents.
- Use Retriever in conjunction with fluoroscopic visualization and proper anti-coagulation agents.
- To prevent thrombus formation and contrast media crystal formation, maintain a constant infusion of appropriate flush solution between guide catheter and Microcatheter and between Microcatheter and Retriever or guidewire.
- Do not attach a torque device to the shaped proximal end of DOC® Compatible Retriever. Damage may occur, preventing ability to attach DOC® Guide Wire Extension.

DOC is a trademark of Abbott Laboratories.



Stryker Neurovascular
47900 Bayside Parkway
Fremont, CA 94538

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Date of Release: APR/2018

EX_EN_US



Now you have **24 hours** to make a lifetime of difference in stroke patients like Nora



The Trevo Retriever is the only device cleared to **reduce disability in stroke patients up to 24 hours** from time last seen well.

For more information, visit strykerneurovascular.com/trevo24hours

Trevo[®] XP
PROVUE RETRIEVER

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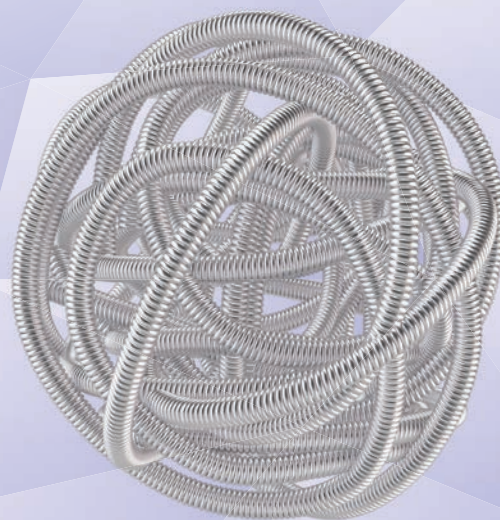
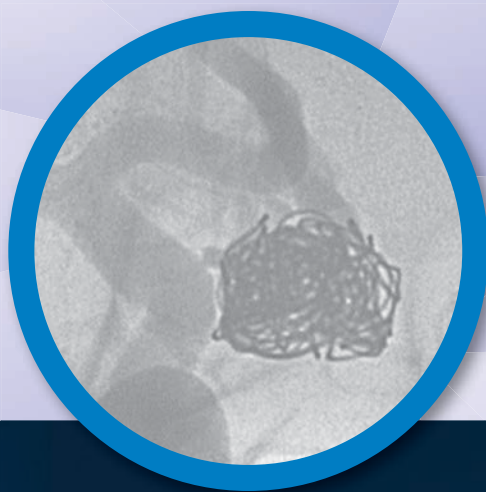
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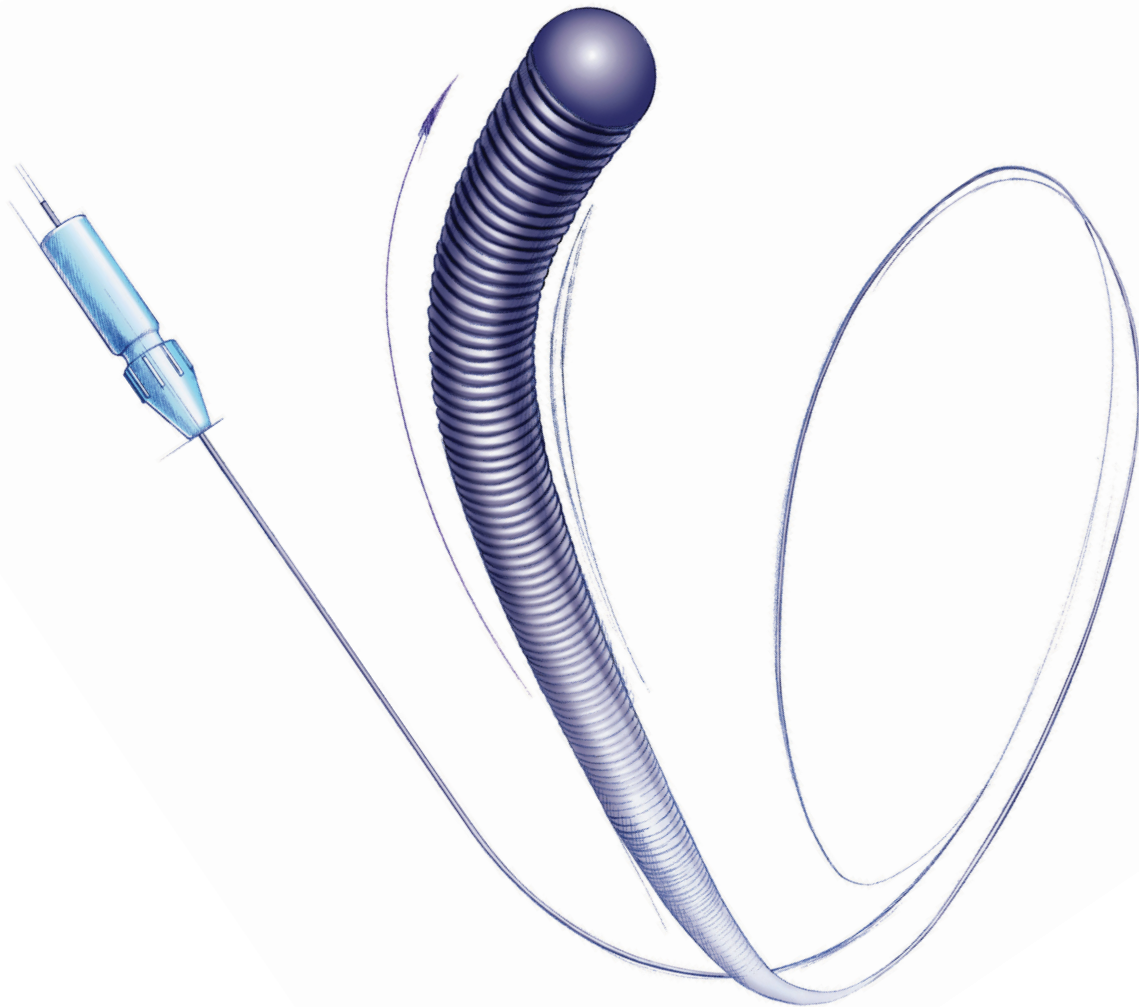
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Title: Ka athi lola?. Acrylic on canvas, 12" × 10". "Ka athi lola?" in Sanskrit means, "Who is more pretty?"

Bejoy Thomas, MD, DNB, PDCC, Trivandrum, Kerala, India

Understanding Subdural Collections in Pediatric Abusive Head Trauma

 D. Wittschieber,  B. Karger,  H. Pfeiffer, and  M.L. Hahnemann



ABSTRACT

SUMMARY: Life-threatening physical abuse of infants and toddlers is frequently correlated with head injuries. A common variant of the abusive head trauma is the shaken baby syndrome. The present review article sheds light on subdural collections in children with abusive head trauma and aims at providing a recent knowledge base for various medical disciplines involved in diagnostic procedures and legal proceedings. To this end, the different subdural collection entities are presented and illustrated. The pathophysiologic background is explained. Differential and age-diagnostic aspects are discussed and summarized by tabular and graphic overviews. Two problematic constellations frequently occurring during initial CT investigations are evaluated: A mixed-density subdural collection does not prove repeated trauma, and hypodense subdural collections are not synonymous with chronicity. The neuroradiologic analysis and assessment of subdural collections may decisively contribute to answering differential diagnostic and forensic questions. In addition to more reference data, a harmonization of terminology and methodology is urgently needed, especially with respect to age-diagnostic aspects.

ABBREVIATIONS: AHT = abusive head trauma; BV = bridging vein; cSDH = chronic subdural hematoma; SDC = subdural collection; SDE = subdural effusion; SDH = subdural hematoma; SDEm = subdural empyema; SDHy = subdural hygroma; SDHHy = subdural hematomahygroma

In light of serious physical, psychological, and legal consequences, physical child abuse attracts increasing attention in terms of health policy and health economy.¹⁻³ Head injuries represent the most frequent cause of lethal outcome and mainly relate to children within their first and second years of life.⁴⁻⁶ Currently, the term “abusive head trauma” (AHT) is used for any nonaccidental or inflicted head injuries in pediatrics.⁷⁻⁹

AHT has a worldwide incidence of 14–30/100,000 live births among children younger than 1 year of age.^{5,10-13} Additionally, a high amount of underreporting has to be assumed because many cases are not identified due to subclinical courses, nonspecific symptoms, or missing medical consultation.¹⁴ Meta-analyses on the outcome revealed an average mortality rate of around 20% among children younger than 2 years of age.¹⁵ Survivors showed severe disability (eg, tetraplegia, epilepsy, or blindness) in ~34%,

and moderate disability (eg, hemiplegia, memory and attention difficulties) in ~25% of the cases.¹⁵

The shaken baby syndrome—a common variant of AHT with increasing general public awareness—is characterized by the following features that are neither obligatory nor evidentiary:

- Acute encephalopathy, being the clinical expression of traumatic damage of the brain parenchyma accompanied by a wide spectrum of neurologic symptoms that depend on the intensity of the trauma.
- Subdural collections with or without additional extra-axial findings such as subarachnoid hemorrhage, arachnoid tear, or bridging vein thrombosis.
- Retinal hemorrhages typically found in many locations, within several layers, disseminated, widespread from the center to the periphery, and with or without additional retinoschisis or intravitreal hemorrhage.
- Spinal trauma such as ligamentous injuries at the craniocervical junction, or spinal sub- or epidural hematomas.
- No or only minimal injuries of the skin because skin bruises caused by firm grip at the arms or the thorax of the child are rare.
- Missing or inadequate anamnesis—that is, no trauma reported or report of just a minor trauma despite the presence of severe brain injury.

With respect to other variants of AHT, further features of head injury may occur, in particular, signs of blunt force (impact)

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trauma against the child's head such as skin lesions or skull fractures.

Relevant differential diagnoses such as metabolic disorders, infectious and hematologic diseases, and birth trauma must be excluded. However, these differential diagnoses usually cannot explain the symptomatology of AHT as a whole. Diagnosing AHT always requires the joint assessment of numerous investigation results from pediatrics, ophthalmology, neurosurgery, laboratory medicine, forensic medicine, and radiology.^{7,16} Pediatric neuroimaging by CT and MR imaging plays a key role in this strategy.^{7,16,17} Traumatic brain injuries and extra-axial indicators of AHT can be depicted and evaluated across time. Besides subarachnoid hemorrhages, fluid collections within the subdural space represent such extra-axial indicators of AHT.

SUBDURAL COLLECTIONS

The term "subdural collection" (SDC) is understood as a nonspecific umbrella term comprising various, in part, successively stagelike findings within the subdural space. The radiologic investigation of SDCs has the potential to contribute to important issues such as type, number, and circumstances of the traumatic force or the age of injury. Apart from the clinical and medicolegal significance for the diagnosis of child abuse, SDCs may also be relevant for criminological aspects because age estimation possibly facilitates further limitation of the circle of suspects.

Differential diagnostics of the various SDC entities is a challenging topic for the radiologist. During the initial image-assessment process, the more careful labeling as SDC may be more reasonable than the possibly hasty determination of a special SDC entity.^{18,19} Terminology and definition criteria of the SDC entities are inconsistent, even among experts. This issue may partly be attributed to the frequent presence of mixed or transitional SDC forms. However, the large body of literature allows the differentiation of at least the following 6 entities.

Subdural Hematoma

In the context of AHT, subdural hematoma (SDH) is described as the most common intracranial pathology in infants and toddlers.²⁰⁻²² SDHs, like all SDCs, may occur unilaterally or bilaterally.²³ The convexities of the cerebral hemispheres (Fig 1A), the falx cerebri, the tentorium cerebelli, and the middle and posterior cranial fossae are considered typical locations.²² In many cases, SDHs have a key role as a diagnostic marker only—that is, though they may represent an important symptom of child abuse, their volumes are often small, resulting in just a minor space-occupying effect.^{8,21,23-25} Hence, frequently, SDHs do not have a prognostic relevance for the extent of brain damage.²⁴ Depending on the developmental stage in which subdural blood is visualized by neuroimaging, SDHs have a wide variety of appearances (Table 1). The chronic SDH has a special position (see below: "Chronic Subdural Hematoma").

Subdural Hygroma

The term subdural hygroma (SDHy) is classically reserved for proteinaceous, clear, pink-tinged, or xanthochromatic collections within the subdural space containing pure CSF or at least CSF-like fluid; blood, blood products, or neomembranes are nonexistent by definition (Fig 1B, -C).^{22,26,27} However, the smallest amounts of

blood within the SDHy cannot always be excluded and may become noticeable on CT by a slightly higher density compared with CSF (see below: "Subdural Hematohygrogram," "homogeneous variant").

Subdural Hematohygrogram

Subdural hematohygrograms (SDHHys) are a combination of blood (or blood products) and CSF (or CSF-like fluid).^{22,28-30} A homogeneous and a heterogeneous variant can be differentiated.

In many cases of an SDC diagnosed as SDHy, it may be assumed that the SDC is actually the homogeneous variant of the SDHHy (Fig 1D) because the blood component may sometimes be relatively small and/or very "young" (hyperacute); furthermore, an intense mixture of blood and CSF may be present.²⁷⁻²⁹ Hence, in our experience, SDHy and SDHHy are used interchangeably or synonymously in radiology reports.

The heterogeneous variant of the SDHHy (Fig 1E, -F) indicates 2 SDC components that coexist within the same subdural compartment (eg, above a brain convexity); these components may be clearly distinguished from one another (fluid-fluid levels possible) and may appear hyper- and hypodense during CT investigations (mixed-density pattern).^{22,28,30-32} The hypodense component is interpretable as the following:

- 1) Acute CSF collection (eg, due to an arachnoid tear, see below: "Pathophysiology")

- 2) Supernatant (and thus an integral part of blood) changed by gravity (serum separation/blood sedimentation/hematocrit effect), in the sense of an SDH.

Of course, a mixed form of both variants is conceivable as well (ie, simultaneous presence of CSF influx and blood sedimentation; see below: "Mixed-Density SDCs: Repeated Trauma?" and Table 2, upper part).

Chronic Subdural Hematoma

Currently, from the pathophysiologic point of view, chronic subdural hematoma (cSDH) is considered a separate SDC entity.²³ cSDH denotes a serosanguinous, petroleum-, or crankcase-like fluid collection surrounded and sometimes loculated (divided into compartments) by neomembranes (Fig 1G, -I).^{26,33-35} Neomembranes contain numerous new blood vessels leading to accumulation of contrast agent in neuroimaging studies.^{22,27} The presence of neomembranes represents an important criterion for distinguishing cSDH and SDHy. In contrast to the situation in adults, genuine cSDHs are relatively rare in infants.^{22,36-38}

Subdural Effusion and Subdural Empyema

These proteinaceous SDC entities are predominantly considered sequelae (in case of subdural effusion [SDE]) or complications (in case of subdural empyema [SDEm], eg, due to an infected SDE) of bacterial meningitis or sinusitis.^{22,39} These conditions usually do not cause diagnostic difficulties because inflammatory symptomatology or a history of CNS infection is typically present. Normally, SDEs and SDEms are nontraumatic, but in rare cases, SDEms may originate following penetrating head trauma or craniotomy, which, of course, is usually known in the clinical setting.

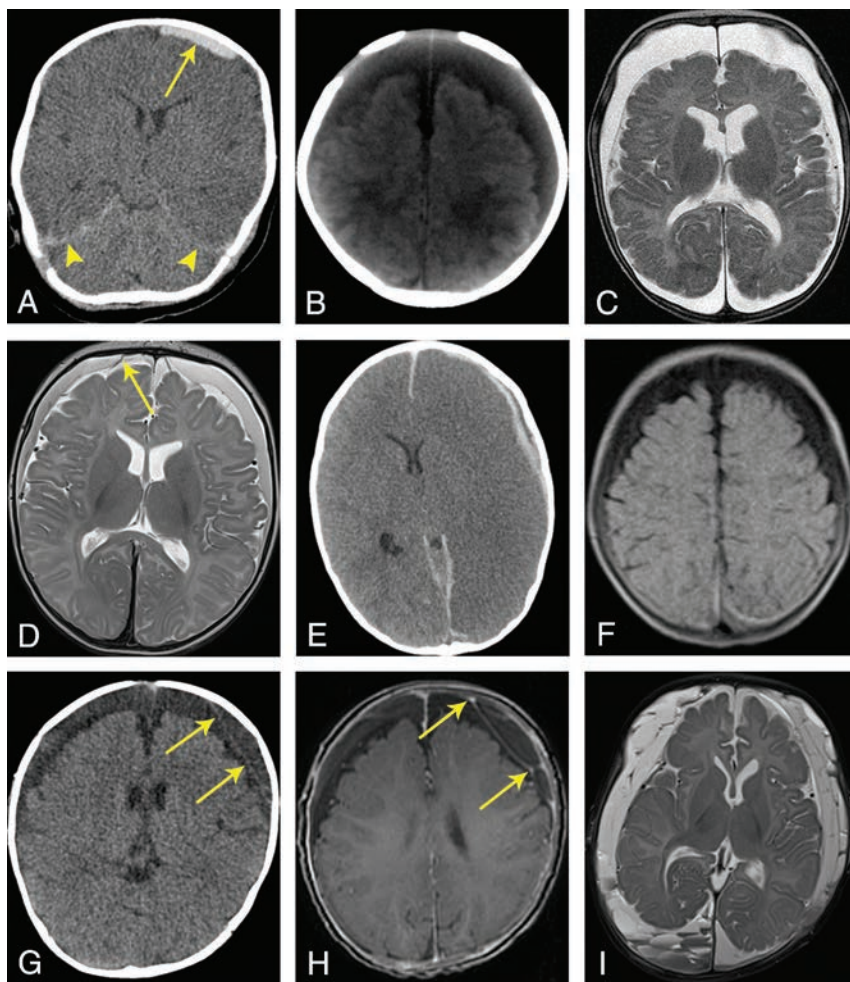


FIG 1. SDC entities in AHT cases. *A*, Acute SDH (nonenhanced CT): a 2-month-old boy with a small hyperdense SDC over the left frontoparietal region (arrow) and hyperdense blood components around the tentorium (arrowheads). *B*, SDHy (nonenhanced CT): a 2-month-old boy with wide, homogeneously hypodense (or CSF-isodense) SDCs over both frontoparietal regions; no neomembranes or septa. *C*, SDHy (MR imaging, T2WI, TSE, nonenhanced): a 4-month-old boy with wide, homogeneously CSF-isointense SDCs over both frontoparietooccipital regions, markedly frontal due to the supine position; no neomembranes or septa. *D*, SDHHy, homogeneous variant (MR imaging, T2WI, TSE, nonenhanced): a 3-month-old boy with homogeneous SDCs over both frontoparietal regions. Compared with CSF within the external and internal CSF spaces, the SDCs appear hypointense. Two intact BVs can be found next to the superior sagittal sinus (arrow shows 1 BV). *E*, SDHHy, heterogeneous variant (nonenhanced CT): a 19-month-old boy with an SDC in the left frontoparietal region. The SDC is composed of a thin, brain-sided, hyperdense component and a thin, dura-sided, hypodense component that runs parallel to the former component (mixed-density pattern). In this case, the study also revealed severe brain edema with a midline shift to the right side as well as hyperdense blood components within the anterior and posterior interhemispheric fissures. *F*, SDHHy, heterogeneous variant (MR imaging, FLAIR, nonenhanced): a 4-month-old girl with wide SDCs over both frontoparietooccipital regions. While the frontoparietal SDC proportions appear hypointense, the parietooccipital proportions are iso- to hyperintense. The transitional zone between the 2 components is almost smooth; fluid-fluid levels cannot be recognized unambiguously. *G*, Chronic SDH (nonenhanced CT): a 7-month-old boy with wide, hypodense SDCs over both frontoparietal regions and subtle formation of subdural neomembranes on the left side (arrows). *H*, Chronic SDH (MR imaging, T1WI, gradient-echo sequence, enhanced by contrast agent): same case as in *G*. Confirmation of the presence of subdurally located septa and chamber formations. In contrast to the nonenhanced T1WI (not shown), this contrast agent-enhanced study revealed focal signal enrichment located at the neomembranes (arrows). *I*, Chronic SDH (MR imaging, T2WI, TSE, nonenhanced): a 4-month-old boy with numerous subdural septa and neomembranes. Note the different signal intensities and multiple fluid-fluid levels within subdural chamber formations, especially in the right occipital region.

PATHOPHYSIOLOGY

AHT is predominantly caused by acceleration-deceleration trauma, blunt force trauma (impact), or a combination of these mechanisms.^{8,9,40} In acceleration-deceleration trauma, the child

is usually held firmly at the thorax or upper arms and is then shaken. These rapid movements result in repeated acceleration and deceleration of the child's head due to missing postural control. Shearing and rotational forces may cause severe injuries within the brain tissue, determining prognosis. In addition, small and medium-sized blood vessels within the cranial cavity, particularly the bridging veins (BVs) that mainly run through the subarachnoid space, may rupture in part or completely. Approximately 50 BVs (diameter, 0.05–3.07 mm) connect the cortical veins of the cerebral and cerebellar surface with the large venous sinuses, thereby penetrating the inner part of the dura mater.⁴¹ Typically, injuries of the BVs cause extra-axial hemorrhage, predominantly within the subarachnoid and subdural spaces.^{23,41–44}

BVs show a different wall thickness at different locations. While the BV wall measures 50–200 μm within the subarachnoid space, the BV segments that penetrate the dura mater may have a wall thickness of only 10 μm and do not show additional external strengthening by connective tissue.⁴⁵ Thus, increased vulnerability of dural BV portions is assumed.⁴⁵ The resulting hemorrhage from the injured BVs fosters opening of the subdural space. This pathologic space does not exist under physiologic conditions and has been recognized as an intradural lesion caused by cleavage of the innermost part of the dura mater, the dura border cell layer.^{22,46,47} Nevertheless, the traditional term “subdural” is still widely in use; thus, BV hemorrhage leads to what is generally referred to as SDH.

Due to shearing forces, the arachnoid membrane may also tear (eg, in the vicinity of strained BVs or at Pacchionian granulations).^{29,48} If this is the case, transfer of CSF from the subarachnoid space to the subdural space is possible. Thus, an SDHy or SDHHy may develop additionally or subsequently (yellow box in Fig 2).^{27,29,49} The laceration of the arachnoid membrane may function as a valve preventing backflow of CSF.^{49,50} Besides this rapid

mechanism, occurring within a few minutes or hours, delayed formations of SDHys and SDHHys, requiring up to several days, have been observed as well.²⁷ Etiopathologically, there are 2 causative mechanisms:

Table 1: Classic SDH stages in CT and MRI (at 1.5T)^a

Characteristics	Stage				
	Hyperacute	Acute	Early Subacute	Late Subacute	Chronic
Assumed time range ^b	Min: 0 hr Max: 24 hr	Min: 1 day Max: 3 days	Min: 2 days Max: 2 wk	Min: 1 wk Max: 3 wk	Min: 2 wk
NECT ^c	↓/↔	↑	↑	↔	↓
MRI ^c (T1)	↔	↔	↑	↑	↓
MRI ^c (T2)	↑	↓	↔/↑	↑	↑
Hb state	Oxy-Hb	Desoxy-Hb	Met-Hb	Met-Hb	Ferritin/hemosiderin
Hb localization	Intracellular	Intracellular	Intracellular	Extracellular	Extracellular
Fe oxidation state	Fe ²⁺	Fe ²⁺	Fe ³⁺	Fe ³⁺	Fe ³⁺
Pathophysiology	Unclotted blood	Clotted blood, clot retraction	Max clot retraction, erythrocytes predominantly (still) intact, oxidative denaturation of the desoxy-Hb into met-Hb	Lysis of erythrocytes, thereby increase of extracellular met-Hb, start of disintegration to heme and globin, Fe ³⁺ is stored within the macromolecule ferritin and the phagocytic product hemosiderin, respectively	In contrast to intraparenchymal hematomas, removal of ferritin and hemosiderin within the extra-axial space is accelerated due to the missing blood-brain barrier (therefore ↑ in T2)

Note:—NECT indicates nonenhanced CT; Hb, hemoglobin; ↑, hyperdense/hyperintense; ↓, hypodense/hypointense; ↔, isodense/isointense; Min, minimum; Max, maximum; Desoxy-Hb, Desoxy-Hemoglobin; Oxy-Hb, Oxy-Hemoglobin; Met-Hb, Met-Hemoglobin.

^a According to Hedlund,²² Vezina,²⁸ Lee et al,⁶¹ Duhem et al,⁶² Tung,⁶³ Cramer et al,⁶⁴ Bradley,⁶⁵ and Bergström et al.⁶⁶

^b Due to insufficient data base, the time intervals stated do not represent absolute borders—that is, the ranges may be exceeded or undercut in single cases.

^c Density/signal intensity compared with cortical brain tissue.

Table 2: Mixed-density and hypodense SDCs—2 typical problem constellations during the initial CT investigation^a

CT Finding	Differential Diagnosis	Pathophysiology	Forensic Relevance
Heterogeneous hypo- and hyperdense SDC (mixed-density pattern)	1) Hyperacute + acute SDH	Unclotted and clotted blood	Compatible with 1 hemorrhagic event Assumed EoA: 0–24 hr
	2) Acute SDH	Compacted clot with serum separation	Compatible with 1 hemorrhagic event Assumed EoA: 1–3 days
	3) SDHHy	“Acute blood” and CSF, eg, due to BV injury and concomitant arachnoid tear	Compatible with 1 hemorrhagic event Assumed EoA: 1 day–min 1 wk
	4) Acute + chronic SDH	Acute hemorrhage within a pre-existing cSDH/SDHy	Compatible with 2 (or more) hemorrhagic events Assumed EoA: 0–min. 2 wk
Homogeneous iso- to hypodense SDC	1) Hyperacute SDH	Unclotted blood	Assumed EoA: 0–24 hr
	2) Acute SDH + anemia	Clotted blood with decreased number of erythrocytes	Assumed EoA: 1–3 days
	3) SDHy/SDHHy	CSF or CSF + acute blood	Assumed EoA: 1 day–min. 1 wk
	4) Late subacute SDH	Lysis of erythrocytes	Assumed EoA: 1–3 wk
	5) cSDH	Serosanguinous fluid	Assumed EoA: min. 2 wk

Note:—EoA indicates estimate of age; min, minimum.

^a According to Hymel et al,²⁰ Hedlund,²² Vezina,²⁸ and Tung et al.³⁰

1) Influx of CSF or CSF-like fluid as a result of a posttraumatic, reactive, vasomotoric (diffusion) disorder within surrounding meningeal structures. This is assumed to occur particularly with decreased intracranial pressure and through the mediation of cytokines.^{20,22,33,34,51,52}

2) Pathologic accumulation of intradural CSF that is assumed to move physiologically within the dural venous plexus from the subarachnoid space to the venous sinuses.⁴⁷

Likewise, the further development toward cSDH is not yet completely understood. However, it seems clear that an outer subdural neomembrane (at the dural side) is primarily formed. Its formation commences at the innermost cell layer of the dura mater cleaved by the SDC. Subsequently, an inner subdural neomembrane (on the arachnoid side) is formed so that, finally, both neomembranes surround the SDC.^{53–56} Particularly the thicker outer neomembrane is highly vascularized. Leakage of

these fragile new blood vessels is held responsible for additional influx of blood, proteins, and fluid and, thereby, for the increase in size of the cSDH.^{39,52–56} Formation of septa is considered a consequence of repeated rebleeding events and may lead to chamber-like structures with multiple fluid-fluid levels appearing differently with regard to density or signal intensity (Fig 1I).⁵⁷ A pathologically expanding SDHy or SDHHy is considered the precursor of the cSDH (blue box in Fig 2).^{20,22,27,34,49} The direct conversion of an acute SDH into a cSDH is infrequently observed in adult cases only and could not be simulated in animal experiments.^{20,58,59}

AGE DIAGNOSTICS

General Aspects

Given the inherent heterogeneity of traumatization and the resulting diversity of SDC appearance and SDC combinations,

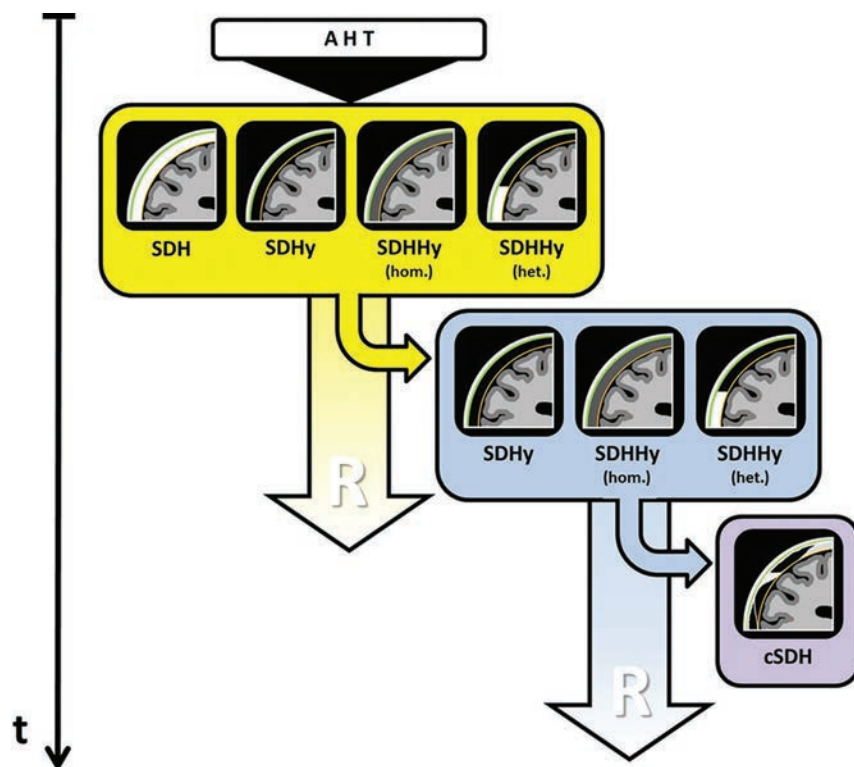


FIG 2. Simplified schematic drawing of the development of cSDHs via SDHys/SDHHys according to Hymel et al.,²⁰ Hedlund,²² Wittschieber et al.,²⁷ Zouros et al.,²⁹ Lee et al.,³⁴ and Lee.⁴⁹ The findings within the *yellow box* demonstrate the possible SDC entities following AHT that can often be found during initial cross-sectional neuroimaging. A portion of these cases develops further toward the findings shown within the *blue box*. With time, these SDC entities may then develop into a cSDH (*purple box*). The pictographs schematically visualize the CT morphologic appearance of the respective SDC. Green indicates the dura mater; orange, the arachnoid membrane; the space in between, the subdural space; hom., homogeneous; het., heterogeneous; t, time; R, resorption/resolution.

precise dating of SDCs based on neuroimaging alone is unrealistic. However, this issue does not mean that any time-related statements on SDCs are impossible. Hence, it seems appropriate to use more reserved terms such as “age estimation” or “staging.”⁶⁰

There is general consensus that when interpreting initial imaging studies (mostly CT), SDC features should be described merely (eg, hypodense, isodense, hyperdense, or mixed-density pattern).^{22,28} The possibly rash labeling with temporal assignments such as “acute” or “chronic” should be avoided.^{22,28} In case of the sedimentation of an SDH (or SDHHy), evaluating the sediment instead of the supernatant has been recommended.³¹

Table 1 shows a compilation of the classic SDH stages based on relatively few data found in the literature.^{22,28,61–66} CT and MR imaging are regarded as complementary methods, which are both indispensable.^{28,32}

At present, this insufficient data situation is the most limiting factor preventing more accurate age estimation by neuroimaging.³⁷ Resilient reference data on SDH stages can rarely be obtained due to the difficult validation of the time of trauma and the highly variable severity of the injuries. Thus, the combination of insufficient reference data, little specific experience (eg, due to usually low AHT case numbers in nonuniversity institutions), heterogeneous pathophysiologic/anatomic knowledge, and gen-

eral lack of consensus concerning methodology (missing guidelines) unsurprisingly results in inconsistent assessments among radiologists as shown recently.^{67,68} These studies reflect the poor data situation and demonstrate the broad and overlapping time intervals of SDH stages, which represent a general argument against age estimation of SDCs.^{67,68}

However, the application of a “minimum age concept” might be an improvement towards an age-diagnostic assessment of the SDC, despite overlapping time intervals of stages. The principle is as follows: If a stage X (eg, “chronic”) is found, according to available study data, a minimum time Y (eg, 2 weeks) has elapsed since the trauma has occurred. The fact that the maximum duration of the antecedent stage often overlaps the earliest occurrence of the next stage does not affect the forensic statement (eg, that the SDC is at least 2 weeks old).

The observation of SDC development could be another possibility to increase the accuracy of age estimations of SDCs. To this end, repeated cranial imaging investigations (serial neuroimaging) are required, as long as the clinical state of the patient allows these procedures.^{22,31,69,70}

Thus, more reliable age-diagnostic assessments of SDCs necessitate more reference studies and special training programs, imparting specific diagnostic experiences. These would also require a harmonization of methodology and terminology as a precondition. Furthermore, focusing on the density or signal intensity of SDCs alone represents only 1 approach. Other imaging findings might have the potential to support the age estimation of AHT cases in the future—that is, parenchymal shear injuries, bridging vein thromboses/venous injuries, brain edema, subdural neomembranes (see also below: “Hypodense Subdurals: Acute or Chronic?”), the size of the SDC, or other signs of brain damage.^{22,63,71} However, as long as large systematic studies on these topics are missing, being cautious with time-related statements on SDCs is recommended.

Mixed-Density SDCs: Repeated Trauma?

In initial CT investigations, SDCs frequently show a mixture of hyper- and hypodense proportions (so-called mixed-density pattern) (Fig 1E). This pattern is significantly more frequent in AHT than in accidental head trauma.^{30,72} In the past, the dogma was that such a pattern would represent a combination of “new” and “old” blood, indicating repeated trauma. Today, this view has changed. At least 4 different scenarios have been proposed as explanations for the mixed-density pattern, and 3 of them may be deduced from only 1 single traumatic event (Table 2, upper part).^{22,28}

Table 3: Possible distinguishing criteria between SDHy and cSDH in neuroimaging^a

Criterion	SDHy	cSDH	Remarks
Neomembranes/septa/chamber formations	No	Yes	MRI more sensitive than CT IV contrast may improve the detection of neomembranes First formation of neomembranes macroscopically visible after ~10 days; ⁷⁴ when using MR imaging contrast after ~2–4 weeks ²² Late (chronifying) SDHys may also have first thin neomembranes (transitional phase to cSDH, terminologic gray zone)
Structure/composition	Rather homogeneous (CSF-like)	Rather heterogeneous/complex (evidence for blood products and CSF)	Heterogeneity of different cSDH fluid areas by neomembrane-associated chamber formations
Coexisting brain edema	Possible	Unlikely	Brain edema = rather acute/subacute
Growth behavior	At first, often rapidly progredient in growth; subsequently, mostly regredient in growth or static	Rather static/only slowly progredient in growth	Requires serial neuroimaging
Density	Very CSF-like, between 3.5 and 11.5 HU ⁶⁶	Slightly higher density than CSF due to admixture of blood components, between 6.4 and 24.6 HU ⁶⁶	Requires standardized measurements of densities CSF = 5–10 HU SDHHys with low blood fraction and high dilution with CSF are likely to show HU values just above 10 HU as well; thus, differentiation between SDHy and SDHHy may be difficult

^a According to Hedlund²² Wittschieber et al,²⁷ Vezina,²⁸ Zouros et al,²⁹ Case,³³ Bergström et al,⁶⁶ and Walter et al.⁷⁴

Scenario 4 (“acute-on-chronic” variant in Table 2) can often be excluded when an acute severe shaking event is suspected because acute rebleeding from cSDH-associated neomembranes is not associated with the typical acute symptomatology of AHT.^{22,24} Then, additional MR imaging and serial neuroimaging may provide more information.^{68,69}

In the context of the mixed-density pattern, it has been proposed that SDCs with 2 different densities in “2 distant locations” may be considered indicators of a so-called “age-different pattern”^{60,73}—that is, a hypodense frontoparietal SDC in combination with a hyperdense SDC in the posterior fossa, or a hypodense frontoparietal SDC associated with hyperdense clots at the vertex.⁶⁰ Those patterns were reported to be strongly associated with confessions of repeated episodes of violence against the child, suggesting that at least 2 traumatic events occurred. However, there are numerous reports of hypodense SDCs that formed very early after the reported traumatic event (partly even within a few hours), namely without an additional trauma and also on the contralateral side of a hyperdense SDC observed initially.^{22,27,28,37,69,70} One possible explanation for those observations may be arachnoid tears resulting in CSF accumulations within the subdural space corresponding to acute formation of an SDHy or SDHHy.

Hypodense Subdurals: Acute or Chronic?

The presence of isolated iso- to hypodense SDCs is another typical problem in CT investigations of SDCs (Fig 1B). At least 5 possibilities of interpretation, besides SDHy and SDHHy, compose nearly all time-related SDH stages from hyperacute to chronic (Table 2, lower part).²² Hence, a reliable diagnosis and age esti-

mation of the SDC are frequently not possible without additional MR imaging and serial neuroimaging, respectively. The diversity of differential diagnoses shown in Table 2 illustrates that the diagnosis of a chronic process (cSDH) may be hasty.

Finally, in many cases, the question is whether the diagnosis is SDHy or cSDH. While the former is compatible with both a rapid and a delayed process, the latter, in fact, suggests a traumatic event that occurred weeks ago. Several distinguishing criteria have been proposed (Table 3) to address this question.^{22,27–29,33,66,74} The most important criterion is the presence of subdural neomembranes, septa, or chamber-like formations characterizing cSDHs. In neuropathology, the first formation of neomembranes is described as macroscopically visible after ~10 days.⁷⁴ Their radiologic detection may be challenging and often requires MR imaging, sometimes even supported by intravenous contrast. In those cases, the presence of neomembranes is described after ~2–4 weeks.²²

CONCLUSIONS

SDCs in infants and toddlers represent frequently occurring indicators of AHT. The radiologic analysis and assessment of SDCs remain a challenging task because different SDC entities may appear radiologically very similar at different developmental stages.

As long as no harmonization of terminology, methodology, and age diagnostic criteria of SDCs exists and as long as the scientific data situation has not improved, only rough time-related statements on SDCs will be possible. However, such statements may be helpful if a “minimum age concept” is applied. For exam-

ple, it is possible to exclude that wide hypodense SDCs with neomembranes formed 2 days ago as suggested by a witness.

In summary, as consensually corroborated by a number of leading medical societies,⁷⁵ the close cooperation and joint evaluation by clinicians, radiologists, and forensic experts remains essential in cases of suspected AHT.

REFERENCES

- Peterson C, Xu L, Florence C, et al. **The medical cost of abusive head trauma in the United States.** *Pediatrics* 2014;134:91–99 CrossRef Medline
- Norman RE, Byambaa M, De R, et al. **The long-term health consequences of child physical abuse, emotional abuse, and neglect: a systematic review and meta-analysis.** *PLoS Med* 2012;9:e1001349 CrossRef Medline
- Brown DS, Fang X, Florence CS. **Medical costs attributable to child maltreatment: a systematic review of short- and long-term effects.** *Am J Prev Med* 2011;41:627–35 CrossRef Medline
- Di Maio VJ, Di Maio DJ. **Neonaticide, infanticide, and child homicide.** In: DiMaio VJ, DiMaio D, eds. *Forensic Pathology*. 2nd ed. Boca Raton: CRC Press; 2001:335–65
- Keenan HT, Runyan DK, Marshall SW, et al. **A population-based study of inflicted traumatic brain injury in young children.** *JAMA* 2003;290:621–26 CrossRef Medline
- Gill JR, Goldfelder LB, Armbrustmacher V, et al. **Fatal head injury in children younger than 2 years in New York City and an overview of the shaken baby syndrome.** *Arch Pathol Lab Med* 2009;133:619–27 Medline
- Christian CW, Block R; Committee on Child Abuse and Neglect, American Academy of Pediatrics. **Abusive head trauma in infants and children.** *Pediatrics* 2009;123:1409–11 CrossRef Medline
- Matschke J, Herrmann B, Spermhake J, et al. **Shaken baby syndrome: a common variant of non-accidental head injury in infants.** *Dtsch Arztebl Int* 2009;106:211–17 Medline
- Herrmann B. **Epidemiologie, Klinik und Konzept des Schütteltrauma-Syndroms.** *Pädiatrische Praxis* 2016;86:297–12. https://cme.mgo-fachverlage.de/uploads/exam/exam_96.pdf. Accessed June 9, 2018
- Barlow KM, Minns RA. **Annual incidence of shaken impact syndrome in young children.** *Lancet* 2000;356:1571–72 CrossRef Medline
- Jayawant S, Rawlinson A, Gibbon F, et al. **Subdural haemorrhages in infants: population-based study.** *BMJ* 1998;317:1558–61 CrossRef Medline
- Herrmann B. **ESPED-Schütteltrauma-Studie.** http://www.kindesmisshandlung.de/mediapool/32/328527/data/ESPED_Schuetteltrauma_-_Zwischenbericht_2009.pdf. Accessed April 14, 2018
- Fanconi M, Lips U. **Shaken baby syndrome in Switzerland: results of a prospective follow-up study, 2002–2007.** *Eur J Pediatr* 2010;169:1023–28 CrossRef Medline
- Jenny C, Hymel KP, Ritten A, et al. **Analysis of missed cases of abusive head trauma.** *JAMA* 1999;281:621–26 CrossRef Medline
- Minns RA, Jones PA, Barlow KM. **Outcome and prognosis of non-accidental head injury in infants.** In: Minns RA, Brown JK, eds. *Shaking and Other Non-Accidental Head Injuries in Children*. London: Mac Keith Press; 2006:364–414
- Royal College of Paediatrics and Child Health (2013) **Child Protection Companion.** <http://pcouk.org/book.aspx?bookid=1674>. Accessed June 9, 2018
- Royal College of Radiologists and Royal College of Paediatrics and Child Health (9/2017). **The radiological investigation of suspected physical abuse in children.** <https://www.rcr.ac.uk/publication/radiological-investigation-suspected-physical-abuse-children>. Accessed June 9, 2018
- Tucker J, Choudhary AK, Piatt J. **Macrocephaly in infancy: benign enlargement of the subarachnoid spaces and subdural collections.** *J Neurosurg Pediatr* 2016;18:16–20 CrossRef Medline
- Adamsbaum C. **Letter to the editor: subdural collections and abusive head trauma.** *J Neurosurg Pediatr* 2017;19:625 CrossRef Medline
- Hymel KP, Jenny C, Block RW. **Intracranial hemorrhage and rebleeding in suspected victims of abusive head trauma: addressing the forensic controversies.** *Child Maltreat* 2002;7:329–48 CrossRef Medline
- Vinchon M, de Foort-Dhellemmes S, Desurmont M, et al. **Confessed abuse versus witnessed accidents in infants: comparison of clinical, radiological, and ophthalmological data in corroborated cases.** *Childs Nerv Syst* 2010;26:637–45 CrossRef Medline
- Hedlund G. **Abusive head trauma: extra-axial hemorrhage and nonhemic collections.** In: Kleinman PK, ed. *Diagnostic Imaging of Child Abuse*. 3rd ed. Cambridge: Cambridge University Press; 2016:394–452
- Case ME, Graham MA, Handy TC, et al; National Association of Medical Examiners Ad Hoc Committee on Shaken Baby Syndrome. **Position paper on fatal abusive head injuries in infants and young children.** *Am J Forensic Med Pathol* 2001;22:112–22 CrossRef Medline
- Herrmann B. **Misshandlungsbedingte Kopfverletzungen und Schütteltrauma-Syndrom.** In: Herrmann B, Dettmeyer R, Banaschak S, et al, eds. *Kindesmisshandlung*. 3rd ed. Berlin: Springer-Verlag; 2016:39–62
- Matschke J, Glatzel M. **Neuropathologische Begutachtung des nicht akzidentellen Schädel-Hirn-Traumas bei Säuglingen und Kleinkindern.** *Rechtsmedizin* 2008;18:29–35 CrossRef Medline
- Osborn AG. **Trauma.** In: Osborn AG, ed. *Osborn's Brain: Imaging, Pathology, and Anatomy*. 2nd ed. Salt Lake City: Amirsys; 2013:1–72
- Wittschieber D, Karger B, Niederstadt T, et al. **Subdural hygromas in abusive head trauma: pathogenesis, diagnosis, and forensic implications.** *AJNR Am J Neuroradiol* 2015;36:432–39 CrossRef Medline
- Vezina G. **Assessment of the nature and age of subdural collections in nonaccidental head injury with CT and MRI.** *Pediatr Radiol* 2009;39:586–90 CrossRef Medline
- Zouros A, Bhargava R, Hoskinson M, et al. **Further characterization of traumatic subdural collections of infancy: report of five cases.** *J Neurosurg* 2004;100(5 Suppl Pediatrics):512–18 CrossRef Medline
- Tung GA, Kumar M, Richardson RC, et al. **Comparison of accidental and nonaccidental traumatic head injury in children on noncontrast computed tomography.** *Pediatrics* 2006;118:626–33 CrossRef Medline
- Vinchon M, Noulé N, Tchofo PJ, et al. **Imaging of head injuries in infants: temporal correlates and forensic implications for the diagnosis of child abuse.** *J Neurosurg* 2004;101:44–52 Medline
- Hedlund G. **Subdural hemorrhage in abusive head trauma: imaging challenges and controversies.** *J Am Osteopath Coll Radiol* 2012;1:23–30
- Case ME. **Inflicted traumatic brain injury in infants and young children.** *Brain Pathol* 2008;18:571–82 CrossRef Medline
- Lee KS, Bae WK, Park YT, et al. **The pathogenesis and fate of traumatic subdural hygroma.** *Br J Neurosurg* 1994;8:551–58 CrossRef Medline
- Squier W, Mack J. **The neuropathology of infant subdural haemorrhage.** *Forensic Sci Int* 2009;187:6–13 CrossRef Medline
- Vinchon M, Noulé N, Soto-Ares G, et al. **Subdural hematoma drainage for subdural hematomas in infants: results in 244 cases.** *J Neurosurg* 2001;95:249–55 CrossRef Medline
- Vinchon M, Noizet O, Defoort-Dhellemmes S, et al. **Infantile subdural hematomas due to traffic accidents.** *Pediatr Neurosurg* 2002;37:245–53 CrossRef Medline
- Hwang SK, Kim SL. **Infantile head injury, with special reference to the development of chronic subdural hematoma.** *Childs Nerv Syst* 2000;16:590–94 CrossRef Medline
- Swift DM, McBride L. **Chronic subdural hematoma in children.** *Neurosurg Clin N Am* 2000;11:439–46 CrossRef Medline
- Frasier LD, Coats B. **Abusive head trauma: clinical, biomechanical, and imaging considerations.** In: Kleinman PK, ed. *Diagnostic Imag-*

- ing of Child Abuse. 3rd ed. Cambridge: Cambridge University Press; 2015;345–56
41. Cheshire EC, Malcomson RD, Sun P, et al. **A systematic autopsy survey of human infant bridging veins.** *Int J Legal Med* 2018;132: 449–61 [CrossRef Medline](#)
 42. Nierenberger M, Wolfram-Gabel R, Decock-Catrin S, et al. **Investigation of the human bridging veins structure using optical microscopy.** *Surg Radiol Anat* 2013;35:331–27 [CrossRef Medline](#)
 43. Minns RA. **Subdural haemorrhages, haematomas, and effusions in infancy.** *Arch Dis Child* 2005;90:883–84 [CrossRef Medline](#)
 44. Morrison CN, Minns RA. **The biomechanics of shaking.** In: Minns RA, Brown JK, eds. *Shaking and Other Non-Accidental Head Injuries in Children.* London: Mac Keith Press; 2006;106–46
 45. Yamashima T, Friede RL. **Why do bridging veins rupture into the virtual subdural space?** *J Neurol Neurosurg Psychiatry* 1984;47: 121–27 [CrossRef Medline](#)
 46. v. Düring M, Dermietzel R, Drenckhahn D. **Hirnhäute, Ventrikelaukleidung, Liquor cerebrospinalis.** In: Benninghoff A, Drenckhahn D, eds. *Anatomie. Bd.2*, 16th ed. München: Urban&Fischer/Elsevier; 2004;266–83
 47. Mack J, Squier W, Eastman JT. **Anatomy and development of the meninges: implications for subdural collections and CSF circulation.** *Pediatr Radiol* 2009;39:200–10 [CrossRef Medline](#)
 48. Fox RJ, Walji AH, Mielke B, et al. **Anatomic details of intradural channels in the parasagittal dura: a possible pathway for flow of cerebrospinal fluid.** *Neurosurgery* 1996;39:84–90; discussion 90–92 [CrossRef Medline](#)
 49. Lee KS. **The pathogenesis and clinical significance of traumatic subdural hygroma.** *Brain Inj* 1998;12:595–603 [CrossRef Medline](#)
 50. Borzone M, Capuzzo T, Perria C, et al. **Traumatic subdural hygromas: a report of 70 surgically treated cases.** *J Neurosurg Sci* 1983;27:161–65 [Medline](#)
 51. Kristof RA, Grimm JM, Stoffel-Wagner B. **Cerebrospinal fluid leakage into the subdural space: possible influence on the pathogenesis and recurrence frequency of chronic subdural hematoma and subdural hygroma.** *J Neurosurg* 2008;108:275–80 [CrossRef Medline](#)
 52. Wilberger JE. **Pathophysiology of evolution and recurrence of chronic subdural hematoma.** *Neurosurg Clin N Am* 2000;11:435–38 [CrossRef Medline](#)
 53. Schachenmayr W, Friede RL. **The origin of subdural neomembranes. I. Fine structure of the dura-arachnoid interface in man.** *Am J Pathol* 1978;92:53–68 [Medline](#)
 54. Friede RL, Schachenmayr W. **The origin of subdural neomembranes, II: fine structure of neomembranes.** *Am J Pathol* 1978;92: 69–84 [Medline](#)
 55. Killeffer JA, Killeffer FA, Schochet SS. **The outer neomembrane of chronic subdural hematoma.** *Neurosurg Clin N Am* 2000;11:407–12 [CrossRef Medline](#)
 56. Yamashima T. **The inner neomembrane of chronic subdural hematomas: pathology and pathophysiology.** *Neurosurg Clin N Am* 2000;11:413–24 [CrossRef Medline](#)
 57. Williams VL, Hogg JP. **Magnetic resonance imaging of chronic subdural hematoma.** *Neurosurg Clin N Am* 2000;11:491–98 [CrossRef Medline](#)
 58. Goodell CL, Mealy J Jr. **Pathogenesis of chronic subdural hematoma: experimental studies.** *Arch Neurol* 1963;8:429–37 [CrossRef Medline](#)
 59. Watanabe S, Shimada H, Ishii S. **Production of clinical form of chronic subdural hematoma in experimental animals.** *J Neurosurg* 1972;37:552–61 [CrossRef Medline](#)
 60. Adamsbaum C, Morel B, Ducot B, et al. **Dating the abusive head trauma episode and perpetrator statements: key points for imaging.** *Pediatr Radiol* 2014;44(Suppl 4):S578–88 [CrossRef Medline](#)
 61. Lee KS, Bae WK, Bae HG, et al. **The computed tomographic attenuation and the age of subdural hematomas.** *J Korean Med Sci* 1997;12: 353–59 [CrossRef Medline](#)
 62. Duhem R, Vinchon M, Tonnelle V, et al. **Main temporal aspects of the MRI signal of subdural hematomas and practical contribution to dating head injury [in French].** *Neurochirurgie* 2006;52:93–104 [CrossRef Medline](#)
 63. Tung GA. **Imaging of abusive head trauma.** In: Jenny C, ed. *Child Abuse and Neglect.* Philadelphia: Saunders; 2011;373–91
 64. Cramer JA, Rassner UA, Hedlund GL. **Limitations of T2*-gradient recalled-echo and susceptibility-weighted imaging in characterizing chronic subdural hemorrhage in infant survivors of abusive head trauma.** *AJNR Am J Neuroradiol* 2016;37:1752–56 [CrossRef Medline](#)
 65. Bradley WG Jr. **MR appearance of hemorrhage in the brain.** *Radiology* 1993;189:15–26 [CrossRef Medline](#)
 66. Bergström M, Ericson K, Levander B, et al. **Computed tomography of cranial subdural and epidural hematomas: variation of attenuation related to time and clinical events such as rebleeding.** *J Comput Assist Tomogr* 1977;1:449–55 [CrossRef Medline](#)
 67. Sieswerda-Hoogendoorn T, Postema FA, Verbaan D, et al. **Age determination of subdural hematomas with CT and MRI: a systematic review.** *Eur J Radiol* 2014;83:1257–68 [CrossRef Medline](#)
 68. Postema FA, Sieswerda-Hoogendoorn T, Majoie CB, et al. **Age determination of subdural hematomas: survey among radiologists.** *Emerg Radiol* 2014;21:349–58 [CrossRef Medline](#)
 69. Dias MS, Backstrom J, Falk M, et al. **Serial radiography in the infant shaken impact syndrome.** *Pediatr Neurol* 1998;29:77–85 [CrossRef Medline](#)
 70. Bradford R, Choudhary AK, Dias MS. **Serial neuroimaging in infants with abusive head trauma: timing abusive injuries.** *J Neurosurg Pediatrics* 2013;12:110–19 [CrossRef Medline](#)
 71. Hahneemann ML, Kinner S, Schweiger B, et al. **Imaging of bridging vein thrombosis in infants with abusive head trauma: the “tadpole sign.”** *Eur Radiol* 2015;25:299–305 [CrossRef Medline](#)
 72. Datta S, Stoodley N, Jayawant S, et al. **Neuroradiological aspects of subdural haemorrhages.** *Arch Dis Child* 2005;90:947–51 [CrossRef Medline](#)
 73. Adamsbaum C, Grabar S, Mejean N, et al. **Abusive head trauma: judicial admissions highlight violent and repetitive shaking.** *Pediatrics* 2010;126:546–55 [CrossRef Medline](#)
 74. Walter T, Meissner C, Oehmichen M. **Pathomorphological staging of subdural hemorrhages: statistical analysis of posttraumatic histomorphological alterations.** *Leg Med (Tokyo)* 2009;11(Suppl 1): S56–62 [CrossRef Medline](#)
 75. Choudhary AK, Servaes S, Slovis TL, et al. **Consensus statement on abusive head trauma in infants and young children.** *Pediatr Radiol* 2018;48:1048–65 [CrossRef Medline](#)

Imaging of Patients with Suspected Large-Vessel Occlusion at Primary Stroke Centers: Available Modalities and a Suggested Approach

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ABSTRACT

SUMMARY: The overwhelming benefit of endovascular therapy in patients with large-vessel occlusions suggests that more patients will be screened than treated. Some of those patients will be evaluated first at primary stroke centers; this type of evaluation calls for standardizing the imaging approach to minimize delays in assessing, transferring, and treating these patients. Here, we propose that CT angiography (performed at the same time as head CT) should be the minimum imaging approach for all patients with stroke with suspected large-vessel occlusion presenting to primary stroke centers. We discuss some of the implications of this approach and how to facilitate them.

ABBREVIATIONS: CSC = comprehensive stroke center; DIDO = door-in-door-out time interval; EVT = endovascular thrombectomy; LAMS = Los Angeles Motor Scale; LVO = large-vessel occlusion; PSC = primary stroke center; P_{PSC}2P_{CSC} = picture at the primary stroke center to puncture at the comprehensive stroke center time

Ischemic stroke due to large-vessel occlusion (LVO) substantially contributes to morbidity and mortality. Despite the improvements in systems of care and the development of effective interventions, a minority of eligible patients receive acute therapies.¹ To increase patients' access to treatment, stroke centers are certified as primary (ie, capable of administering intravenous thrombolytics) and comprehensive (ie, capable of administering thrombolytics and endovascular thrombectomy [EVT]).

The evidence for the benefit from EVT in patients with LVO is overwhelming, with a number needed to treat of 2.6 to reduce functional disability on the modified Rankin Scale by at least 1 level.² This benefit is evident across all subgroups and is indepen-

dent of age, stroke severity, or the extent of early ischemic changes on imaging. This effect makes most patients with LVO potentially eligible for EVT within 6 hours from onset. While early treatment is associated with greater benefit,³ EVT is still associated with better outcomes in selected patients in the 6- to 24-hour time window.^{4,5} Therefore, it is critical that all potential EVT candidates be screened for LVO rapidly and then rushed to comprehensive stroke centers (CSCs) for EVT.

Because many patients will first arrive at primary stroke centers (PSCs), the improvement of workflow processes at PSCs to identify EVT candidates is a priority. To achieve this, we recommend that all patients triaged as having potential LVO (eg, the Los Angeles Motor Scale [LAMS] score⁶ is ≥ 4) receive a standardized, 1-stop imaging with noncontrast head CT and CTA at the same time to confirm the presence of LVO and initiate the transfer process. Key challenges to this approach include reliable head CT interpretation and detection of LVO on CTA by nonexpert readers. Advanced imaging, such as multiphase CTA or CTP, can help overcome challenges related to variability in head CT interpretation. Multiphase CTA simplifies LVO detection even for nonexpert readers⁷ and provides collateral assessment and core/penumbra estimation.^{8,9} While evidence from the Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke trial supports MR imaging–based selection of patients with unknown time of onset,¹⁰ CT-based paradigms are more widely available and faster and have fewer contraindications compared with MR imaging, making them more appropriate for the PSC setting.¹¹

Herein, we discuss the driving principles behind our proposed

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imaging approach at PSCs and how they relate to the core concepts of stroke therapy. These recommendations are not meant to be binding, but they aim to engage physicians from all relevant disciplines in both PSCs and CSCs and policymakers in a discussion to streamline the imaging approach in patients with suspected LVO in PSCs.

Appropriateness of Transfer

A critical PSC-related challenge is the appropriateness of transferring patients with suspected LVO. We have recently debated this topic and proposed a classification scheme to assess the appropriateness of patient transfer for EVT.¹² Some of the clinical and imaging characteristics of patients who are not candidates for transfer include those with the following:

- 1) Completed infarct in which recanalization will be both futile and risky¹³
- 1) High likelihood of reperfusion with intravenous thrombolytic therapy (distal occlusion, small thrombus, favorable thrombus characteristics)^{14,15}
- 3) Severe comorbidities or poor premorbid status.

While PSCs should err toward overtransferring rather than undertransferring because of the significant effect size of EVT, the above-mentioned characteristics highlight the role of advanced imaging in modern stroke care.

Time Matters

Fast treatment is essential for good stroke outcome. This is emphasized in the pooled analyses in the highly effective reperfusion using multiple endovascular devices (HERMES) collaboration.³ Hence, one must balance the time spent on obtaining and interpreting imaging and the value and relevance of the information it provides. At the CSC level, use of CTA has been linked to shorter onset-to-treatment times.¹⁶ The need for and feasibility of routinely performing advanced imaging at PSCs are less clear. While it will exhaust the limited resources of PSCs if CTA is performed on all patients with stroke without discrimination, there are merits to performing CTA in all patients with suspected LVO (based on the LAMS, NIHSS, presence of cortical signs, and so forth) at the same time as head CT. Patients not suspected of having LVO such as those with minor stroke symptoms or those who are not candidates for EVT, for example due to pre-existing disability or functional impairment, could be assessed with head CT alone as an initial step.

One approach to advanced imaging at the PSC level is to protocol the technique on the basis of the time from symptom onset. Patients who present early (<6 hours from onset) undergo head CT/CTA, while those arriving at later times (6–24 hours from onset) or those with suspected LVO stroke on awakening also undergo CTP. Ultimately, a standardized, protocol-driven advanced imaging pathway is likely to be the most efficient strategy in triaging patients at the PSC.

Technique and Technical Support Matter

For advanced imaging to be used at PSCs, imaging protocols need to be well-developed, and qualified technologists need to be available to perform them around the clock. Results should be conveyed promptly to the managing physicians for the transfer pro-

cess to be initiated rapidly. Also, images need to be accessible to the CSC team. These prerequisites may pose challenges for the PSC, given their limited resources, especially outside of the working hours. Teleradiology consult with CSCs may be a potential solution by using image transfer or a sharing platform or the cloud. Alternatively, automated postprocessing software can be used to immediately alert physicians to the presence of potential thrombectomy candidates. Such software needs to be fast and adequately tested, and personnel involved need to be trained to recognize factors that may result in erroneous interpretation (eg, patient motion). Another pitfall common to images obtained at the PSC is the risk of decay (progression of infarction during transfer), requiring repeat imaging based on a variety of clinical characteristics (Figure).¹⁷

Door-In-Door-Out Is Critical

Workflow time metrics influence the outcomes of patients with LVO stroke who initially present to PSCs (Figure). These include the time from arrival at the PSC emergency door to the start of intravenous thrombolytic therapy (door-to-needle time), the time from arriving at the PSC door until the patient leaves the PSC for a CSC (door-in-door-out time interval [DIDO]), and the time from imaging at the PSC to the arterial puncture time at the CSC ($P_{PSC}2P_{CSC}$).¹⁸ Some of these metrics depend on the efficiency of workflow in the PSC (door-to-needle time, DIDO), while the $P_{PSC}2P_{CSC}$ integrates the time needed for transfer and that of any additional imaging performed at the CSC. The DIDO metric has become the chief measure for efficient management of patients with LVO stroke within PSCs. Shortening the DIDO is feasible and results in a shorter time to groin puncture.¹⁹ A target DIDO of ≤ 45 minutes was achieved by McTaggart et al.¹⁹ Health care systems should aim to achieve a DIDO as short as safely possible in their stroke network based on the available resources.

The same paramedic team that brings the patient to the PSC should accompany the patient during imaging and transfer to the CSC if needed, to achieve an ultrashort DIDO. This arrangement has many advantages, including the continuity of care, because the same personnel at the first medical contact will be more likely to pick up any improvement or deterioration. This approach will save time and reflect positively on patient outcomes. One disadvantage is making certain that ambulance team is unavailable for other emergencies during that entire time. However, if an ultrashort DIDO can be implemented and consistently achieved, the door-to-decision time at the PSC will be extremely short and it will be an incentive for the paramedics to remain at the patient's side. To facilitate this ultrashort DIDO, the decision to transfer to a CSC will need to be made directly after CTA once the presence of proximal occlusion is confirmed. The complete interpretation of NCCT and CTA with formal written reports can follow later and should not be required for transfer. Built-in software for automated ASPECTS interpretation, LVO detection, and perfusion imaging (for patients with a late window) will expedite this process.

In summary, to maximize the workflow efficiency and decision-making at the PSC level, the same paramedic crew should accompany the patient from first medical contact, during the stay in PSC, and to the CSC if needed. Imaging modalities at the PSC should do the following:

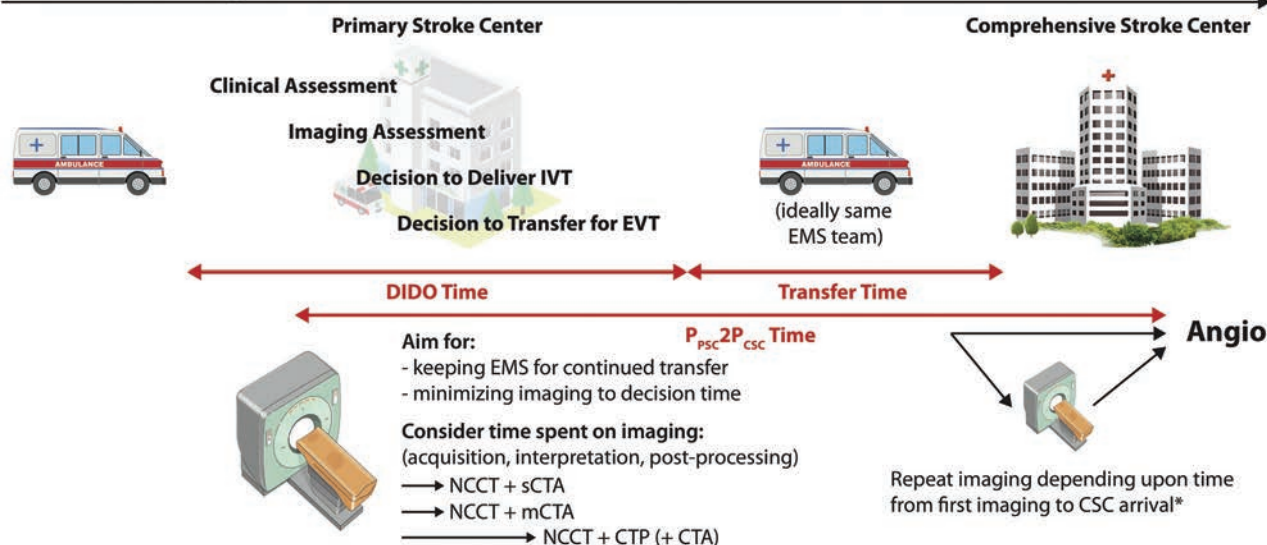


FIGURE. The workflow of patients with LVO stroke arriving first at a primary stroke center. Once patients arrive at the PSC, steps that can introduce delay in the door-in-door-out time interval include clinical and imaging assessments and the time spent on each of the various imaging modalities (the length of the arrows corresponds to the relative duration needed to complete, process, and interpret each technique). Following imaging, the decisions to administer intravenous thrombolytics (IVT) and whether to transfer to comprehensive stroke centers for endovascular thrombectomy can introduce some delay. Transfer to CSCs is preferably done by the same Emergency Medical Service (EMS) team that brought the patient to the PSC. Once the patient arrives at a CSC, repeat imaging can be considered in selected patients (*), given the low likelihood of recanalization of LVO with intravenous thrombolytics and the variability of CT ASPECTS decay. Repeat imaging at the CSC will further delay the time interval from imaging at the PSC to arterial puncture. mCTA indicates multiphase CTA; sCTA, single-phase CTA; angio, angiography.

Imaging options, advantages, and limitations at primary stroke centers

Imaging Modality	Pros	Cons
Plain CT only	Highly time-efficient	Detection of LVO is not reliable. Dense MCA sign is not reliable ²⁰ Variability in ASPECTS reading, especially in the very early time window ²¹
CT plus single-phase CTA (arch to vertex)	Exact occlusion site Basic assessment of collaterals Roadmap for EVT procedure	Considerable risk of collateral underestimation if acquisition timed too early Distal occlusions might be missed; challenges with training and maintaining competence for technologists in low-volume community settings
CT plus multiphase CTA	Robust collateral assessment (independent of timing) Diagnosis of LVO in inexperienced readers Easier detection of distal occlusions ⁷ No additional contrast needed Can be done on any modern scanner	Collateral assessment may require training
CT plus CTP	Easier identification of patients eligible for EVT Easier identification of stroke mimics in the absence of LVO ²²	More sensitive to patient motion Time-consuming; may create a bottleneck in a workflow wherein the paramedic team that brings the patient in is the same team that takes the patient to the CSC Limited comparability of CTP results across protocols and postprocessing software ^{23,24} Higher contrast and radiation dose needed CTP pitfalls ²⁵ Cost of additional postprocessing software, optional

- 1) Rule out intracerebral hemorrhage
- 2) Identify large-vessel occlusion
- 3) Identify a large-infarction core (eg, ASPECTS <6 or core >50 mL; consider eloquence of the affected or spared brain regions) and the infarction dynamics/decay (collaterals versus the effect of the P_{PSC-2P_{CSC}}).

The Table compares the various imaging options at the PSC level.

DISCUSSION

The choice of imaging technique at the PSC implies a certain threshold for CSC transfer based on the information that each technique provides. A minimalist imaging approach may set

lower thresholds for transfer that consider all suspected patients but come at the expense of relatively high inappropriate transfers. The use of perfusion imaging implies strict thresholds based on the presence of a target mismatch to allow the transfer. This perfusion mismatch paradigm comes at the expense of excluding patients with proved benefit from EVT as shown by the Multi-center Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands²⁶ and the Trial and Cost Effectiveness Evaluation of Intra-arterial Thrombectomy in Acute Ischemic Stroke,²⁷ which selected patients on the basis of NCCT and the presence of proximal occlusion. Thus, the 2018 American Stroke Association guidelines did not recommend the use of perfusion imaging for selecting patients for EVT in the <6-hour time window.²⁸ Advanced imaging also comes at the expense of DIDO.

The imaging approaches in a given institution are dependent on its available resources, expected patient volume, the distance to the CSC (the closer the CSC, the less the need to perform advanced imaging at the PSC), and the availability of an imaging-sharing platform with the CSC. The imaging approach can be revisited, depending on the door-to-needle time and DIDO, and according to infrastructure and resources. In addition, the approach needs to be tailored to the patient's onset time.

We support the implementation of vascular imaging at the PSC level as a goal that all stroke systems of care should achieve. While it is estimated that around 10%–20% of LVOs will recanalize with intravenous thrombolytics en route to the CSC,²⁹ the rate of ASPECTS/collateral decay is not known. One study described ASPECTS decay in 19.6% of patients transferred to CSCs for EVT.^{30,31} This was noted in patients with poor baseline ASPECTS and poor collateral flow and higher baseline stroke severity, irrespective of the onset-to-imaging time or the duration of the transfer.

While we propose that CT and CTA need to be the basis of imaging in all patients with suspected LVO, the limitations of these imaging modalities need to be considered. In addition to the points discussed earlier (Table), the reliability of CT ASPECTS in the early time window (<3 hours) may lead to excluding/including inappropriate transfers for EVT.²¹ A training Web site for ASPECTS is available to tackle many of the perceived challenges related to CT (and CTA) interpretation in the acute stroke setting (www.aspectsinstroke.com). Single-phase CTA assessment of collaterals could be clouded by poor injection timing. Here, multiphase CTA has a clear advantage. While the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness trial enrolled patients up to 12 hours on the basis of CTA (or multiphase CTA) collaterals,³² patient selection based on collateral imaging has not been directly compared with perfusion imaging for selecting patients in the 6- to 24-hour time window. Prospective cohorts have shown that multiphase CTA fared better than CTP in selecting patients within 6 hours from onset.⁸

Future Directions and Conclusions

The advent of EVT in patients with LVO has opened the field for innovation and technology. One promising aspect is the use of automated aids for decision-making.³³ Some of the developed software tools were found to be noninferior to interpretation of

the ASPECTS by a neuroradiologist.³⁴ There is innovation in the prehospital detection of LVO. The volumetric impedance phase shift spectroscopy (VIPS) device (Cerebrotech Medical Systems, Pleasanton, California) has shown >90% sensitivity and specificity for detecting severe strokes.³⁵ If this technology or similar ones reliably identify patients with LVO in the field, it will provide the opportunity for rational, direct transfer of some patients to nearby CSCs, eliminating the need for stopping at PSCs.

In conclusion, EVT has proved efficacy for a wide range of patients with LVO stroke and in selected cases up to 24 hours from onset. While PSCs have increased the proportion of patients with stroke receiving thrombolytic therapy, delays can be encountered until patients with LVO are identified and transferred from the PSC to the CSC. Therefore, any extra steps need to be carefully weighed. The use of CTA (especially multiphase) at the PSC level has many advantages in expediting the transfer of appropriate patients to CSCs. However, the routine implementation of CTA requires resources and training in addition to the infrastructure for sharing images with CSCs.

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REFERENCES

1. Messé SR, Khatri P, Reeves MJ, et al. **Why are acute ischemic stroke patients not receiving IV tPA? Results from a national registry.** *Neurology* 2016;87:1565–74 CrossRef Medline
2. Goyal M, Menon BK, van Zwam WH, et al; HERMES collaborators. **Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials.** *Lancet* 2016;387:1723–31 CrossRef Medline
3. Saver JL, Goyal M, van der Lugt A, et al; HERMES collaborators. **Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis.** *JAMA* 2016;316:1279–88 CrossRef Medline
4. Albers GW, Marks MP, Kemp S, et al; DEFUSE 3 Investigators. **Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging.** *N Engl J Med* 2018;378:708–18 CrossRef Medline

5. Nogueira RG, Jadhav AP, Haussen DC, et al; DAWN Trial Investigators. **Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct.** *N Engl J Med* 2018;378:11–21 [CrossRef Medline](#)
6. Llanes JN, Kidwell CS, Starkman S, et al. **The Los Angeles Motor Scale (LAMS): a new measure to characterize stroke severity in the field.** *Prehosp Emerg Care* 2004;8:46–50 [CrossRef Medline](#)
7. Amy Y, Zerna C, Assis Z, et al. **Multiphase CT angiography increases detection of anterior circulation intracranial occlusion.** *Neurology* 2016;87:609–16 [CrossRef Medline](#)
8. Menon BK, d'Este CD, Qazi EM, et al. **Multiphase CT angiography: a new tool for the imaging triage of patients with acute ischemic stroke.** *Radiology* 2015;275:510–20 [CrossRef Medline](#)
9. Tan BY, Wan-Yee K, Paliwal P, et al. **Good intracranial collaterals trump poor ASPECTS (Alberta Stroke Program Early CT Score) for intravenous thrombolysis in anterior circulation acute ischemic stroke.** *Stroke* 2016;47:2292–98 [CrossRef Medline](#)
10. Thomalla G, Simonsen CZ, Boutitie F, et al; WAKE-UP Investigators. **MRI-guided thrombolysis for stroke with unknown time of onset.** *N Engl J Med* 2018;379:611–22 [CrossRef Medline](#)
11. Jovin TG. **MRI-guided intravenous alteplase for stroke: still stuck in time.** *N Engl J Med* 2018;379:682–83 [CrossRef Medline](#)
12. Goyal M, Menon BK, Wilson AT, et al. **Primary to comprehensive stroke center transfers: appropriateness, not futility.** *Int J Stroke* 2018;13:550–53 [CrossRef Medline](#)
13. Liebeskind DS, Bracard S, Guillemin F, et al. **eTICI reperfusion: defining success in endovascular stroke therapy.** *J Neurointerv Surg* 2018;neurintsurg-2018-014127
14. Mishra SM, Dykeman J, Sajobi TT, et al. **Early reperfusion rates with IV tPA are determined by CTA clot characteristics.** *AJNR Am J Neuroradiol* 2014;35:2265–72 [CrossRef Medline](#)
15. Menon BK, Al-Ajlan FS, Najm M, et al; INTERSeCT Study Investigators. **Association of clinical, imaging, and thrombus characteristics with recanalization of visible intracranial occlusion in patients with acute ischemic stroke.** *JAMA* 2018;320:1017–26 [CrossRef Medline](#)
16. Menon BK, Campbell BC, Levi C, et al. **Role of imaging in current acute ischemic stroke workflow for endovascular therapy.** *Stroke* 2015;46:1453–61 [CrossRef Medline](#)
17. Sun CH, Connelly K, Nogueira RG, et al. **ASPECTS decay during inter-facility transfer predicts patient outcomes in endovascular reperfusion for ischemic stroke: a unique assessment of dynamic physiologic change over time.** *J Neurointerv Surg* 2015;7:22–26 [CrossRef Medline](#)
18. Sun CH, Nogueira RG, Glenn BA, et al. **“Picture to puncture”: a novel time metric to enhance outcomes in patients transferred for endovascular reperfusion in acute ischemic stroke.** *Circulation* 2013;127:1139–48 [CrossRef Medline](#)
19. McTaggart RA, Yaghi S, Cutting SM, et al. **Association of a primary stroke center protocol for suspected stroke by large-vessel occlusion with efficiency of care and patient outcomes.** *JAMA Neurol* 2017;74:793–800 [CrossRef Medline](#)
20. Kharitonova T, Thorén M, Ahmed N, et al; SITS investigators. **Disappearing hyperdense middle cerebral artery sign in ischaemic stroke patients treated with intravenous thrombolysis: clinical course and prognostic significance.** *J Neurol Neurosurg Psychiatry* 2009;80:273–78 [CrossRef Medline](#)
21. Bal S, Bhatia R, Menon BK, et al. **Time dependence of reliability of noncontrast computed tomography in comparison to computed tomography angiography source image in acute ischemic stroke.** *Int J Stroke* 2015;10:55–60 [CrossRef Medline](#)
22. Hopyan J, Ciarallo A, Dowlatshahi D, et al. **Certainty of stroke diagnosis: incremental benefit with CT perfusion over noncontrast CT and CT angiography.** *Radiology* 2010;255:142–53 [CrossRef Medline](#)
23. Austin F, Riedel C, Kerby T, et al. **Comparison of perfusion CT software to predict the final infarct volume after thrombectomy.** *Stroke* 2016;47:2311–17 [CrossRef Medline](#)
24. Bivard A, Kleinig T, Miteff F, et al. **Ischemic core thresholds change with time to reperfusion: a case control study.** *Ann Neurol* 2017;82:995–1003 [CrossRef Medline](#)
25. Goyal M, Menon BK, Derdeyn CP. **Perfusion imaging in acute ischemic stroke: let us improve the science before changing clinical practice.** *Radiology* 2013;266:16–21 [CrossRef Medline](#)
26. Berkhemer OA, Fransen PS, Beumer D, et al. **A randomized trial of intraarterial treatment for acute ischemic stroke.** *N Engl J Med* 2015;372:11–20 [CrossRef Medline](#)
27. Bracard S, Ducrocq X, Mas JL, et al; THRACE investigators. **Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomized controlled trial.** *Lancet Neurol* 2016;15:1138–47 [CrossRef Medline](#)
28. Powers WJ, Rabinstein AA, Ackerson T, et al; American Heart Association Stroke Council. **2018 Guidelines for the Early Management of Patients with Acute Ischemic Stroke: A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association.** *Stroke* 2018;49:e46–110 [CrossRef Medline](#)
29. Tsvigoulis G, Katsanos AH, Schellinger PD, et al. **Successful reperfusion with intravenous thrombolysis preceding mechanical thrombectomy in large-vessel occlusions.** *Stroke* 2018;49:232–35 [CrossRef Medline](#)
30. Boulouis G, Lauer A, Siddiqui AK, et al. **Clinical imaging factors associated with infarct progression in patients with ischemic stroke during transfer for mechanical thrombectomy.** *JAMA Neurol* 2017;74:1361–67 [CrossRef Medline](#)
31. Mokin M, Gupta R, Guerrero WR, et al. **ASPECTS decay during inter-facility transfer in patients with large vessel occlusion strokes.** *J Neurointerv Surg* 2017;9:442–44 [CrossRef Medline](#)
32. Goyal M, Demchuk AM, Menon BK, et al; ESCAPE Trial Investigators. **Randomized assessment of rapid endovascular treatment of ischemic stroke.** *N Engl J Med* 2015;372:1019–30 [CrossRef Medline](#)
33. Lee EJ, Kim YH, Kim N, et al. **Deep into the brain: artificial intelligence in stroke imaging.** *J Stroke* 2017;19:277 [CrossRef Medline](#)
34. Nagel S, Sinha D, Day D, et al. **e-ASPECTS software is non-inferior to neuroradiologists in applying the ASPECT score to computed tomography scans of acute ischemic stroke patients.** *Int J Stroke* 2017;12:615–22 [CrossRef Medline](#)
35. Kellner CP, Sauvageau E, Snyder KV, et al. **The VITAL study and overall pooled analysis with the VIPS non-invasive stroke detection device.** *J Neurointerv Surg* 2018;10:1079–84 [CrossRef Medline](#)

3T MRI Whole-Brain Microscopy Discrimination of Subcortical Anatomy, Part 1: Brain Stem

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ABSTRACT

BACKGROUND AND PURPOSE: The brain stem is compactly organized with life-sustaining sensorimotor and autonomic structures that can be affected by numerous pathologies but can be difficult to resolve on conventional MR imaging.

MATERIALS AND METHODS: We applied an optimized TSE T2 sequence to washed postmortem brain samples to reveal exquisite and reproducible brain stem anatomic MR imaging contrast comparable with histologic atlases. This resource-efficient approach can be performed across multiple whole-brain samples with relatively short acquisition times (2 hours per imaging plane) using clinical 3T MR imaging systems.

RESULTS: We identified most brain stem structures at 7 canonical axial levels. Multiplanar or oblique planes illustrate the 3D course and spatial relationships of major brain stem white matter pathways. Measurements of the relative position, course, and cross-sectional area of these pathways across multiple samples allow estimation of pathway location in other samples or clinical subjects. Possible structure-function asymmetries in these pathways will require further study—that is, the cross-sectional area of the left corticospinal tract in the midpons appeared 20% larger ($n = 13$ brains, $P < .10$).

CONCLUSIONS: Compared with traditional atlases, multiplanar MR imaging contrast has advantages for learning and retaining brain stem anatomy for clinicians and trainees. Direct TSE MR imaging sequence discrimination of brain stem anatomy can help validate other MR imaging contrasts, such as diffusion tractography, or serve as a structural template for extracting quantitative MR imaging data in future postmortem investigations.

ABBREVIATIONS: ACPC = anterior/posterior commissure; CST = corticospinal tract; CTT = central tegmental tract; ML = medial lemniscus; MLF = medial longitudinal fasciculus; SUDC = sudden unexplained death of childhood

The human brain stem is phylogenetically the oldest brain region, serving critical integrative functions and linking the spinal cord, cerebellum, basal ganglia, limbic system, and neocortex. The brain stem consists of numerous small fiber tracts and nuclei that regulate sensory, motor, and autonomic functions.¹ Small

lesions due to diverse disorders (eg, multiple sclerosis,² neoplasm,³ infection,⁴ or neurodegeneration⁵) can cause devastating consequences due to the compact juxtaposition of vital structures. Furthermore, the brain stem also contains anatomic targets for functional neurosurgery.^{6,7} Conventional MR imaging does not provide adequate contrast or spatial resolution of many brain stem substructures to define their involvement in specific clinical cases or direct precise surgical targeting.

Because clinical 3T MR imaging cannot reliably discriminate many small brain stem structures, clinicians and researchers must infer brain stem anatomy relative to craniocaudal position, a few identifiable internal features, and surface topography. Susceptibility-weighted MR imaging⁸ demonstrates some additional in-

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ternal features that can improve indirect localization, but images from this sequence are also vulnerable to distortion from the skull base. Ultra-high-field in vivo MR imaging⁹⁻¹² and advanced diffusion methods¹³⁻¹⁵ also improve discrimination of more brain stem structures. Diffusion methods though are vulnerable to spatial distortions, require long acquisition times, and depend on modeling assumptions that are difficult to validate directly in human tissue.¹⁶⁻¹⁸ Ultra-high-field MR imaging is limited by increased geometric distortion and signal loss at the skull base and is only available at major academic centers with dedicated technical support staff.

MR imaging microscopy can help characterize dissected, isolated ex vivo human brain stem samples^{19,20} and can illustrate detailed anatomy for teaching and guiding image interpretation in living subjects. These acquisitions require long scan times (>12 hours) using small dedicated radiofrequency coils that cannot accommodate the whole brain and are limited to single or few specimens. Furthermore, image contrast may be altered relative to typical clinical MR imaging in living subjects by MR imaging water-relaxation changes associated with higher field strengths,²¹ the post-mortem interval,²² and formaldehyde fixation.²³⁻²⁵ We recently developed a rapid 3T postmortem anatomic MR imaging protocol²⁶ to screen postmortem whole brains in sudden unexplained death of childhood (SUDC).²⁷ This protocol washes the brain thoroughly, then uses optimized-but-conventional MR imaging sequences, a 3T MR imaging system, and a head coil available at most institutions. The optimized 2D TSE sequence, in particular, produces exquisite anatomic contrast for subcortical structures in all 3 planes, comparable with neuroanatomic atlases with histologic stains.²⁸⁻³¹ Here we demonstrate how the optimized TSE sequence can precisely delineate brain stem anatomy across multiple samples.

MATERIALS AND METHODS

Sample Procurement and Preparation

Whole-brain samples were obtained from an institutional review board (New York University)-approved and Health Insurance Portability and Accountability Act-compliant multisite research study, the SUDC Registry and Research Collaborative,³² which used ex vivo MR imaging screening before gross pathologic assessment, brain cutting, and histopathology for forensic investigation. For each subject, the postmortem brain was removed intact by the local medical examiner; then, it was immersion-fixed in a 4% formaldehyde solution for at least 21 days to reach near equilibrium with presumed fixative-induced nervous tissue T2 changes.²⁴ The brain was shipped to our institution and was then washed continuously in water for 48 hours to eliminate MR imaging relaxation changes from the free aldehyde fixative solution.²³ Individual brains with MR imaging data included for the figures and tables in this study ($n = 13$) met the following criteria: 1) transected at or below the pyramidal decussation; 2) no MR imaging or pathological abnormality (outside the hippocampus) identified by a board-certified neuroradiologist and neuropathologist respectively; 3) no T1-hyperintense fixation bands in the brain stem or diencephalon structures due to variable fixation penetration²⁵; and 4) a prerefrigeration postmortem interval of <24 hours.²²

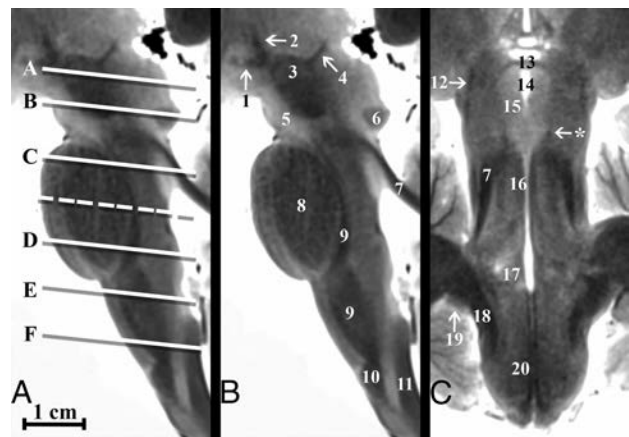


FIG 1. Parasagittal and coronal T2-weighted MR images of the post-mortem human brain stem. A, Canonical axial brain stem levels parallel to the anterior/posterior commissure plane that are found in Fig 2 are represented with the *solid lines* and On-line Fig 1 with the *dashed line*. Only selected brain stem substructures are labeled in coaligned sagittal and coronal images to orient the reader relative to the craniocaudal axial slice positions. The On-line Table provides a complete list of labeled anatomy for all figures, indicated by the numbers in parentheses in the legends. Note the trochlear nerve (asterisk, C) only seen in some brains.

Whole-Brain MR Imaging Protocol

Each brain was immersed under water within a custom 3D-printed container specifically designed to conform to a 64-channel head and neck coil on a 3T Magnetom Prisma MR imaging scanner (Siemens, Erlangen, Germany). Sealed water-filled disposable powderless latex medical gloves were gently wedged between the container and brain to prevent motion and to optimize the coil-filling factor. Scout sequences identified the brain position; then, 2D high-resolution TSE MR imaging sequences of the whole brain were obtained in coronal, sagittal, and axial planes relative to the anterior/posterior commissure (ACPC) plane. In selected cases, additional images were obtained in oblique planes to illustrate specific anatomic relationships within the brain stem. T2-weighted TSE sequence parameters were the following: TR = 5380 ms, TE = 53 ms, echo-train length = 7, echo spacing = 10.8 ms, bandwidth = 415 Hz/pixel, slice thickness = 0.8 mm, 116 slices (no interslice gap), in-plane resolution = 0.35×0.35 mm, concatenations = 2, averages = 10, total time = 2 hours (full protocol available on request). Optimization of sequence parameters for contrast resolution within the brain stem, diencephalic structures, and cerebral hemispheres using TSE sequences with 3T MR imaging is reported separately.²⁶

MR Imaging Data Anatomic Analysis

For each subject, we characterized brain stem detail at 7 canonical axial levels for anatomy and reproducibility parallel to the ACPC plane³³: rostral and caudal midbrain; rostral, middle, and caudal pons; and rostral and caudal medulla (Fig 1). The MR images were labeled with standard nomenclature.^{20,29,30} Only tracts and nuclei identified in all samples by consensus between 2 board-certified neuroradiologists are reported. We measured 4 major brain stem white matter tracts (the corticospinal tract [CST], medial lemniscus [ML], medial longitudinal fasciculus [MLF], and the central tegmental tract [CTT]) for shape and cross-sectional area in the

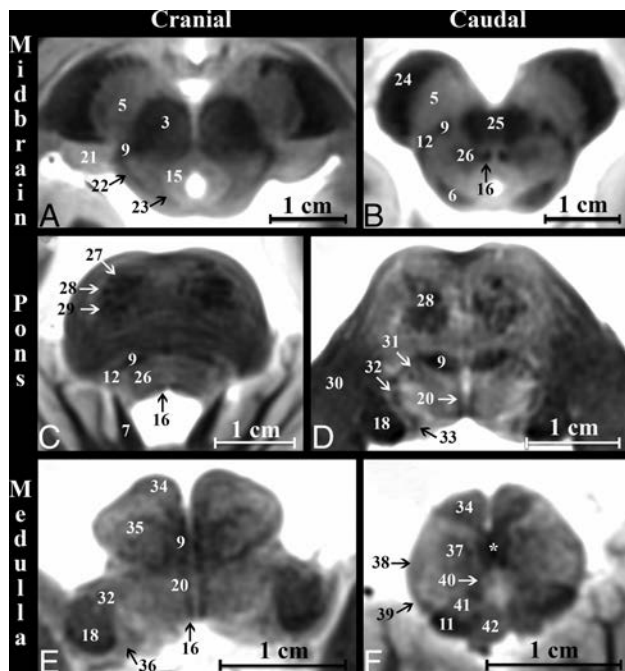


FIG 2. Axial modified T2-weighted TSE images at 6 canonical levels of the postmortem brain stem orientated parallel to the anterior/posterior commissure plane. *Upper row:* A, cranial midbrain; B, caudal midbrain. *Middle row:* C, cranial pons; D, caudal pons. *Lower row:* E, cranial medulla; F, caudal medulla. Improved image contrast from the modified TSE sequence directly demonstrates even small structures like the medial longitudinal fasciculus (16). Note the sensory decussation of the medial lemniscus in the caudal medulla (asterisk, F). The motor decussation is demonstrated in Fig 3.

axial plane at the caudal midbrain, middle pons, and cranial medulla levels. The area was derived from the formula for an ellipse in all structures and reproducibility was assessed by repeating measurements of the left and right CST in the cranial medulla and midpons on 3 separate days for 3 randomly selected brains. We compared the right and left CST cross-sectional areas for possible asymmetries using an unpaired 2-tailed *t* test. The craniocaudal extent of these pathways was measured; then, the 3D course of the tracts was precisely defined. The cranial limit of the CST was defined as its superiormost extent in the cerebral peduncle before joining the posterior limb of the internal capsule. The cranial extent of the ML was its fibers before entering the thalamus. The inferior limit of the CST and ML was the inferior margins of their respective medullary decussations. The visualized MLF and CTT remained within the brain stem. The inferior half of the dentato-rubrothalamic tract within the superior cerebellar peduncle also was analyzed at midbrain levels.

RESULTS

Axial images of the brain stem at 7 canonical anatomic levels are shown in Fig 2 and On-line Fig 1, with labeled substructures (see The On-line Table for the complete list of labeled substructures). While brain stem anatomy is typically shown in the axial plane, Fig 1 also demonstrates selected sagittal and coronal views with axial section positions on the sagittal image. On-line Fig 1 demonstrates the reproducibility of anatomic contrast for 4 selected brains at both the caudal midbrain and middle pons levels. Videos of the brain stem in 3 planes are provided in On-line Videos 1–3.

All numbered structures could be directly identified for each subject by both board-certified neuroradiologists. The mean postnatal age for the subjects included in this study was 32.1 ± 6.1 months.

We briefly describe the course, orientation, and shape of 5 major white matter pathways based on the 13 whole-brain specimens (all measurements are reported as mean $\pm$ SD). The numbers in parentheses refer to the numbers of the brain structures listed in the On-line Table. The corticospinal tract (28) (Fig 3) is the major motor pathway controlling the voluntary movements of the limbs and trunk. The CST at the midbrain level is 1.3 ± 0.1 cm lateral to the midsagittal plane and descends within the cerebral peduncle (24) from the posterior limb of the internal capsule at a $31^\circ \pm 7^\circ$ angle from superolateral to inferomedial in the coronal plane. The center of the tract is 0.6 ± 0.05 cm deep to the ventral surface and 0.4 ± 0.09 cm lateral to the midsagittal plane at the midpons, while maintaining a rounded shape before converging fibers descend to the medullary pyramids (34) at a less steep superolateral-to-inferomedial $14^\circ \pm 2^\circ$ angle. The pyramids form the ventral surface of the medulla and are 0.26 ± 0.04 cm lateral to the midsagittal plane. The CST descends at a $5^\circ \pm 2^\circ$ anterosuperior-to-inferoposterior angle relative to the long axis of the brain stem in the sagittal plane. CST signal intensity remains T2-hypointense even with tract dispersion in the pontine levels (Fig 2).

After the internal arcuate fibers (37) decussate, the medial lemniscus (9) (Fig 4) is in the central paramedian medulla with an elongated ovoid shape and its long axis oriented anterior to posterior on axial images. The ML is a sensory pathway conveying fine touch, vibration, and proprioception of the skin and joints. As the ML ascends, its long axis rotates at $56^\circ \pm 11^\circ$, $80^\circ \pm 9^\circ$, $115^\circ \pm 13^\circ$, and $130^\circ \pm 4^\circ$ angles relative to the midsagittal plane at the caudal pons, middle pons, cranial pons, and caudal midbrain levels, respectively. The tract is located 0.3 ± 0.05 cm and 0.8 ± 0.06 cm lateral to the midsagittal plane at the pons and midbrain levels, respectively. In the sagittal plane, the ML ascends at a $4^\circ \pm 1^\circ$ antero-inferior-to-posterosuperior angle relative to the long axis of the brain stem at the medulla but pivots posteriorly $18^\circ \pm 5^\circ$ at the pontomedullary junction and pivots again posteriorly $17^\circ \pm 3^\circ$ at the midbrain. The ML maintains uniform signal intensity until the fibers become less distinct just before terminating in the ventral posterolateral thalamic nucleus (50).

The medial longitudinal fasciculus (16) (Fig 5) is a small tear drop-shaped tract just deep to the rhomboid fossa, 0.05 ± 0.01 cm lateral to the midsagittal plane. The MLF coordinates connections among the oculomotor, trochlear, and abducens nuclei for control of conjugate eye movements. The tract ascends at a $5^\circ \pm 2^\circ$ angle posteroinferior to anterosuperior relative to the long axis of the brain stem on sagittal images in the medullary and pontine levels. At the midbrain, the tract takes a $20^\circ \pm 6^\circ$ ventral turn to terminate along the walls of the inferior third ventricle (58). At its cranial termination, the MLF signal becomes less conspicuous. On axial midbrain slices, the MLF is 0.16 ± 0.02 cm lateral to the midsagittal plane with the long axis oriented at $137^\circ \pm 7^\circ$ antero-medial to posterolateral.

Fibers descending from the red nucleus (3) to the ipsilateral inferior medullary olive (35) are within the central tegmental tract (26) (On-line Fig 2), located 0.3 ± 0.04 cm lateral to the midsag-

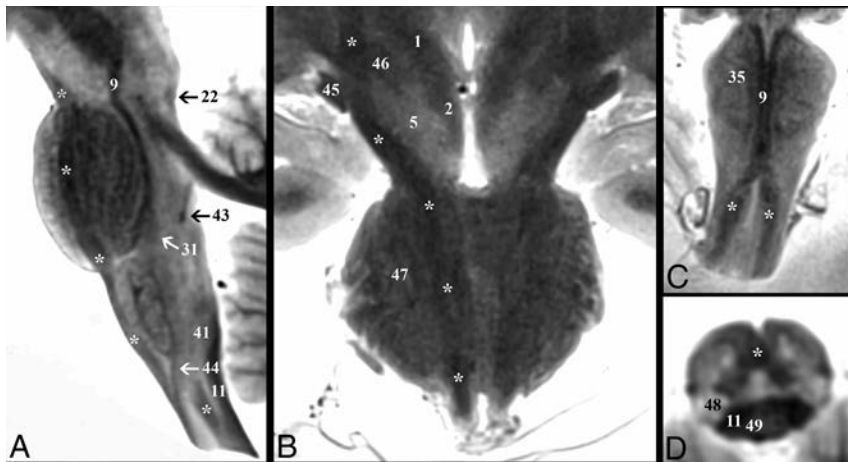


FIG 3. Demonstration of the corticospinal tract (*asterisk*) throughout the brain stem. *A*, Parasagittal image depicts the corticospinal tract descending within the brain stem from the cerebral peduncle to the upper cervical cord. *B*, Coronal image shows the course of the corticospinal tract from the posterior limb of the internal capsule to the most superior aspect of the medullary pyramids. Note in the diencephalic junction, the close relationship of the corticospinal tract to the optic tract (45) laterally and the subthalamic nucleus (46) medially. Oblique coronal (*C*) and oblique axial (*D*) images highlight the decussation of the corticospinal tracts at the cervicomedullary junction. *C*, The *paramedian dark lines* are the medial lemniscus (9), which is superficial to the corticospinal tract on this oblique axial image.

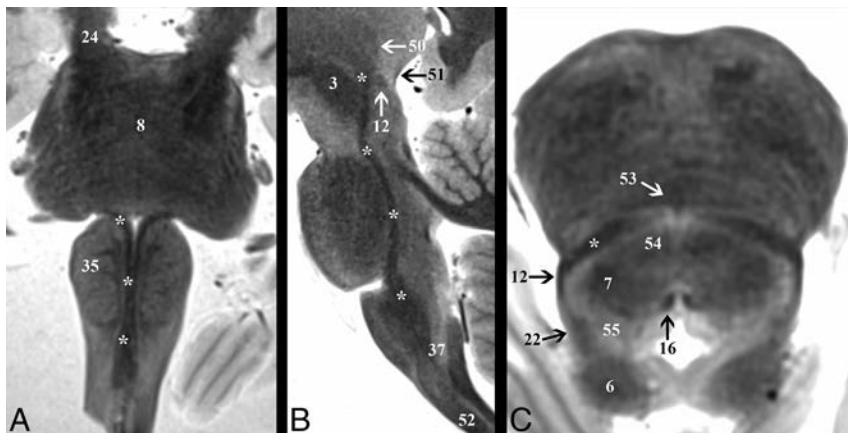


FIG 4. Demonstration of the medial lemniscus (*asterisk*) throughout the brain stem. *A*, Coronal image shows the change in the long-axis orientation of the medial lemniscus from anteroposterior to transverse as it ascends the medulla to the pontomedullary junction. *B*, Parasagittal image highlights the terminations of the medial lemniscus in the ventral posterolateral thalamic nucleus (50). *C*, Axial image angled anteroinferior to posterosuperior 20° relative to the ACPC plane through the inferior colliculus (6) shows the relationship of the medial lemniscus to the spinothalamic tract (12) and lateral lemniscus (22) at the lateral tegmentum.

ittal plane. The tract is round and maintains a less distinct hypointense signal compared with the other major tracts described here. The CTT courses inferiorly and parallel to the long axis of the brain stem in the sagittal plane until a $10^\circ \pm 2^\circ$ anterior bend to meet the inferior olive. The CTT contains ascending taste fibers from the solitary nucleus, whereas the descending fibers are part of a feedback circuit (dentatorubro-olivary) responsible for modulating motor activity.

The inferior half of the dentatorubrothalamic tract (On-line Fig 3) ascends to the superior cerebellar peduncle (7) at a $27^\circ \pm 3^\circ$ inferoposterior to the anterosuperior angle in the sagittal plane. On axial images, the superior cerebellar peduncle has a parabolic configuration with an inner concave angle of $114^\circ \pm 8^\circ$. The apex is 0.6 ± 0.07 cm lateral to the midsagittal plane. The fibers become

less distinct just before entering the superior cerebellar decussation (25) but then have very T2-hypointense signal in the decussation. The center point of the superior cerebellar decussation is 1.5 ± 0.1 cm inferior to the ACPC plane and 0.3 ± 0.06 cm deep to the interpeduncular fossa surface. The dentatorubrothalamic tract acts to coordinate the initiation, planning, and timing of movement.

The Table provides measurements of 5 major craniocaudally oriented white matter tracts at selected axial levels of the brain stem for all 13 brains. The MLF (16) was the smallest tract in the cross-sectional area at the midbrain, pons, and medulla levels (eg, transverse dimension, <0.8 mm). The long axis of the ML in the axial plane rotates as the tract ascends (9), but the ML showed the least variation in the cross-sectional area within the 3 levels. The CST (28) had the largest cross-sectional area and was largest in the midpons where the fibers intermix with the pontocerebellar fibers (47). The mean transaxial cross-sectional area of the left CST was 20% larger than the right CST in the medulla (1.5-mm^2 difference, $P = .099$) and pons (5.7-mm^2 difference, $P = .063$). The left and right CST cross-sectional areas were measured for 3 brains at 4 separate sessions at the same cranial medulla and midpons levels to assess repeatability; within-subject SDs were 0.8 and 1.6 mm^2 , respectively. There were no additional observable left-right asymmetries in the other measured major white matter tracts.

Major brain stem nuclei were also consistently identified directly (On-line Fig 4). At the cranial midbrain level, the red nucleus (3), substantia nigra (5), and superior colliculus (62) were seen. The oculomotor nucleus (60) was best visualized with an oblique axial plane tipped 20° superiorly anterosuperior to posteroinferior relative to the ACPC plane (Fig 5), but the Edinger-Westphal nucleus was not identified. The trochlear nucleus could not be discriminated from the medial longitudinal fasciculus (16) in the caudal midbrain, but its fascicles were identifiable for some brains in the coronal plane (Fig 1). The mesencephalic trigeminal nucleus (23) was seen with an oblique axial image angled 10° superiorly anterosuperior to posteroinferior relative to the ACPC plane (On-line Fig 2). The interpeduncular nucleus (53) was most clearly identified on an oblique axial image 20° superior relative to the ACPC plane through the level of the inferior colliculi (6) (Fig 4). At the cranial pons, the locus coeruleus was not identified in any subject.

The midpons contains the spinal sensory (48) and motor nuclei (66) of the trigeminal nerve. The trigeminal motor nucleus was best seen at the cranial-midpons level junction just medial to the superior cerebellar peduncles (7). The trigeminal sensory spinal nucleus was not reliably seen in the pons in all brains but could be identified at the cervicomedullary junction (Fig 3). The facial nucleus was not seen, but its fascicles (67) were identified in the midpons within the respective genu and colliculus bordering the abducens nucleus (17). The superior olivary complex (31) was identified at the lower pons level, posterolateral to the medial lemniscus (9) (Fig 2). Within the medulla, the inferior olivary nucleus (35) was clearly seen, but the dorsal and medial accessory olivary nuclei and ambiguous nucleus were not. Cochlear (19) and vestibular (36) nuclear group positions were seen along the lateral and dorsal medullary surface, but their subnuclei could not be discerned. The dorsal motor nucleus of the vagus (57) and the hypoglossal nucleus (40) could be identified on axial images and

further directly distinguished on a parasagittal image at the level of the medial longitudinal fasciculus (Fig 5). The cuneate (41) and gracile (42) nuclei in the caudal dorsal medulla were identified giving rise to the internal arcuate fibers (37).

DISCUSSION

This modified TSE sequence provided detailed images of brain stem anatomy using whole postmortem brains and a widely available clinical 3T MR imaging system. Previous studies have used ultra-high-field MR imaging, dissected and isolated brain stem samples, specialized radiofrequency coils, and/or relatively long acquisition times.³⁴⁻³⁶ Anatomic image contrast was generated directly from the MR imaging sequence without mathematically complex, off-line, model-based reconstructions as required for relaxation-mapping^{9,37} or advanced diffusion-based contrasts.^{15,38} Such techniques have been difficult to validate.¹⁸ This postmortem MR imaging protocol directly visualizes many small brain stem structures such as the MLF (<1 mm in transverse dimension) that are beyond the spatial resolution or detection limits of current state-of-the-art diffusion-weighted imaging techniques.^{9,15} Furthermore, direction-encoded color images of diffusion anisotropy cannot discriminate adjacent structures with parallel craniocaudal orientations (eg, vertical columns within the midbrain; Fig 5B). Conversely, T2-weighted contrast reported here cannot discriminate all brain stem structures identified with histology such as distinguishing the dentatorubrothalamic projections from the red nucleus they envelope (On-line Fig 3C). T2-weighted contrast detects but cannot resolve the individual crossing or interdigitating fiber bundles of the sensory, motor, or superior cerebellar peduncle decussations (Figs 2F, 3D, and On-line Fig 3B, respectively). Future work will evaluate potential synergies for brain stem structure resolution when this TSE contrast is combined with diffusion, susceptibility, and other MR imaging contrasts at 3T (or ultra-high-field MR imaging). This optimized TSE sequence also produces exquisite contrast resolution of subthalamic, thalamic, and basal ganglia structures that will be described in a separate companion report.

For clinicians, it is challenging to learn and retain brain stem anatomy because internal structures are only discriminated on stained histology slides, unlike imaging performed in clinical practice. We must mentally juxtapose structures discriminated by specific histology stains onto MR images on the basis of mostly the craniocaudal position and brain stem surface features. Here, knowledge and mental maps of brain stem neuroanatomy may be facilitated because this postmortem protocol provides anatomic discrimination of brain stem structures comparable with histology atlases,²⁸⁻³¹ yet it is derived from a commonly used clinical

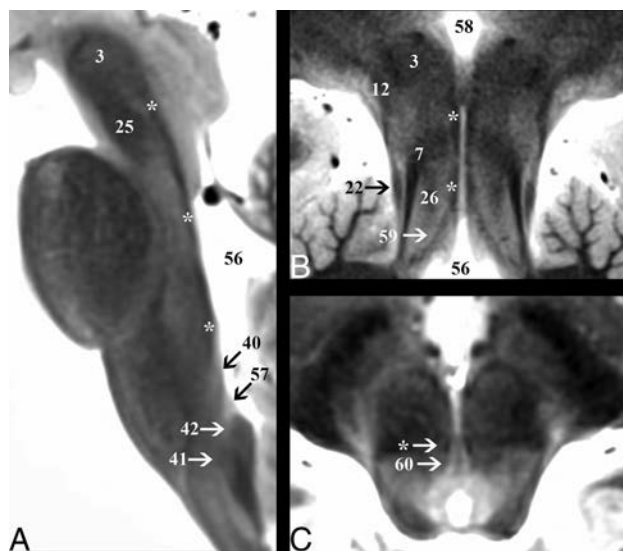


FIG 5. Demonstration of the medial longitudinal fasciculus (asterisk) throughout the brain stem. A, Sagittal image depicts the dorsal course of the medial longitudinal fasciculus from its origin in the cranial medulla just superior to the hypoglossal nucleus (40) to the level of the red nucleus (3). B, Coronal oblique image that is perpendicular to the long axis of the hippocampus (structure not shown) at the level of the posterior commissure shows the terminations of the tract in the inferior walls of the third ventricle (58). This coronal image also highlights vertical columns of the central midbrain from lateral to medial: lateral lemniscus (22), superior cerebellar peduncle (7), central tegmental tract (26), and medial longitudinal fasciculus (asterisk). C, Axial cranial midbrain image angled anterosuperior to posteroinferior 20° relative to the ACPC plane highlights the close relationship of the medial longitudinal fasciculus to the oculomotor nucleus (60).

Selected measurements for 5 major brain stem white matter tracts at 3 canonical axial planes^a

Tract	Fig	Cranial Medulla				Mid Pons			Caudal Midbrain		
		CC	AP	TV	Area	AP	TV	Area	AP	TV	Area
CST (L)	3	51.7 ± 4.8	2.9 ± 0.6	3.7 ± 0.5	8.8 ± 2.6 ^b	6.6 ± 1.0	6.5 ± 0.7	33.9 ± 6.8 ^b	6.1 ± 0.6	3.5 ± 0.5	17.1 ± 3.0 ^b
CST (R)	3	51.7 ± 4.8	2.7 ± 0.3	3.3 ± 0.4	7.3 ± 1.4 ^b	5.7 ± 0.9	6.2 ± 0.8	28.2 ± 8.1 ^b	6.1 ± 0.8	3.2 ± 0.8	15.5 ± 5.2 ^b
ML	4	46.9 ± 3.5	5.6 ± 0.8	0.6 ± 0.1	2.9 ± 0.6	1.2 ± 0.4	4.6 ± 0.7	4.7 ± 1.9	2.0 ± 0.4	3.0 ± 0.4	4.9 ± 1.4
MLF	5	39.6 ± 3.4	1.0 ± 0.3	0.5 ± .06	0.5 ± 0.2	1.4 ± 0.3	0.8 ± 0.1	0.9 ± 0.2	3.2 ± 0.4	0.7 ± 0.1	1.9 ± 0.5
CTT	6	37.7 ± 4.0	2.6 ± 0.4	1.6 ± 0.3	3.4 ± 0.8	1.7 ± 0.2	2.1 ± 0.4	2.9 ± 0.8	3.2 ± 0.3	3.6 ± 0.4	9.1 ± 1.5

Note:—CC indicates craniocaudal; AP, anteroposterior; TV, transverse; Fig, figure; L, left; R, right.

^a Units are millimeters or square millimeters, and data are mean ± SD, with 13 SUDC samples.

^b All measurements of the right and left corticospinal tracts were compared separately. Cross-sectional areas trended toward small statistical differences in the medulla ($P = .099$) and pons ($P = .063$), but not the midbrain ($P = .361$).

MR imaging sequence and contrast mechanism (albeit with higher spatial resolution). MR imaging data facilitate the creation of user-controllable videos to evaluate the orientation and evolution of specific pathways throughout the brain stem (On-line Videos 1–3). Furthermore, multiplanar images or series can illustrate specific brain stem tracts or key anatomic relationships in novel ways—that is, the oblique coronal plane perpendicular to the long axis of the hippocampus, just deep to the rhomboid fossa, illustrates functional cell columns of cranial nuclei V, VI, VII, VIII, X, and XII (On-line Fig 4). It would be technically challenging and resource- and time-intensive to obtain such images from histologic sections of individual human brain stem samples; hence, previous histologic or MR imaging–based brain stem images emphasized idealized axial views.^{19,20,33} The postmortem MR imaging protocol can be applied quickly and inexpensively across many samples without tissue consumption. This feature should enhance the experiential component of learning by exposing trainees to more individual variations in brain stem anatomy (On-line Fig 1).

The ability to directly visualize specific brain stem structures in multiple individual brains also facilitates creation of normative coordinates for structures in specific fiducial planes and surfaces that can be used in clinical studies. For example, our data from SUDC brains predict that a lesion in the midbrain tegmentum, 0.1, 0.3, or 0.8 cm lateral to the midsagittal plane, would involve the MLF, CTT, or ML, respectively. We estimated the size and cross-sectional areas of several major brain stem tracts (Table). We observed a trend ($P < .10$) toward ~20% larger cross-sectional areas for the left corticospinal tract in the pons and medulla (Table). While handedness is less established in young children,³⁹ functional asymmetries in brain stem structures may alter the numbers of axons, degree of myelination, and/or myelin compaction that could affect TSE MR imaging contrast. These asymmetries may change during childhood. The potential corticospinal tract asymmetries and brain stem pathway coordinates and sizes will require further future investigation in adult brains without neurologic disease and documented handedness. Future work could also produce a group-based brain atlas and/or a normative data base of brain stem structures across different ages and sex. These data could assess changes to brain stem structure with aging or subcortical dementias^{40–43} or could be used as a structural template for extracting other forms of quantitative MR imaging data in postmortem investigations.

The use of pediatric brains from an SUDC study is a limitation for the measurements reported in this study. Deformity or relaxation of the posterior fossa structures from procurement, agonal hydration status, or brain changes associated with formaldehyde fixation also may affect the external validity of these results. While repeatability measures of the cross-sectional area in this preliminary study were lower than the differences observed among tracts or between the right and left CST, manual measurements are prone to error from image noise, slice orientation, and rater biases. Measurements in the sagittal plane may also be confounded by variable posterior angulation of the lower brain stem created during specimen procurement. Assignments of brain stem structures were made by consensus between 2 board-certified neuroradiologists using standard reference texts based on histologic

staining^{28–31}; inter- or intraobserver variability for structure identification was not assessed. TSE signal intensity correlated inversely with myelin staining in the histology of different brain samples; however, the biophysical basis for gradations of T2-weighted signal variation in the brain stem will require further investigation. Histology sampling and specific stains were restricted to the SUDC forensic investigation. MR imaging relaxation parameters of these ex vivo brains differ from those in vivo due to the postmortem interval,²² formaldehyde fixation and tissue penetration,^{23–25} incomplete myelination,^{44,45} or subtle unrecognized SUDC pathology.⁴⁶ Preliminary experiments suggested that true 3D T2-weighted MR imaging acquisitions⁴⁷ did not produce such exquisite contrast resolution of the brain stem, but this will be the subject of future investigation.

CONCLUSIONS

An optimized TSE T2 sequence applied to washed postmortem brain samples revealed exquisite and reproducible brain stem anatomic MR imaging contrast comparable with histologic atlases. The current results suggest that intrinsic nervous tissue T2 differences could potentially generate sufficient contrast to also identify brain stem structures in vivo. It will be challenging to feasibly adapt this MR imaging protocol to living subjects, yet this would greatly enhance its applicability to neuroanatomy training, clinical practice, and future research.

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REFERENCES

1. Carpenter MB, Strong OS, Truex RC. *Human Neuroanatomy: (Formerly Strong and Elwyn's Human Neuroanatomy)*. 7th ed. Baltimore: Lippincott Williams & Wilkins; 1976
2. Tintore M, Rovira A, Arrambide G, et al. **Brainstem lesions in clinically isolated syndromes.** *Neurology* 2010;75:1933–38 [CrossRef Medline](#)
3. Donaldson SS, Laningham F, Fisher PG. **Advances toward an understanding of brainstem gliomas.** *J Clin Oncol* 2006;24:1266–72 [CrossRef Medline](#)
4. Tan IL, Mowry EM, Steele SU, et al. **Brainstem encephalitis: etiolo-**

- gies, treatment, and predictors of outcome. *J Neurol* 2013;260:2312–19 CrossRef Medline
5. Grinberg LT, Rueb U, Heinsen H. **Brainstem: neglected locus in neurodegenerative diseases.** *Front Neurol* 2011;2:42 CrossRef Medline
 6. Mazzone P, Vilela Filho O, Viselli F, et al. **Our first decade of experience in deep brain stimulation of the brainstem: elucidating the mechanism of action of stimulation of the ventrolateral pontine tegmentum.** *J Neural Transm (Vienna)* 2016;123:751–67 CrossRef Medline
 7. Golfinos JG, Roland JT Jr, Rodgers SD. **Auditory brainstem implants.** *J Neurosurg* 2014;120:543–44 CrossRef Medline
 8. Manova ES, Habib CA, Boikov AS, et al. **Characterizing the mesencephalon using susceptibility-weighted imaging.** *AJNR Am J Neuroradiol* 2009;30:569–74 CrossRef Medline
 9. Deistung A, Schäfer A, Schweser F, et al. **High resolution MR imaging of the human brainstem in vivo at 7 Tesla.** *Front Hum Neurosci* 2013;7:710 CrossRef Medline
 10. Gizewski ER, Maderwald S, Linn J, et al. **High-resolution anatomy of the human brain stem using 7-T MRI: improved detection of inner structures and nerves?** *Neuroradiology* 2014;56:177–86 CrossRef Medline
 11. Cho ZH, Calamante F, Chi JG, eds. *7.0 Tesla MRI Brain White Matter Atlas*. 2nd ed. Heidelberg: Springer-Verlag; 2015
 12. Eapen M, Zald DH, Gatenby JC, et al. **Using high-resolution MR imaging at 7T to evaluate the anatomy of the midbrain dopaminergic system.** *AJNR Am J Neuroradiol* 2011;32:688–94 CrossRef Medline
 13. Calamante F, Tournier JD, Jackson GD, et al. **Track density imaging (TDI): super-resolution white matter imaging using whole-brain track density mapping.** *Neuroimage* 2010;53:1233–43 CrossRef Medline
 14. Naganawa S, Yamazaki M, Kawai H, et al. **Anatomical details of the brainstem and cranial nerves visualized by high resolution readout-segmented multi-shot echo-planar diffusion-weighted images using unidirectional MPG at 3 T.** *Magnetic Resonance in Medical Sciences* 2011;10:269–75 CrossRef
 15. Hoch MJ, Chung S, Ben-Eliezer N, et al. **New clinically feasible 3T MRI protocol to discriminate internal brain stem anatomy.** *AJNR Am J Neuroradiol* 2016;37:1058–65 CrossRef Medline
 16. Jones DK, Knösche TR, Turner R. **White matter integrity, fiber count, and other fallacies: the do's and don'ts of diffusion MRI.** *Neuroimage* 2013;73:239–54 CrossRef Medline
 17. Jones DK, Cercignani M. **Twenty-five pitfalls in the analysis of diffusion MRI data.** *NMR Biomed* 2010;23:803–20 CrossRef Medline
 18. Maier-Hein KH, Neher PF, Houde J, et al. **The challenge of mapping the human connectome based on diffusion tractography.** *Nature Comm* 2017;8:1349 CrossRef Medline
 19. Soria G, De Notaris M, Tudela R, et al. **Improved assessment of ex vivo brainstem neuroanatomy with high-resolution MRI and DTI at 7 Tesla.** *Anat Rec (Hoboken)* 2011;294:1035–44 CrossRef Medline
 20. Naidich TP, Duvernoy HM, Delman BN, et al. *Duvernoy's Atlas of the Human Brain Stem and Cerebellum*. New York: Springer-Verlag/Wien; 2009
 21. de Graaf RA, Brown PB, McIntyre S, et al. **High magnetic field water and metabolite proton T1 and T2 relaxation in rat brain in vivo.** *Magn Reson Med* 2006;56:386–94 CrossRef Medline
 22. Shepherd TM, Flint JJ, Thelwall PE, et al. **Postmortem interval alters the water relaxation and diffusion properties of rat nervous tissue: implications for MRI studies of human autopsy samples.** *Neuroimage* 2009;44:820–26 CrossRef Medline
 23. Shepherd TM, Thelwall PE, Stanisz GJ, et al. **Aldehyde fixative solutions alter the water relaxation and diffusion properties of nervous tissue.** *Magn Reson Med* 2009;62:26–34 CrossRef Medline
 24. Dawe RJ, Bennett DA, Schneider JA, et al. **Postmortem MRI of human brain hemispheres: T2 relaxation times during formaldehyde fixation.** *Magn Reson Med* 2009;61:810–18 CrossRef Medline
 25. Yong-Hing CJ, Obenaus A, Stryker R, et al. **Magnetic resonance imaging and mathematical modeling of progressive formalin fixation of the human brain.** *Magn Reson Med* 2005;54:324–32 CrossRef Medline
 26. Miller S, Goldberg J, Bruno M, et al. **Intrinsic T2-weighted MRI contrast of the subcortical human brain.** In: *Proceedings of the Scientific Assembly and National Meeting of the Radiological Society of North America*, Chicago, Illinois. November 26 to December 1, 2017; Abstract ID: 27997
 27. Hesdorffer DC, Crandall LA, Friedman D, et al. **Sudden unexplained death in childhood: a comparison of cases with and without a febrile seizure history.** *Epilepsia* 2015;56:1294–300 CrossRef Medline
 28. Haines DE. *Neuroanatomy: An Atlas of Structures, Sections and Systems*. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2004
 29. Warner JJ. *Atlas of Neuroanatomy: With Systems Organization and Case Correlations*. Boston: Butterworth-Heinemann; 2001
 30. DeArmond SJ, Fusco MM, Dewey MM. *Structure of the Human Brain: A Photographic Atlas*. 3rd ed. New York: Oxford University Press; 1989
 31. Olszewski J, Baxter D. *Cytoarchitecture of the Human Brain Stem*. 2nd ed. Basel: Karger; 1982
 32. Crandall LA, Devinsky O. **Sudden unexplained death in children.** *Lancet Child Adolesc Health* 2017;1:8–9 CrossRef Medline
 33. Hirsch WL, Kemp SS, Martinez AJ, et al. **Anatomy of the brainstem: correlation of in vitro MR images with histologic sections.** *AJNR Am J Neuroradiol* 1989;10:923–28 Medline
 34. Miller KL, Stagg CJ, Douaud G, et al. **Diffusion imaging of whole, post-mortem human brains on a clinical MRI scanner.** *Neuroimage* 2011;57:167–81 CrossRef Medline
 35. Gallay MN, Jeanmonod D, Liu J, et al. **Human pallidothalamic and cerebellothalamic tracts: anatomical basis for functional stereotactic neurosurgery.** *Brain Struct Funct* 2008;212:443–63 CrossRef Medline
 36. Morel A, Magnin M, Jeanmonod D. **Multiarchitectonic and stereotactic atlas of the human thalamus.** *J Comp Neurol* 1997;387:588–630 CrossRef Medline
 37. Lambert C, Chowdhury R, Fitzgerald TH, et al. **Characterizing aging in the human brainstem using quantitative multimodal MRI analysis.** *Front Hum Neurosci* 2013;7:462 CrossRef Medline
 38. Tang Y, Sun W, Toga AW, et al. **A probabilistic atlas of human brainstem pathways based on connectome imaging data.** *Neuroimage* 2018;169:227–39 CrossRef Medline
 39. Scharoun SM, Bryden PJ. **Hand preference, performance abilities, and hand selection in children.** *Front Psychol* 2014;5:82 CrossRef Medline
 40. Urban PP, Caplan LR, eds. *Brainstem Disorders*. Berlin: Springer-Verlag; 2011
 41. Janzen J, van't Ent D, Lemstra AW. **The pedunculopontine nucleus is related to visual hallucinations in Parkinson's disease: preliminary results of a voxel-based morphometry study.** *J Neurol* 2012;259:147–54 CrossRef Medline
 42. Rolland Y, Vérin M, Payan CA, et al; NNIPPS Study Group. **A new MRI rating scale for progressive supranuclear palsy and multiple system atrophy: validity and reliability.** *J Neurol Neurosurg Psychiatry* 2011;82:1025–32 CrossRef Medline
 43. Makino T, Ito S, Kuwabara S. **Involvement of pontine transverse and longitudinal fibers in multiple system atrophy: a tractography-based study.** *J Neurol Sci* 2011;303:61–66 CrossRef Medline
 44. Gay CT, Hardies LJ, Rauch RA, et al. **Magnetic resonance imaging demonstrates incomplete myelination in 18q- syndrome: evidence for myelin basic protein haploinsufficiency.** *Am J Med Genet* 1997;74:422–31 CrossRef Medline
 45. Baierl P, Förster Ch, Fendel H, et al. **Magnetic resonance imaging of normal and pathological white matter maturation.** *Pediatr Radiol* 1988;18:183–89 CrossRef Medline
 46. Krous HF, Chadwick AE, Crandall LA, et al. **Sudden unexpected death in childhood: a report of 50 cases.** *Pediatr Dev Pathol* 2005;8:307–19 CrossRef Medline
 47. Mugler JP 3rd. **Optimized three-dimensional fast-spin-echo MRI.** *J Magn Reson Imaging* 2014;39:745–67 CrossRef Medline

Dynamic Contrast-Enhanced MRI Reveals Unique Blood-Brain Barrier Permeability Characteristics in the Hippocampus in the Normal Brain

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ABSTRACT

SUMMARY: We report a prospective dynamic contrast-enhanced MR imaging analysis of region-specific blood-brain barrier permeability in 5 healthy subjects. By means of standardized postprocessing and ROI sampling methods, the hippocampi revealed significantly elevated area under the dynamic contrast-enhanced curve and significantly increased blood-brain barrier permeability metrics (volume transfer constant and volume in the extravascular extracellular space) from model-based quantitation. These findings suggest unique blood-brain barrier permeability characteristics in the hippocampus, which are concordant with previous animal studies, potentially laying the groundwork for future studies assessing patient populations in which hippocampal pathology plays a role.

ABBREVIATIONS: BBBP = blood-brain barrier permeability; DCE = dynamic contrast-enhanced; K^{trans} = volume transfer constant; SLE = systemic lupus erythematosus; VE = volume in the extravascular extracellular space

The utility of in vivo BBB permeability (BBBP) assessment using dynamic contrast-enhanced MR imaging has been demonstrated in a wide range of diseases, including cerebrovascular ischemia and Alzheimer disease. The extended Tofts algorithm describes a well-perfused 2-compartment model, allowing bidirectional transport of contrast between the intravascular space and extravascular extracellular space and quantitative assessment of BBBP parameters, including volume transfer constant (K^{trans}) or intravascular space-to-extravascular extracellular space flux per tissue volume, and volume in the extravascular extracellular space (VE).

In humans, region-specific BBBP data are limited and heterogeneous, given region-specific differences in microvascular architecture and in BBB-related protein expression profiles.^{1,2} The hippocampus exhibits unique anatomic and physiologic proper-

ties³ and unique perfusion characteristics with dual arterial blood supply from the anterior and posterior circulation.⁴ Recent human studies in systemic lupus erythematosus correlated cognitive decline with region-specific abnormal findings in the hippocampus with FDG-PET.⁵ Additionally, animal studies have revealed increased protein expression of CD36, matrix metalloproteinase-13, and osteopontin correlated with increased hippocampal BBBP,⁶ and dynamic contrast-enhanced (DCE)-MR imaging–derived baseline contrast enhancement curves were highest in the hippocampi in control subjects.⁷ The purpose of our study was to evaluate region-specific BBBP metrics in healthy human subjects.

MATERIALS AND METHODS

Subject Cohort

In this prospective institutional review board (Department of Radiology, Northwell Health)–approved study, 6 subjects underwent DCE-MR imaging and clinical and neuropsychological evaluations under an ongoing National Institutes of Health/National Institute of Allergy and Infectious Diseases protocol, 1P01A1073693. Exclusion criteria were active or prior neuropsychiatric symptoms; use of antidepressant, antipsychotic, or anxiolytic drugs; or a history of excessive alcohol or illicit drug use.

Data Acquisition

All subjects underwent DCE-MR imaging on a 3T magnet (Siemens Prisma, Erlangen, Germany). MR imaging sequences included 3D-T1WI (0.9 × 0.9 × 0.9 mm resolution, 256 × 256 × 240 matrix size, and 0.9-mm slice thickness), axial T2WI, FLAIR, and susceptibility- and diffusion-weighted imaging according to standard departmental

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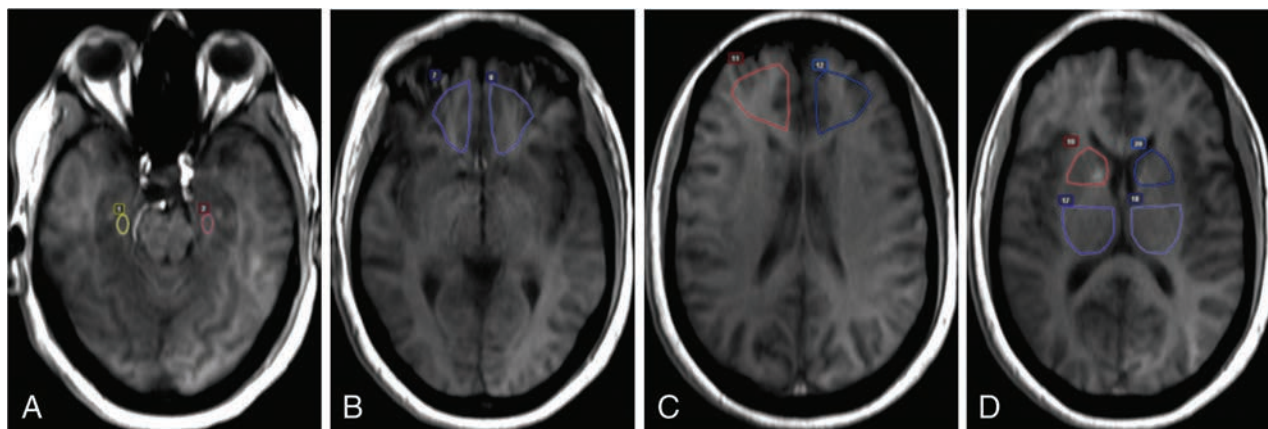


FIG 1. Illustration of ROI placement in a representative subject. ROIs were placed onto coregistered axial T1-weighted images in the following regions: hippocampus (A), orbitofrontal (B), prefrontal (C), and anterior putamen/caudate and posterior putamen/thalamus (D). Mirror ROIs were placed for bilateral sampling. Region-specific DCE curves were generated.

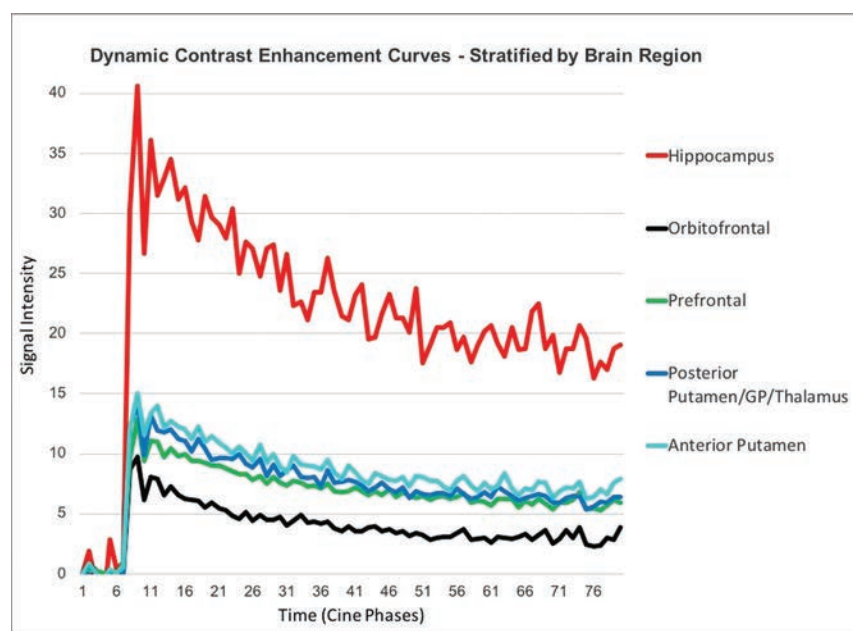


FIG 2. DCE curves in healthy control subjects, stratified by brain region. The hippocampi demonstrate statistically significantly higher areas under the curve compared with all other regions, indicating higher BBB permeability under normal conditions.

protocols. Whole-brain permeability imaging was performed using a DCE technique with 22-slice axial 3D spoiled gradient-recalled T1WI sequences at $0.5 \times 0.5 \times 5$ mm resolution and 80 cine phases using $TR = 25$ ms, $TE = 3.8$ ms, $FOV = 24$ mm.

Data Analysis

Postprocessing into K^{trans} (mL/100 g/min), VE (mL/100 g), and CBF (mL/100 g/min) parametric maps was performed using Olea Sphere (Olea Medical, La Ciotat, France) with the Tofts extended-permeability model by trained research personnel. The postprocessing technique was standardized with the arterial input function placed at the center of the cavernous internal carotid artery.

A standardized method was used for selective ROI placement by trained research personnel directly supervised by a board-certified neuroradiologist (with 19 years of experience). ROIs were placed onto coregistered axial T1-weighted images sampling the hippocam-

pus, orbitofrontal and prefrontal regions, anterior putamen/caudate (including the globus pallidus and anterior limb of the internal capsule), and posterior putamen/thalamus (including the globus pallidus and posterior limb of the internal capsule) (Fig 1), and meticulous care was taken not to include vascular structures, the choroid plexus, ventricles, CSF, and skull. ROIs with CBF values of >100 mL/100 g/min were excluded from the statistical analysis to minimize contributions from vascular structures.⁸ Mirror ROIs were placed, and region-specific DCE curves were generated. The average size of the ROIs sampling each brain region was the following: hippocampus, 45 mm²; orbitofrontal, 454 mm²; prefrontal, 654 mm²; anterior putamen/caudate, 280 mm²; and posterior putamen/thalamus, 530 mm².

Statistical Analysis

For statistical analysis, region-specific K^{trans} , VE, and CBF means and SDs were computed. ANOVA was performed to

determine statistical differences. The mean DCE curves for each brain region were generated. The area under the curve was computed in reference to the baseline before contrast arrival. The mean area under the curve was compared among brain regions using pair-wise *t* test statistics. *P* values $<.05$ were considered statistically significant.

RESULTS

Five subjects were included in the statistical analysis, with a total of 50 region-specific ROIs. One subject was excluded from statistical analysis due to motion degradation precluding postprocessing. The average age was 34.2 ± 10.5 years. All neuropsychological screening scores were within the normal range.

When we compared the generated mean DCE curves for each brain region across all subjects, the hippocampus demonstrated increased BBBP compared with all other regions (Fig 2). The mul-

tiple pair-wise *t* test comparisons revealed statistically significant higher areas under the curve for the hippocampus compared with the orbitofrontal ($P < .001$) and prefrontal ($P < .001$) regions, anterior putamen/caudate ($P < .002$), and posterior putamen/thalamus ($P < .001$). This pattern was also observed across the individual subject data and was maintained even when brain regions were separated by right and left sides.

The model-based quantitative data in the hippocampus region yielded a mean K^{trans} of 0.019 ± 0.049 and a mean VE of 0.008 ± 0.016 , respectively. In contrast, the other sampled brain regions demonstrated a mean K^{trans} of 0 ± 0 and mean VE of 0 ± 0 for both K^{trans} and VE. ANOVA revealed a significantly increased BBBP in the hippocampal region compared with all other brain regions ($P = .03$). Additionally, the hippocampi demonstrated the highest variability in quantitative data.

DISCUSSION

The BBB plays a critical role in limiting the entry of blood-derived toxins, pathogens, and cells into the brain. Our study investigated region-specific BBB permeability in healthy subjects, suggesting unique characteristics in the hippocampal region derived from the model-based quantitative analysis and area under the DCE curve. The DCE curve comprises 4 phases: 1) the initial rapid rise of the curve, depending on tissue perfusion flow rate; 2) the early peak, depending on tissue blood volume; 3) the downslope, depending on leakage into the interstitium; and 4) the later plateau phase, depending on the interstitial volume after return of the contrast agent into the blood compartment.⁹ Most important, the area under the DCE curve is affected by both perfusion (CBV, CBF) and permeability (K^{trans} , VE) characteristics.

A review of the literature revealed that increased BBBP in the hippocampus has been previously demonstrated with DCE-MR imaging in control subjects in a mouse model of BBB disruption, in which histologic assessment of BBB integrity served as the reference standard.⁷ Because the hippocampal microvasculature is supplied from both the anterior and posterior circulation,⁴ hypothetical explanations have related the increased susceptibility of the hippocampus to cerebrovascular autoregulatory dysfunction that has been similarly described in the sympathetic vascular innervation of the posterior circulation.¹⁰ Most important, there is molecular evidence for elevated expression of biomarkers of BBB disruption in the hippocampus.⁶

Another potential contributory factor is the concept of selective neuronal vulnerability of hippocampal neurons, which describes hippocampal neurons in the cornu ammonis 1 region as most sensitive to neurodegeneration cascades occurring in Alzheimer disease¹¹ and demonstrating heightened sensitivity to oxidative stress,¹² cerebral ischemia,¹³ and toxic-metabolic and inflammatory processes.¹⁴ This selective neuronal vulnerability can manifest in deficient DNA repair, calcium dysregulation, and glutamate hyperactivity in hippocampal neurons.¹⁵ Age-related hippocampal BBB breakdown has been demonstrated in individuals with mild cognitive impairment as well.¹⁶ In a mouse model of Alzheimer disease, microvascular impairment was found as a consequence of increased β amyloid deposition.¹⁷ In patients with systemic lupus erythematosus, anti-DNA and anti-*N*-methyl-D-aspartate-receptor antibodies crossing the BBB were associated

with abnormal findings on hippocampal imaging and memory dysfunction.¹⁸ Furthermore, there is evidence that these antibodies were found to contribute to hippocampal neuronal apoptosis in patients with neuropsychiatric systemic lupus erythematosus.^{5,19} However, BBBP characteristics in the hippocampus compared with other distinct brain regions have not been previously described in healthy individuals, to our knowledge.

Even though our pilot study was adequately powered for the primary analysis, caution should be exercised not to overinterpret these results, given the small sample size demonstrating unique BBBP characteristics in the hippocampus. Given the challenge in avoiding choroid plexus contamination to obtain absolute ROI sampling of the hippocampal region, meticulous attention or innovative methods or both are warranted in further studies evaluating BBBP characteristics of the hippocampus in healthy and diseased subjects. Our findings are concordant with previous animal and human studies assessing hippocampal BBBP in neurodegenerative and neuroinflammatory diseases because increased baseline hippocampal vulnerability suggests that BBB disruption in the hippocampus may potentially contribute to early pathophysiologic disease manifestations. Most important, larger cohort studies in healthy individuals are needed to further substantiate these findings.

CONCLUSIONS

We evaluated region-specific DCE-MR imaging–derived BBBP in healthy subjects, which suggests unique BBBP characteristics in the hippocampus, concordant with prior animal studies. This work may help further our understanding of specific brain regions susceptible to neurologic diseases affecting the BBB. Larger scale prospective studies evaluating hippocampal BBBP characteristics are needed to confirm these findings and potentially incorporate them into diagnostic and therapeutic strategies.

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REFERENCES

1. Bartels AL, Kortekaas R, Bart J, et al. **Blood-brain barrier P-glycoprotein function decreases in specific brain regions with aging: a possible role in progressive neurodegeneration.** *Neurobiol Aging* 2009;30:1818–24 [CrossRef Medline](#)
2. Loeffler C, Dietz K, Schleich A, et al. **Immune surveillance of the normal human CNS takes place in dependence of the locoregional blood-brain barrier configuration and is mainly performed by CD3(+)/CD8(+) lymphocytes.** *Neuropathology* 2011;31:230–38 [CrossRef Medline](#)
3. Jeneson A, Squire LR. **Working memory, long-term memory, and medial temporal lobe function.** *Learn Mem* 2012;19:15–25 [CrossRef Medline](#)
4. Tatu L, Vuillier F. **Structure and vascularization of the human hippocampus.** *Front Neurol Neurosci* 2014;34:18–25 [CrossRef Medline](#)
5. Mackay M, Tang CC, Volpe BT, et al. **Brain metabolism and auto-**

- antibody titres predict functional impairment in systemic lupus erythematosus. *Lupus Sci Med* 2015;2:e000074 [CrossRef Medline](#)
6. Ueno M, Chiba Y, Murakami R, et al. **Blood-brain barrier and blood-cerebrospinal fluid barrier in normal and pathological conditions.** *Brain Tumor Pathol* 2016;33:89–96 [CrossRef Medline](#)
 7. Weidman EK, Foley CP, Kallas O, et al. **Evaluating permeability surface-area product as a measure of blood-brain barrier permeability in a murine model.** *AJNR Am J Neuroradiol* 2016;37:1267–74 [CrossRef Medline](#)
 8. Sanelli PC, Ugorec I, Johnson CE, et al. **Using quantitative CT perfusion for evaluation of delayed cerebral ischemia following aneurysmal subarachnoid hemorrhage.** *AJNR Am J Neuroradiol* 2011;32:2047–53 [CrossRef Medline](#)
 9. Cuenod CA, Balvay D. **Perfusion and vascular permeability: basic concepts and measurement in DCE-CT and DCE-MRI.** *Diagn Interv Imaging* 2013;94:1187–204 [CrossRef Medline](#)
 10. Sanelli PC, Jacobs MA, Ougorets I, et al. **Posterior reversible encephalopathy syndrome on computed tomography perfusion in a patient on “Triple H” therapy.** *Neurocrit Care* 2005;3:46–50 [CrossRef Medline](#)
 11. Hyman BT, Van Hoesen GW, Damasio AR, et al. **Alzheimer’s disease: cell-specific pathology isolates the hippocampal formation.** *Science* 1984;225:1168–70 [CrossRef Medline](#)
 12. Wang X, Pal R, Chen XW, et al. **High intrinsic oxidative stress may underlie selective vulnerability of the hippocampal CA1 region.** *Brain Res Mol Brain Res* 2005;140:120–26 [CrossRef Medline](#)
 13. Olsson T, Wieloch T, Smith ML. **Brain damage in a mouse model of global cerebral ischemia. Effect of NMDA receptor blockade.** *Brain Res* 2003;982:260–69 [CrossRef Medline](#)
 14. Bartsch T, Döhring J, Reuter S, et al. **Selective neuronal vulnerability of human hippocampal CA1 neurons: lesion evolution, temporal course, and pattern of hippocampal damage in diffusion-weighted MR imaging.** *J Cereb Blood Flow Metab* 2015;35:1836–45 [CrossRef Medline](#)
 15. Wang X, Michaelis EK. **Selective neuronal vulnerability to oxidative stress in the brain.** *Front Aging Neurosci* 2010;2:12 [CrossRef Medline](#)
 16. Montagne A, Barnes SR, Sweeney MD, et al. **Blood-brain barrier breakdown in the aging human hippocampus.** *Neuron* 2015;85:296–302 [CrossRef Medline](#)
 17. Dorr A, Sahota B, Chinta LV, et al. **Amyloid- β -dependent compromise of microvascular structure and function in a model of Alzheimer’s disease.** *Brain* 2012;135:3039–50 [CrossRef Medline](#)
 18. Gulinello M, Wen J, Putterman C. **Neuropsychiatric symptoms in lupus.** *Psychiatr Ann* 2012;42:322–28 [CrossRef Medline](#)
 19. Lauvsnes MB, Beyer MK, Kvaloy JT, et al. **Association of hippocampal atrophy with cerebrospinal fluid antibodies against the NR2 subtype of the N-methyl-D-aspartate receptor in patients with systemic lupus erythematosus and patients with primary Sjögren’s syndrome.** *Arthritis Rheumatol* 2014;66:3387–94 [CrossRef Medline](#)

Disorder in Pixel-Level Edge Directions on T1WI Is Associated with the Degree of Radiation Necrosis in Primary and Metastatic Brain Tumors: Preliminary Findings

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ABSTRACT

BACKGROUND AND PURPOSE: Co-occurrence of local anisotropic gradient orientations (COLLAGE) is a recently developed radiomic (computer extracted) feature that captures entropy (measures the degree of disorder) in pixel-level edge directions and was previously shown to distinguish predominant cerebral radiation necrosis from recurrent tumor on gadolinium-contrast T1WI. In this work, we sought to investigate whether COLLAGE measurements from posttreatment gadolinium-contrast T1WI could distinguish varying extents of cerebral radiation necrosis and recurrent tumor classes in a lesion across primary and metastatic brain tumors.

MATERIALS AND METHODS: On a total of 75 gadolinium-contrast T1WI studies obtained from patients with primary and metastatic brain tumors and nasopharyngeal carcinoma, the extent of cerebral radiation necrosis and recurrent tumor in every brain lesion was histopathologically defined by an expert neuropathologist as the following: 1) “pure” cerebral radiation necrosis; 2) “mixed” pathology with coexistence of cerebral radiation necrosis and recurrent tumors; 3) “predominant” (>80%) cerebral radiation necrosis; 4) predominant (>80%) recurrent tumor; and 5) pure tumor. COLLAGE features were extracted from the expert-annotated ROIs on MR imaging. Statistical comparisons of COLLAGE measurements using first-order statistics were performed across pure, mixed, and predominant pathologies of cerebral radiation necrosis and recurrent tumor using the Wilcoxon rank sum test.

RESULTS: COLLAGE features exhibited decreased skewness for patients with pure (0.15 ± 0.12) and predominant cerebral radiation necrosis (0.25 ± 0.09) and were statistically significantly different ($P < .05$) from those in patients with predominant recurrent tumors, which had highly skewed (0.42 ± 0.21) COLLAGE values. COLLAGE values for the mixed pathology studies were found to lie between predominant cerebral radiation necrosis and recurrent tumor categories.

CONCLUSIONS: With additional independent multisite validation, COLLAGE measurements might enable noninvasive characterization of the degree of recurrent tumor or cerebral radiation necrosis in gadolinium-contrast T1WI of posttreatment lesions.

ABBREVIATIONS: COLLAGE = co-occurrence of local anisotropic gradient orientations; CRN = cerebral radiation necrosis; Gd-C = gadolinium-contrast; RT = recurrent tumor; TCIA = The Cancer Imaging Archive

Currently >200,000 patients in the United States annually undergo chemoradiation as a standard-of-care treatment in pri-

mary and metastatic brain tumors.¹ Following chemoradiation treatment, these patients typically undergo regular MR imaging (usually comprising T1WI, T2WI, FLAIR) for monitoring signs of tumor recurrence. A major clinical challenge in evaluating these posttreatment MR images is the differentiation of these lesions as recurrent tumor (RT) or cerebral radiation necrosis (CRN).² CRN is an irreversible radiation-induced injury caused by aggres-

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sive radiation treatment and is challenging to diagnose on conventional MR imaging due to its close visual resemblance to tumor recurrence. The differentiation is further complicated by the simultaneous presence of varying proportions of CRN and recurrence/residual tumor confounding the diagnosis on imaging. Currently, the only definitive diagnosis of CRN rather than RT is via surgical intervention, followed by extensive histopathologic evaluation for establishing the extent of CRN or tumor recurrence in a lesion. On the basis of the extent of CRN intermixed with tumor, lesions can be characterized on histopathology as “pure” CRN (complete absence of tumor tissue), “predominant” CRN (>80% CRN), predominant RT (>80% tumor, <20% CRN), and “mixed” CRN (between 30% and 70% CRN). The current criterion standard diagnostic test for evaluating lesions posttreatment is surgical resection followed by extensive pathologic evaluation. Existing advanced noninvasive imaging protocols (ie, MR spectroscopy and PET) are known have interreader variability and have reported poor specificity in distinguishing RT from CRN.^{3,4}

Recently, a few radiomics (computational feature-extraction approaches) studies in conjunction with routinely available MR imaging sequences have attempted to capture lesion heterogeneity for survival prediction and response assessment in brain tumors.⁵ Specifically, gray-level co-occurrence matrix-based features from active tumor regions were found to be predictive of brain tumor survival by Sottoriva et al.¹⁸ Gray-level co-occurrence matrix-based features have also been shown to be discriminative of phenotypes in glioblastoma.¹⁹ It has been shown by Rathore et al²⁰ that peritumoral radiomic signatures could predict recurrence in glioblastoma and have further implications in personalized radiation therapy planning. While several of these recent studies have shown success in using radiomic analysis for survival prediction, only a few studies^{4,21} have explored distinguishing posttreatment changes (ie, CRN and pseudoprogression) from tumor recurrence using radiomic analysis.

In Prasanna et al,⁶ we presented a new radiomic feature, co-occurrence of local anisotropic gradient orientations (COLLAGE), that computes entropy (quantitative measurement that captures the degree of disorder) in voxelwise gradient orientations on routine gadolinium-contrast (Gd-C) T1WI. Specifically, we demonstrated that the COLLAGE entropy feature allowed differentiation between predominant CRN and predominant RT, with elevated expression of COLLAGE (reflective of high disorder in intensity gradients) being associated with tumor, and lower COLLAGE values, with RN.² However, our study⁷ and other studies^{8,9} that have previously attempted to distinguish CRN from RT on imaging have been limited to investigating cases that were histologically identified as either predominant CRN or predominant tumor. This limitation is because posttreatment brain tumor lesions are rarely pure and largely exhibit a heterogeneous appearance owing to the prevalence of both CRN and tumor (referred to as mixed pathology).

The objective of this study was to reliably characterize different lesion pathologies of CRN and RT on routinely acquired posttreatment Gd-C T1WI using radiomics. On the basis of our previous observations using COLLAGE in predominant CRN/RT cases,⁶ in this feasibility study, we sought to investigate whether

COLLAGE measurements are capable of distinguishing extreme (pure) from mixed pathologies for CRN and RT.

Specifically, in this study, we explored the association of COLLAGE measurements on posttreatment Gd-C T1WI with the extent of CRN and recurrent tumors across a cohort of 75 patients histologically confirmed and treated for nasopharyngeal carcinoma, primary, and metastatic brain tumors. Instances of pure CRN were obtained from patients with nasopharyngeal carcinoma¹⁰; CRN is an adverse effect of radiation in nasopharyngeal carcinoma because brain is a bystander during treatment. The manifestation of CRN in nasopharyngeal carcinoma, unlike in brain tumors, is unadulterated (pure) because there is no known malignant tumor presence in these brain lesions. Additionally, treatment-naïve brain tumor MR imaging from aggressive brain tumors (ie, grade IV glioblastoma) represents instances of pure tumor on imaging.

We investigated the following: 1) if and how first-order statistics (mean, median, skewness, and kurtosis) of COLLAGE measurements differ across different grades of pure, predominant, and mixed CRN and recurrent tumor in primary and metastatic tumors, and 2) whether these statistics provide improved discrimination across different pathologies of RT and CRN than using just MR imaging intensities alone.

MATERIALS AND METHODS

Study Population

For this study, we accrued imaging scans of patients who had been diagnosed and treated for primary/metastatic brain tumors and nasopharyngeal carcinoma. The studies of patients with brain tumor were collected at the University Hospitals, Cleveland (site 1) and University of Texas Southwestern (site 2), while the nasopharyngeal carcinoma studies were obtained from the Tuen Mun Hospital, Hong Kong (site 3), with all cohorts accrued between 1990 and 2014.

Preoperative MRIs of subjects with glioblastoma used under the “pure tumor” category were made available for public download from The Cancer Imaging Archive (TCIA). TCIA is an open archive of cancer-specific medical images and associated clinical metadata established by the National Cancer Institute and collaborating institutions in the United States. A total of 10 MR imaging studies were randomly chosen from the TCIA cohort to be used as controls for pure tumor cases to maintain class balance across all categories.

A total of 75 studies were histologically confirmed with different degrees of CRN and tumor (categorized as pure, predominant, or mixed) in a lesion, details of which are provided in the Table. Inclusion criteria for studies across the 3 sites were the following: 1) the availability of 1.5 or 3T Gd-C T1WI, and 2) the pathology specimen obtained by resection or by at least 2 biopsies via stereotactic guidance for disease confirmation.

For sites 1 and 2, following the standard dose of concomitant radiation and chemotherapy, the patients who presented with suspicious posttreatment lesion artifacts, indicative of CRN or RT, were identified. Forty-two cases were accrued from site 1, consisting of 22 primary tumors identified as 12 predominant tumors and 10 cases of predominant CRN, and 20 metastatic tumors identified as 12 predominant tumors and 8 cases of pre-

Patient cohorts with corresponding diagnosis as identified by an expert neuropathologist on postsurgical specimens

Site No., Initial Diagnosis	Category	Percentage CRN/Tumor as Identified by Expert	No. of Cases
Site 1	Primary tumors	Predominant tumor	<20% CRN, >80% tumor
		Predominant CRN	>80% CRN, <20% tumor
	Metastatic tumors	Predominant tumor	<20% CRN, >80% tumor
		Predominant CRN	>80% CRN, <20% tumor
Site 2	Primary tumors	Predominant tumor	<20% CRN, >80% tumor
		Predominant CRN	>80% CRN, <20% tumor
		Mixed	30% CRN, >70% tumor
	Metastatic tumors	Predominant tumor	<20% CRN, >80% tumor
		Predominant CRN	>80% CRN, <20% tumor
		Mixed	50% CRN, 50% tumor
Site 3	NPC	Pure	100% CRN
	TCIA		
	Glioblastoma	Pure	100% Tumor

Note:—NPC indicates nasopharyngeal carcinoma.

dominant CRN. Similarly, 10 studies were accrued from site 2, with 7 primary and 3 metastatic tumors. Of the 7 cases of primary tumors, 4 had predominant tumor, 1 case was predominant CRN, and 1 case each had mixed pathologies of 30% and 75% CRN, respectively. The 3 metastatic cases consisted of 1 case each of predominant tumor, predominant CRN, and mixed pathologies.

Site 3 consisted of patients with pure CRN ($n = 13$) originally diagnosed with nasopharyngeal carcinoma who were symptomatic of CRN in the temporal lobe. Patients were treated with a standard dose of radiation therapy, 66–70 Gy in 33–35 fractions for radical treatment of nasopharyngeal carcinoma. The medial temporal lobe received nearly 100% of the prescribed dose to the nasopharynx. MR images were obtained for patients who developed CNS symptoms or as a part of the regular work-up for suspected local recurrence of nasopharyngeal carcinoma.

Studies from site 1 have previously been used in the initial development of the COLLAGE descriptor.⁵ Similarly, studies from site 2 have been used as an independent validation set by Prasanna et al.⁶

All MR images were acquired in axial sections with a 1.5T or 3T scanner. We acquired T1-weighted postcontrast images with the following parameters: For sites 1 and 2, the mean TR and TE were 250 and 2.48 ms, respectively. For site 3, the corresponding values were 620 and 20 ms, respectively.

Confirmation of Disease Presence

For sites 1 and 2, the patient cohort was selected by performing a retrospective review of neuropathology in all patients with brain tumors who underwent a surgical intervention for a recurrent or progressive Gd-C T1WI-enhancing lesion identified during follow-up at 9 months (or later) after the initial radiation therapy. Follow-up MR images within 0–21 days before the second resection or multiple biopsies (for disease confirmation) were used for analysis. Histology was rereviewed by a neuropathologist (M.C. at site 1 and K.H. at site 2) blinded to the original diagnosis and type of RT, to quantify the percentage of CRN and RT. Histopathologic diagnosis was based on World Health Organization criteria, which included factors like the degree of pleomorphism, mitoses, and vascular proliferation among others.^{11,12}

For site 3, disease confirmation was obtained by histologic diagnosis by an expert who analyzed the presence of pathologic features of CRN such as fibrinoid and coagulative necrosis. For limited cases in which confirmation was not feasible using histologic analysis, radiographic monitoring on follow-up MR images was used for disease confirmation.

Preprocessing

To account for variability in pixel resolutions across the studies, we resampled every MR imaging slice to a uniform pixel spacing of $1 \times 1 \text{ mm}^2$. Similarly, every MR imaging volume was interpolated to a 3-mm slice thickness. We then corrected every study for intensity

nonstandardness, which refers to the inherent drift in MR imaging signal intensities during acquisition, an artifact causing image-intensity values within tissue-specific compartments to vary across sites, scanners, and even within multiple repeat scans of a single patient. Correction for intensity nonstandardness was implemented using the approach as described in Madabhushi and Udupa¹³ and implemented in Matlab R2016a (MathWorks, Natick, Massachusetts). Specifically, we used a piecewise continuous histogram-matching method (bins = 255, points = 64) for normalizing the multi-institutional MR imaging studies. Additional preprocessing involving skull stripping was performed¹⁴ via the skull-stripping module in 3D Slicer (<http://www.slicer.org>).¹⁵ Then, lesions were annotated on Gd-C T1WI by 2 radiology experts (L.W., A.S.) on the slice that presented the maximum lesion conspicuity. The 2 radiologists (L.W., A.S.) worked in conjunction to establish a consensus to define an ROI that was used for further analysis.

Feature Extraction and Statistical Analysis

Within the ROI identified by consensus across the expert radiology readers on Gd-C T1WI, COLLAGE measurements were extracted on a per-pixel basis for all the pixels within the ROI. Briefly, COLLAGE involves extracting the dominant gradient orientation along the X and Y directions for every pixel via principal component analysis.¹⁶ A co-occurrence matrix is then computed for every pixel within the neighborhood to capture co-occurring arrangements of the dominant gradient orientations. Thirteen different second-order measurements (such as energy, entropy, and variance) are then computed from this co-occurrence matrix of the dominant gradient orientations. We chose to focus on entropy because it captures the disorder of pixel gradient orientations on a per-pixel basis. In Prasanna et al.,⁶ we showed that the entropy values for the localized orientations were high for tumor, while the values were low for benign pathologies (ie, CRN). A detailed description of the algorithm and methodology for computing 3D COLLAGE can be found in Prasanna et al.⁶ For our analysis, every image voxel within the enhancing lesion was assigned a COLLAGE entropy value. We subsequently extracted 4

different first-order statistics of the features (mean, SD, skewness, and kurtosis) across all the voxels within the most conspicuous lesion per study. For each of the 4 statistics, the range of values was rescaled between 0 and 1. Each study was hence represented by a 4×1 feature vector, comprising the 4 statistics of COLLAGE entropy within that ROI.

Comparison of COLLAGE Radiomic Features across Different Grades of Radiation Necrosis and Recurrent Tumor in Primary and Metastatic Tumors

Statistics of COLLAGE values (mean, SD, skewness, and kurtosis) were compared for the pure CRN pathology against mixed and predominant CRN/recurrent tumor pathologies, using the Wilcoxon rank sum test, independently across primary and metastatic tumors. We included COLLAGE statistics from the TCIA glioblastoma studies to represent the pure tumor class, while comparing pathologies within the primary tumor cohort. The statistics obtained from COLLAGE were also compared with those obtained from average Gd-C T1WI intensity values across different CRN and recurrent tumor pathologies.

Classification Analysis to Distinguish CRN from RT Using Pure and Predominant CRN and Tumor COLLAGE Features

A random forest classifier was trained separately on primary and metastatic cases, in a leave-one-out cross-validation setting. First, COLLAGE features from only predominant CRN/tumor (from site 1) were used within the training cohort. Next, we incorporated the pure CRN signatures (from site 3) into the training set and repeated the classifier analysis separately for primary and metastatic tumors. It was ensured that all the folds within leave-one-out cross-validation contained pure CRN studies within the training set. Receiver operating characteristic curves were obtained for the training set analysis along with the corresponding areas under the curve.

We used the classifier trained with both pure and predominant COLLAGE features and evaluated its performance on the predominant cases on the held-out cases from site 2 ($n = 10$). Three studies from site 2 that had mixed degrees of CRN and tumor were excluded from the test set because the samples in the training cohort were not exposed to mixed degrees of CRN. However, the statistics obtained from the COLLAGE values for these studies were compared with those obtained from the training cohort and were reported.

RESULTS

Comparison of COLLAGE Radiomic Features across Different Grades of Radiation Necrosis and Recurrent Tumor in Primary and Metastatic Tumors

The original Gd-C T1WI intensity values were not found to be statistically different across predominant CRN, predominant tumor, pure CRN, and pure tumor groups for the primary cohort (Fig 1A). While mean, SD, and kurtosis statistics of COLLAGE did not demonstrate significant differences, the corresponding COLLAGE skewness values were found to be statistically significantly different ($P < .05$) across the 3 categories (excluding pure tumor in which the results were not statistically significantly different from predominant CRN) as shown in Fig 1C,

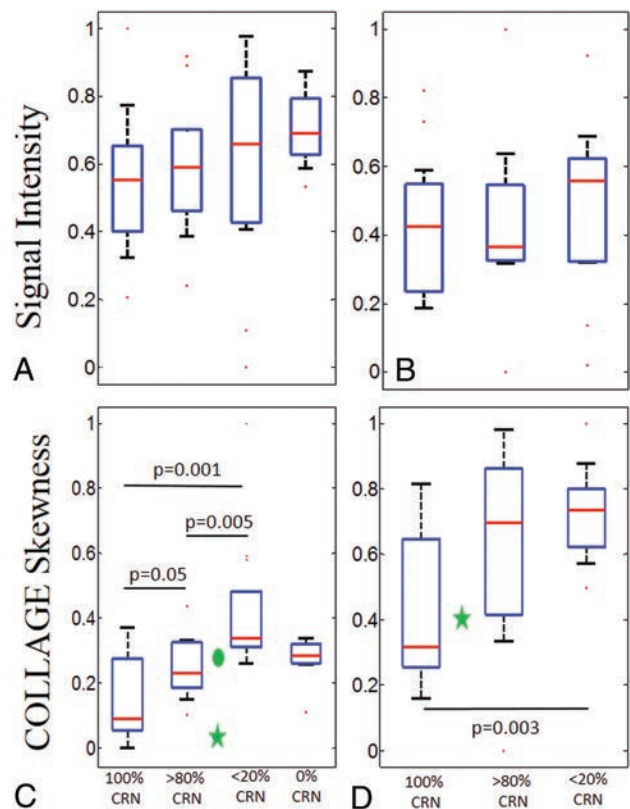


FIG 1. Box-and-whisker plots showing the distributions of T1WI signal intensities and skewness of COLLAGE entropy values for pure and different grades of CRN for primary and metastatic cases, respectively. A and B, The signal intensities in primary and metastatic cases, respectively. C and D, The COLLAGE skewness values for the same cases. C, The green star and circle represent the cases from site 2 with 75% CRN and 30% CRN, respectively. D, The green star represents the case from site 2 with 50% CRN. P values for the pairs of groups exhibiting statistically significant difference are also shown.

with higher skewness values suggesting a skewed distribution toward elevated COLLAGE entropy. Most interesting, for primary tumors, COLLAGE skewness values were lowest for pure CRN with a mean of 0.15 ± 0.12 and 0.25 ± 0.09 for predominant CRN, 0.42 ± 0.21 for predominant recurrence, and 0.27 ± 0.07 for pure tumor, respectively. The values were statistically significantly different between predominant CRN and predominant tumor recurrence with $P = .005$, between pure CRN and predominant tumor recurrence with $P = .001$, and between pure CRN and predominant CRN with $P = .05$.

Qualitative results of COLLAGE feature maps of pure CRN, predominant CRN, and predominant tumor reflecting corresponding changes in radiomic values are shown in Fig 2. COLLAGE values for both mixed pathology studies were found to lie between predominant CRN and tumor categories. The study with 75% CRN (the green star in Fig 1C) had a low skewness value of 0.013 compared with the one with 30% CRN (the green circle in Fig 1C) with a skewness value of 0.285.

Similarly, for the metastatic cases, the intensity values (Fig 1B) and mean, SD, and kurtosis of COLLAGE features were found not to be statistically significantly different across the 3 groups. However, COLLAGE skewness values (ranging between 0 and 1) were significantly different, with the lowest values for pure CRN with a

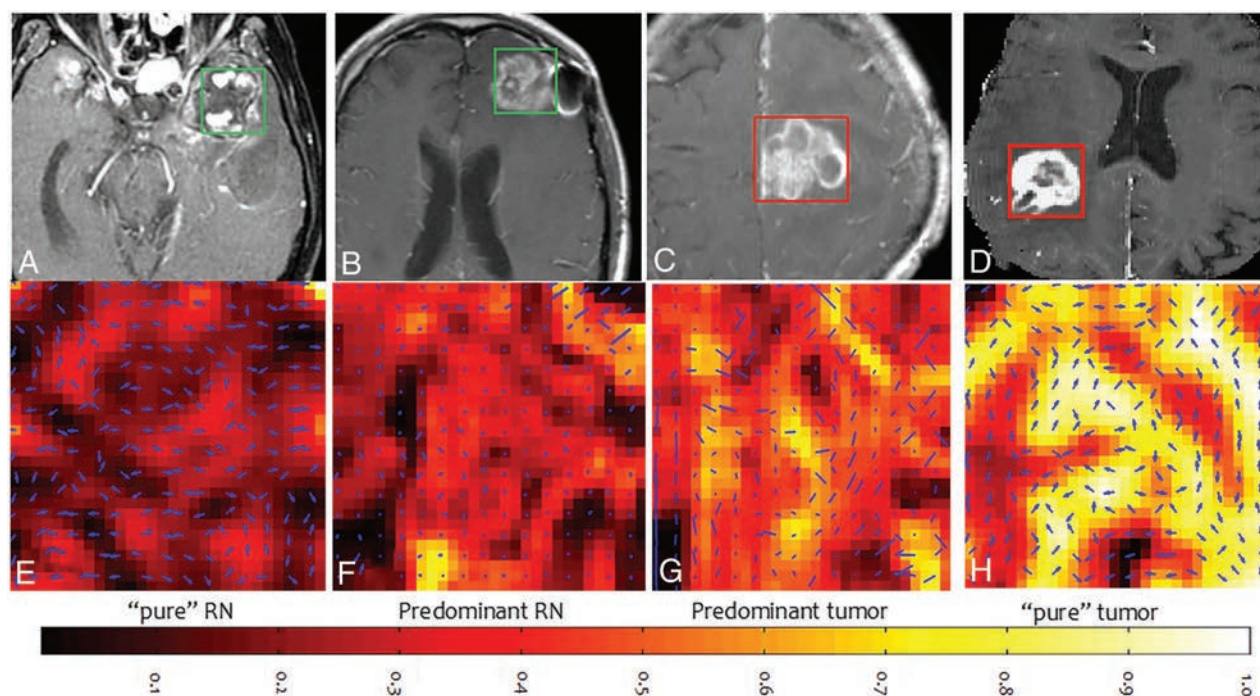


FIG 2. Gd-C T1WI for CRN from nasopharyngeal carcinoma (A), predominant (>80%) CRN (B), predominant recurrent tumor (<20% CRN) (C), and glioblastoma (0% CRN) (D), and the corresponding COLLAGE entropy maps of the ROIs (E–H).

mean of -0.41 ± 0.22 and 0.61 ± 0.33 for predominant CRN, and 0.72 ± 0.14 for predominant recurrence, respectively. COLLAGE values were statistically significantly different only between pure CRN and predominant recurrence with $P = .003$, and not across predominant and pure CRN. The study in site 3 with 50% CRN (green star in Fig 1D) had a skewness value of 0.4.

Classification Analysis to Distinguish CRN from RT Using Pure and Predominant CRN and Tumor COLLAGE Features

For primary brain tumor cases, the area under the curve for the classifier, using COLLAGE features from both pure CRN and predominant studies in the training cohort, was found to be 0.67, while for metastatic tumors, the area under the curve was 0.66. The corresponding accuracies at the optimal operating point were found to be 68.2% and 65%, respectively. However, the area under the curve using only the COLLAGE features from predominant studies was found to be 0.64 for primary and 0.56 for metastatic tumors. The corresponding accuracies at the optimal operating point were found to be 59.1% and 65%, respectively. On the independent test set at site 2, a total of 4 of 5 primary tumor cases with predominant CRN/tumor were correctly classified. For the metastatic tumor cases, 1 of the 2 cases was correctly classified.

DISCUSSION

COLLAGE, a recently developed radiomic feature, has previously been shown to be effective in distinguishing predominant recurrent brain tumors from cerebral radiation necrosis on MR imaging⁶ and also in predicting a pathologic complete response to neoadjuvant chemotherapy in breast cancer.¹⁷ In this work, we attempted to interrogate differences in COLLAGE values on post-

treatment Gd-C T1WI across different posttreatment pathologies in brain tumors by associating the extent of CRN and tumor with the corresponding expression levels of COLLAGE. We present our findings of associations of COLLAGE features across pathologically proved pure, predominant, and mixed categories of CRN and tumor.

While in the metastatic cohort, statistically significant differences were observed only between pure CRN and predominant recurrence, COLLAGE values in the primary cohort were statistically significantly different between predominant CRN and predominant recurrence, pure CRN and predominant recurrence, and pure CRN and predominant CRN. Over and above the results reported in Chao et al,² the findings in this work suggest that COLLAGE may potentially characterize the spectrum of pathologies of CRN and RT on posttreatment Gd-C T1WI, as confirmed on the corresponding histopathology.

Furthermore, our results show that COLLAGE entropy values were skewed toward higher values for the predominant tumor cases compared with the pure CRN or predominant CRN for both primary and metastatic tumors (Fig 1). The difference in skewness may be attributed to the low COLLAGE values in lesions having lower concentrations of CRN, likely characterizing relatively inactive necrotic tissue. Given that tumors have increased heterogeneity,¹⁸ it is intuitive that COLLAGE features tend to be overexpressed, resulting in higher skewness, while radiation necrosis, which tends to have a more coherent microarchitecture, results in a muted COLLAGE response and consequently lower skewness values.

The reason for lower COLLAGE skewness in predominant RT than in pure RT is likely the presence of more heterogeneous tissue pathologies in the predominant RT group. Predominant RT often exhibits tissue heterogeneity owing to the varying pres-

ence of radiation-induced vascular hyalinization, telangiectasia, and zonal necrosis. This tissue heterogeneity is possibly manifested on the imaging scale and may therefore be captured by the skewness of COLLAGE entropy. A similar trend was observed in the variance of the skewness values in the boxplots, with low variance in COLLAGE observed in pure tumor compared with predominant RT.

Our results further demonstrate that incorporating COLLAGE features from pure CRN in the training set resulted in improved classification performance of the predominant CRN/RT, compared with using COLLAGE features from the predominant CRN/RT alone. These findings are consistent from a machine learning perspective, wherein an ideal classifier is expected to be exposed to the entire spectrum of cases—that is, a learning set comprising features corresponding to “pure CRN and no cancer” and mixed classes comprising co-existing CRN and cancer.

There were a few limitations of this feasibility study. Our cohort was retrospectively acquired as a part of a study that was concluded in 2016. Because we limited the analysis to pathologically proved grades of CRN/RT, the sample size was relatively small. While our retrospective cohort contained pathologically proved CRN and RT cases, it lacked cases that were histologically confirmed to be pure metastatic brain tumor. Hence, we could not perform a similar analysis on the metastatic cases, as was performed on the cases with primary brain tumors. Furthermore, differences in radiation therapy protocols in CNS tumors (both primary and metastatic) and nasopharyngeal carcinoma were not considered in the analysis. The analysis was limited to only Gd-C T1WI in this study and did not consider other routine or advanced imaging protocols. No independent large-scale validation of the findings was performed as a part of this study.

CONCLUSIONS

In this feasibility analysis, we presented the initial results of using a new radiomic feature, COLLAGE, to capture the extent of cerebral radiation necrosis and recurrent tumor on posttreatment Gd-C T1WI. We identified associations of COLLAGE features with the extent of CRN and RT on Gd-C T1WI on a unique cohort of patients histologically confirmed and treated for nasopharyngeal carcinoma, and primary and metastatic brain tumors. These preliminary findings suggest that COLLAGE may be potentially capturing subtle differences across different pathologic categories of RT and CRN (pure, predominant, and, to some extent, mixed) on posttreatment Gd-C T1WI. Learning such signatures, following extensive multisite validation, may, in the future, help in improved discrimination of CRN and RT, which still remains an extremely challenging clinical problem in neuro-oncology. In future work, we intend to prospectively validate our preliminary findings on a larger, multi-institutional cohort.

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licensed to Inspirata through Rutgers and Case Western*; Royalties: Royalties are paid out to Case Western and Rutgers by Inspirata and Elucid Bioimaging*; Stock/Stock Options: Elucid Bioimaging, Inspirata. Pallavi Tiwari—RELATED: Grant: The Dana Foundation, Ohio Third Frontier, I Corps.* *Money paid to the institution.

REFERENCES

1. Lee YW, Cho HJ, Lee WH, et al. **Whole brain radiation-induced cognitive impairment: pathophysiological mechanisms and therapeutic targets.** *Biomol Ther (Seoul)* 2012;20:357–70 [CrossRef Medline](#)
2. Chao ST, Ahluwalia MS, Barnett, GH et al. **Challenges with the diagnosis and treatment of cerebral radiation necrosis.** *Int J Radiat Oncol Biol Phys* 2013;87:449–57 [CrossRef Medline](#)
3. Verma N, Cowperthwaite MC, Burnett MG, et al. **Differentiating tumor recurrence from treatment necrosis: a review of neuro-oncologic imaging strategies.** *Neuro Oncol* 2013;15:515–34 [CrossRef Medline](#)
4. Kashimura H, Inoue T, Beppu T, et al. **Diffusion tensor imaging for differentiation of recurrent brain tumor and radiation necrosis after radiotherapy: three case reports.** *Clin Neurol Neurosurg* 2007;109:106–10 [CrossRef Medline](#)
5. Prasanna P, Patel J, Partovi S, et al. **Radiomic features from the peritumoral brain parenchyma on treatment-naïve multi-parametric MR imaging predict long versus short-term survival in glioblastoma multiforme: preliminary findings.** *Eur Radiol* 2017;27:4188–97 [CrossRef Medline](#)
6. Prasanna P, Tiwari P, Madabhushi A. **Co-occurrence of Local Anisotropic Gradient Orientations (CoLLAGE): a new radiomics descriptor.** *Sci Rep* 2016;6:37241 [CrossRef Medline](#)
7. Tiwari P, Prasanna P, Wolansky L, et al. **Computer-extracted texture features to distinguish cerebral radionecrosis from recurrent brain tumors on multiparametric MRI: a feasibility study.** *AJNR Am J Neuroradiol* 2016;37:2231–36 [CrossRef Medline](#)
8. Larroza A, Moratal D, Paredes-Sánchez A, et al. **Support vector machine classification of brain metastasis and radiation necrosis based on texture analysis in MRI.** *J Magn Reson Imaging* 2015;42:1362–68 [CrossRef Medline](#)
9. Asao C, Korogi Y, Kitajima M, et al. **Diffusion-weighted imaging of radiation-induced brain injury for differentiation from tumor recurrence.** *AJNR Am J Neuroradiol* 2005;26:1455–60 [Medline](#)
10. Lam TC, Wong FC, Leung TW, et al. **Clinical outcomes of 174 nasopharyngeal carcinoma patients with radiation-induced temporal lobe necrosis.** *Int J Radiat Oncol Biol Phys* 2012;82:e57–65 [CrossRef Medline](#)
11. Martins AN, Johnston JS, Henry JM, et al. **Delayed radiation necrosis of the brain.** *J Neurosurg* 1977;47:336–45 [Medline](#)
12. Burger PC, Vollmer RT. **Histologic factors of prognostic significance in the glioblastoma multiforme.** *Cancer* 1980;46:1179–86 [CrossRef Medline](#)
13. Madabhushi A, Udupa JK. **New methods of MR image intensity standardization via generalized scale.** *Med Phys* 2006;33:3426–34 [CrossRef Medline](#)
14. Ségonne F, Dale AM, Busa E, et al. **A hybrid approach to the skull stripping problem in MRI.** *Neuroimage* 2004;22:106–75 [Medline](#)
15. Pieper S, Halle SM, Kikinis R. **3D Slicer.** Biomedical Imaging: Nano to Macro, 2004. *IEEE International Symposium on. IEEE*, 2004:632–35
16. Jolliffe I. **Principal Component Analysis.** *International Encyclopedia of Statistical Science.* Springer: Berlin, Heidelberg; 2011:1094–96
17. Braman NM, Etesami M, Prasanna P, et al. **Intratumoral and peritumoral radiomics for the pretreatment prediction of pathological complete response to neoadjuvant chemotherapy based on breast DCE-MRI.** *Breast Cancer Res* 2017;19:57 [CrossRef Medline](#)
18. Sottoriva A, Spiteri I, Piccirillo SG, et al. **Intratumor heterogeneity in human glioblastoma reflects cancer evolutionary dynamics.** *Proc Natl Acad Sci U S A* 2013;110:4009–14 [CrossRef Medline](#)

Accurate Patient-Specific Machine Learning Models of Glioblastoma Invasion Using Transfer Learning

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ABSTRACT

BACKGROUND AND PURPOSE: MR imaging–based modeling of tumor cell density can substantially improve targeted treatment of glioblastoma. Unfortunately, interpatient variability limits the predictive ability of many modeling approaches. We present a transfer learning method that generates individualized patient models, grounded in the wealth of population data, while also detecting and adjusting for interpatient variabilities based on each patient's own histologic data.

MATERIALS AND METHODS: We recruited patients with primary glioblastoma undergoing image-guided biopsies and preoperative imaging, including contrast-enhanced MR imaging, dynamic susceptibility contrast MR imaging, and diffusion tensor imaging. We calculated relative cerebral blood volume from DSC-MR imaging and mean diffusivity and fractional anisotropy from DTI. Following image coregistration, we assessed tumor cell density for each biopsy and identified corresponding localized MR imaging measurements. We then explored a range of univariate and multivariate predictive models of tumor cell density based on MR imaging measurements in a generalized one-model-fits-all approach. We then implemented both univariate and multivariate individualized transfer learning predictive models, which harness the available population-level data but allow individual variability in their predictions. Finally, we compared Pearson correlation coefficients and mean absolute error between the individualized transfer learning and generalized one-model-fits-all models.

RESULTS: Tumor cell density significantly correlated with relative CBV ($r = 0.33, P < .001$), and T1-weighted postcontrast ($r = 0.36, P < .001$) on univariate analysis after correcting for multiple comparisons. With single-variable modeling (using relative CBV), transfer learning increased predictive performance ($r = 0.53$, mean absolute error = 15.19%) compared with one-model-fits-all ($r = 0.27$, mean absolute error = 17.79%). With multivariate modeling, transfer learning further improved performance ($r = 0.88$, mean absolute error = 5.66%) compared with one-model-fits-all ($r = 0.39$, mean absolute error = 16.55%).

CONCLUSIONS: Transfer learning significantly improves predictive modeling performance for quantifying tumor cell density in glioblastoma.

ABBREVIATIONS: FA = fractional anisotropy; GBM = glioblastoma; LOOCV = leave-one-out cross-validation; MD = mean diffusivity; OMFA = one-model-fits-all; rCBV = relative CBV; T1 + C = T1-weighted postcontrast; TCD = tumor cell density; TL = transfer learning; EPI + C = post-contrast T2*WI

Surgical debulking and radiation therapy represent first-line treatments for glioblastoma (GBM), which rely heavily on image guidance to delineate tumor from adjacent nontumoral brain.

Contrast-enhanced MR imaging currently serves as the clinical standard for image guidance, but its diagnostic accuracy remains limited. Specifically, contrast-enhanced MR imaging localizes contrast-enhancing tumor for surgical resection and/or biopsy but poorly identifies nonenhancing invasive tumor in the sur-

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rounding T2-weighted/FLAIR abnormality.¹⁻³ This invasive tumor segment can represent a substantial proportion of overall burden for many GBM tumors and contributes to recurrent disease and poor survival if left unresected.⁴⁻⁶ In addition to surgical guidance, contrast-enhanced MR imaging also fails to localize nonenhancing tumor during dosimetric radiation treatment planning. To compensate, most radiation oncologists must apply submaximal doses across the entire nonenhancing T2/FLAIR volume, which risks toxicity to normal brain and undertreatment of nondetected bulk tumor.^{7,8} These issues underscore the need to improve the image-based detection and targeted treatment of the nonenhancing tumor segment in GBM.

Advanced MR imaging techniques can help characterize nonenhancing tumor by measuring an array of biophysical features that complement contrast-enhanced MR imaging. These include tissue cell density (TCD) on diffusion-weighted imaging,^{2,9} white matter infiltration on diffusion tensor imaging,^{2,10,11} and microvessel morphology on dynamic susceptibility contrast perfusion MR imaging.^{2,12-14} Multiple studies have used image-guided biopsies to compare these advanced MR imaging features with TCD in a spatially accurate manner.^{3,5,9,11,15-22} These studies have revealed promising trends between MR imaging signal and tumor abundance but also surprising discrepancies in correlations among studies. For instance, some groups have reported that higher TCD correlates negatively with lower fractional anisotropy (FA) on DTI, presumably from greater white matter tract disruption.^{5,11} Yet, opposite (positive) correlations between FA and tumor content have also been reported.²¹ Similarly, published studies have differed on whether TCD correlates negatively or positively with mean diffusivity (MD) measures on DWI.^{9,11,16,19} These discrepancies present obvious challenges for developing generalized MR imaging-based models to prospectively quantify TCD and extent of invasion.

We hypothesized that the relationship between MR imaging signal (for any given contrast) and regional TCD demonstrates patient-to-patient variability within a given cohort. This may underlie the aforementioned discrepancies among published reports in the literature. In this study, we set out to quantify interpatient variability and determine whether it can strengthen the predictive accuracy of MR imaging-based models for quantifying TCD and invasion. Specifically, we have developed a transfer learning (TL) approach that quantifies concordance and variability of MR imaging-histologic relationships across patients. TL builds 1 model for each patient to account for potential interpatient variabilities in MR imaging-histologic relationships, while coupling the estimation processes of each patient-specific model to allow knowledge transfer between models. As proof of concept, we trained and cross-validated this TL approach in a cohort of patients with primary GBM using multiparametric MR imaging and spatially matched image-guided biopsies. Our overarching goal was to optimize predictive models that guide targeted treatment for the problematic nonenhancing tumor segment of GBM.

MATERIALS AND METHODS

Acquisition and Processing of Clinical MR Imaging and Histologic Data

Patient Recruitment. We recruited patients with clinically suspected primary GBM undergoing preoperative stereotactic MR

imaging for first-line surgical resection before any treatment, as per our institutional review board protocol at Barrow Neurological Institute. All patients provided written and informed consent before enrollment. The patient cohort presented here has also been described in previous studies.^{3,6}

Preoperative MR Imaging Acquisition Protocol. We acquired preoperative 3T MR imaging (Sigma HDx; GE Healthcare, Milwaukee, Wisconsin) within 1 day of stereotactic surgery, including T2-weighted, T1-weighted precontrast, and T1-weighted postcontrast (T1 + C) sequences.^{3,6,14} T1 + C images were acquired after completion of dynamic susceptibility contrast perfusion MR imaging following a total Gd-DTPA dosage of 0.15 mmol/kg.^{3,6,14} In brief, for the DSC protocol, we administered an IV preload dose (0.1 mmol/kg of Gd-DTPA) to minimize T1-weighted leakage errors, after which we administered a second IV bolus injection (0.05 mmol/kg of Gd-DTPA) during the 3-minute DSC acquisition (gradient-echo echo-planar imaging: TR/TE/flip angle = 1500/20 ms/60°, matrix = 128 × 128, thickness = 5 mm).^{3,6,14} We derived postcontrast T2*WI (EPI+C) from the initial-source DSC volume.^{3,23} DTI acquisition consisted of spin-echo EPI (TR/TE = 10,000/85.2 ms, matrix = 256 × 256, FOV = 30 cm, thickness = 3 mm, 30 directions, array spatial sensitivity encoding technique, $b=0, 1000$).^{3,6}

Surgical Biopsy. Neurosurgeons used T1 + C and T2-weighted imaging to guide stereotactic biopsies following the smallest possible diameter craniotomies to minimize brain shift, as previously described.^{3,6} On average, we collected 5–6 tissue specimens from each tumor, selecting targets ≥ 1 cm apart from both T1 + C enhancing regions and nonenhancing T2-weighted hyperintense regions (so called brain-around-tumor) in pseudorandom fashion from different poles of the enhancing lesion periphery while avoiding centrally necrotic regions on the basis of the clinical feasibility as per clinical protocol. Enhancing and nonenhancing regions were distinguished on the basis of visual assessment by the neurosurgeon at the time of surgical biopsy and/or resection, as per clinical protocol. The target volume of each biopsy sample was approximately 125 mg. The neurosurgeons recorded biopsy locations via screen capture to allow subsequent coregistration with multiparametric MR imaging datasets. The neurosurgeon visually validated stereotactic imaging locations with corresponding intracranial anatomic landmarks, such as vascular structures and ventricle margins, before recording specimen locations.

Histologic Analysis and TCD Measurements from Image-Localized Biopsies. Tissue specimens (volume = 125 mg) were flash frozen in liquid nitrogen in the operating suite and stored in a -80°C freezer until subsequent retrieval for embedding in an optimal cutting temperature compound and sectioning (thickness = 4 mm) in a -20°C cryostat (Microm-HM-550; Richard-Allan Scientific Company, Canton, Michigan) using a Microtome Blade (Thermo Scientific, Waltham, Massachusetts).^{3,6} Hematoxylin-eosin-stained slides were reviewed blinded to diagnosis by our neuropathologist (J.M.E.) to assess tumor content. Taking into account all visible cells (neurons, inflammatory cells, reactive glia, tumor cells, and so forth), we estimated the percentage of tumor nuclei (ie, tumor cells relative to all visible cells) (0%–100%), rounded to the nearest fifth percentile, and recorded it for

each tissue sample as a $\pm 5\%$ range of TCD (eg, 30%–40%, 75%–85%, and so forth).^{3,6} This method served as a compromise between the resolution of TCD measurements and the precision of the neuropathologist's estimates.

Image Signal Normalization, DSC and DTI Analysis, Image Coregistration, and ROI analysis. We normalized the signal for T1 + C, T2-weighted, and EPI + C image datasets using the Simple Insight Segmentation and Registration Toolkit (SimpleITK, Version 1.0.1; <http://www.simpleitk.org/>)²⁴ in Python (Version 3.6.2; <https://www.python.org/>). The CurvatureFlow ITK algorithm was applied to remove image noise,²⁵ and the N4ITK algorithm to correct for image-intensity nonuniformity bias that could be due to factors such as local magnetic field heterogeneity.²⁶ Following these corrections, the CSF of the lateral ventricles was used as a reference tissue to normalize the intensity distributions of each dataset using a previously described linear scaling process.²⁷ For DTI, we generated mean diffusivity and fractional anisotropy maps.⁵ For DSC, we generated relative cerebral blood volume (rCBV) maps using IB Neuro (Imaging Biometrics, Elm Grove, Wisconsin), using leakage correction^{28,29} and white matter normalization.^{3,6,14} We coregistered all images using ITK tools (<https://itk.org/>) and IB Suite (Imaging Biometrics), using the DTI B_0 anatomic volume as the coregistration target.^{3,6,14} A board-certified neuroradiologist (L.S.H.) placed ROIs (8×8 voxels) for all coregistered multiparametric MR imaging datasets at the stereotactic biopsy locations.^{3,6,14} We selected this ROI size (0.93×0.93 cm) to encompass a broader area relative to the expected biopsy dimensions (125 mg). This selection helped to offset any potential minor shifts in biopsy localization (at the time of tissue sampling) that might otherwise result in misregistration. We measured mean signal values within ROIs for all MR imaging contrasts to correlate with spatially matched estimates of TCD from corresponding biopsies.

Statistical Analysis and Predictive Modeling

Univariate Statistical Analysis and Predictive Modeling. To broadly survey potential associations between MR imaging signal and TCD, we performed univariate analysis using linear regression and Pearson correlations for each contrast (eg, T1 + C, rCBV, and so forth) against spatially matched biopsies across the entire patient cohort. We used the false discovery rate to adjust for multiple testing.³⁰ To quantify intersubject variability, we also plotted MR imaging signal-versus-TCD in each patient separately.

Multivariate Statistical Analysis and Predictive Modeling Using the Conventional One-Model-Fits-All Approach. To evaluate the potential complementary function of multiple combined MR imaging contrasts to characterize TCD, we performed multivariable linear regression to correlate MR imaging contrasts with histologic quantification of TCD across all biopsies and patients with GBM.^{16,22} This entailed the conventional approach in which a single static multivariable model was applied uniformly to all biopsy samples within the cohort (ie, one-model-fits-all [OMFA]). We evaluated a range of combined MR imaging contrasts to create various linear regression OMFA models. For instance, a model using signal intensities on rCBV, MD, and FA would be defined by the following: $F(x) = ax_1 + bx_2 + cx_3 + d$, where the predicted

TCD, $F(x)$, was a linear function of signal intensity on rCBV, MD, and FA maps (x_1 , x_2 , and x_3 , respectively).

Transfer Learning Predictive Modeling. Interpatient variability is a known limiting factor for many types of predictive models. For instance, a single model applied uniformly across all patients within a cohort (ie, one-model-fits-all) is unable to adjust for likely interpatient variabilities in MR imaging–histologic relationships. In contrast, individual models developed for each patient using only that patient's data (ie, one-model-each-patient) are unable to benefit from general population patterns and thus inherently have small sample sizes.

TL represents a compromise between the 2 aforementioned approaches. TL is a subfield of Machine Learning (ML), with various algorithms having been developed to allow knowledge transfer in jointly building different-but-inherently related models.^{31,32} We have previously published a TL algorithm under the Bayesian framework.³³ With our TL algorithm, 1 model is built for each patient, but a Bayesian framework is used to bias the model parameter-estimation process toward the population pattern in the case in which the individual data are not sufficient to precisely determine the individual's variation. In essence, the population pattern represents a generalized model, and TL uses each patient's own MR imaging and biopsy data to modify that generalized model to more appropriately fit that particular individual patient. Thus, TL models can account for potential variabilities in MR imaging–histologic relationships across different patients, while also coupling the estimation processes of each patient-specific model to allow knowledge transfer between models. We detailed TL theory and methodology in the On-line Appendix and in our previous publication.³³

Leave One-Out Cross-Validation. To reduce overfitting, we used leave-one-out cross-validation (LOOCV) for all OMFA and TL model training. Briefly, all samples except 1 (randomly selected in each patient) were used to train the predictive model, while the excluded sample served as the test case to generate predicted TCD. We repeated this iteratively so that all 82 samples served as the test case.^{3,34} We then plotted model-predicted TCD against actual TCD for all biopsies to determine cross-validated Pearson correlation coefficients and mean absolute error rates (the difference between predicted versus actual TCD) for each model.

RESULTS

Patients and Biopsy Samples

We collected 82 image-recorded biopsy samples (median = 4/patient, range = 2–14) from 18 patients with primary GBM (9:9 = female/male, median age = 60 years, range = 18–81 years). We collected ≥ 3 biopsies from 14/18 patients. In total, 33 biopsy samples originated from regions of nonenhancement (ie, brain-around-tumor), with 14 of 18 patients contributing at least 1 biopsy from nonenhancing regions. The remaining 49 biopsy samples originated from enhancing tumor regions.

OMFA Univariate and Multivariate Correlations between TCD and MR Imaging

We performed univariate analysis (Table 1) across all 82 samples comparing TCD with the 6 MR imaging features individually. We

Table 1: Univariate correlations for spatially matched MRI features vs TCD ($n = 82$ biopsies, 18 patients)

MRI Feature	Pearson Correlation Coefficient (r)	P Value	FDR-Corrected P Value
T1 + C ^a	+0.36	<.001	.01
T2WI	+0.13	.25	.38
rCBV ^a	+0.33	<.001	.01
EPI + C	−0.02	.85	.85
FA	−0.24	.03	.06
MD	+0.03	.78	.85

Note:—FDR indicates false discovery rate; EPI + C, post-contrast T2*WI.

^a Statistical significance after correcting for multiple comparisons.

found significant correlations for T1 + C ($r = 0.36$, $P < .001$), rCBV ($r = 0.33$, $P < .001$), and FA ($r = -0.24$, $P < .03$), though only T1 + C and rCBV remained significant after correcting for multiple comparisons ($P = .01$). Our observed T1 + C correlation with TCD supports the long-held assumption that regions of MR imaging enhancement (and higher T1 + C signal) generally correspond with higher tumor content compared with peripherally nonenhancing regions (with lower T1 + C signal).³⁵ This assumption underlies the clinical rationale for guiding surgical cytoreduction based on MR imaging enhancement. However, because nonenhancing regions, by definition, lack MR imaging enhancement, then T1 + C would presumably have much lower correlation with TCD within nonenhancing regions containing invasive tumor content. In fact, separate subgroup analysis (On-line Table) showed much lower correlation values between T1 + C and TCD when restricted to only nonenhancing biopsy samples. Meanwhile, the same subgroup analysis showed more consistent rCBV correlations across enhancing and nonenhancing biopsy subgroups, suggesting the potential utility of rCBV as a biomarker for both tumor segments. We also address any potential risks of overfitting by performing LOOCV to estimate the predictive performance of rCBV for quantifying TCD. Using the generalized one-model-fits-all approach, we generated a single variable linear regression model, with rCBV as the sole predictor input, and plotted predicted-versus-actual TCD ($n = 82$ samples). This generalized OMFA approach (based on rCBV alone) demonstrated poor performance, with a low correlation coefficient ($r = 0.27$) and high error (mean absolute error = 17.79%) (Table 2). We then evaluated other MR imaging features (combined with rCBV) using multivariable linear regression analysis. Regardless of the combination of MR imaging features (with rCBV), the generalized multivariate OMFA models failed to significantly improve performance (Table 2).

Individualized Patient Plots and Interpatient Variability

To investigate interpatient variability, we separately plotted MR imaging signal versus TCD for each of the 14 (of 18) patients who contributed ≥ 3 separate biopsies (which allowed for LOOCV, as described in the Materials and Methods section above). The other 4 contributed < 3 biopsies, which was insufficient for LOOCV analysis. Patient-by-patient plots are also shown in On-line Figs 1–6. Of the MR imaging correlations with TCD, rCBV demonstrated the greatest consistency across patients, with 13/14 patients (92.5%) having a positive correlation ($r > 0.00$), though these varied in strength from patient to patient (range of $r = 0.07$

Table 2: OMFA vs transfer learning for various MRI model predictors^a

Predictors for Model	OMFA, LOOCV (r), and MAE		TL, LOOCV (r), and MAE	
rCBV	0.27	17.79	0.53	15.19
rCBV, EPI + C	0.25	18.03	0.63	11.65
rCBV, FA	0.34	17.24	0.58	11.31
rCBV, MD	0.28	17.74	0.60	11.93
rCBV, T1 + C	0.33	16.69	0.69	11.15
rCBV, T2WI	0.26	17.96	0.59	12.30
rCBV, FA, MD	0.32	17.47	0.66	11.93
rCBV, T1 + C, T2WI	0.35	16.61	0.75	9.03
rCBV, T1 + C, FA	0.39	16.55	0.73	9.07
rCBV, T1 + C, MD	0.35	16.77	0.74	9.41
rCBV, T2WI, FA	0.32	17.47	0.64	10.94
rCBV, T2WI, MD	0.26	18.02	0.64	11.15
rCBV, T1 + C, FA, MD	0.37	16.78	0.85	6.73
rCBV, T2WI, FA, MD	0.30	17.68	0.69	10.95
rCBV, T1 + C, T2WI, FA	0.37	16.79	0.73	9.41
rCBV, T1 + C, T2WI, MD	0.34	16.88	0.78	7.01
rCBV, T1 + C, T2WI, FA, MD	0.35	17.05	0.88	5.66
rCBV, T1 + C, T2WI, FA, MD, EPI + C	0.34	17.17	0.86	6.09

Note:—MAE indicates mean absolute error.

^a OMFA models were generated on the basis of linear regression analysis. Both (r) and MAE were determined using LOOCV to plot model-predicted TCD against actual TCD from spatially matched biopsies ($n = 82$).

to 0.95) (On-line Fig 1). Conversely, FA correlations showed greater variability ($r = -0.75$ to $+0.78$), with only 57.1% (8/14) of patients having negative correlations with TCD (versus 42.9% with positive correlations) (On-line Fig 2). MD correlations were also highly variable (range, $r = -0.96$ to $+0.78$), with 50% of patients split between negative and positive correlations (On-line Fig 3). These data suggest that while certain MR imaging features may be highly correlated with tumor content in a particular patient (or subset of patients), other patients may exhibit weaker or even opposite correlations that mask the overall effect in group analysis. We recognize that some of these individual plots may have small sample sizes that limit the statistical confidence of the correlation coefficients. Therefore, the individual plot coefficient values themselves should be viewed with this limitation in mind. At the same time, the directionality of the individual correlation plots (ie, positive-versus-negative) appears to show distinct population trends, and we intend to use the results here to illustrate some of the interpatient variabilities that may exist between TCD and imaging measurements. These interpatient variabilities motivate the use of the transfer learning approach detailed in the next section.

Transfer Learning

On the basis of the results from univariate analysis and individual scatterplots, we prioritized rCBV for training of TL and constrained knowledge transfer from patients with an arbitrary threshold for correlation between rCBV and TCD ($r \geq 0.10$). By means of LOOCV, the TL model with rCBV as the sole model predictor improved the correlation between predicted-versus-actual TCD ($r = 0.53$, $P < .001$, $n = 82$), compared with the generalized OMFA model, which also used rCBV as the sole predictor ($r = 0.27$ using LOOCV) (Table 2). We then quantified incremental gains from adding other MR imaging contrasts to the rCBV-based TL model. As shown in Table 2, individualized transfer

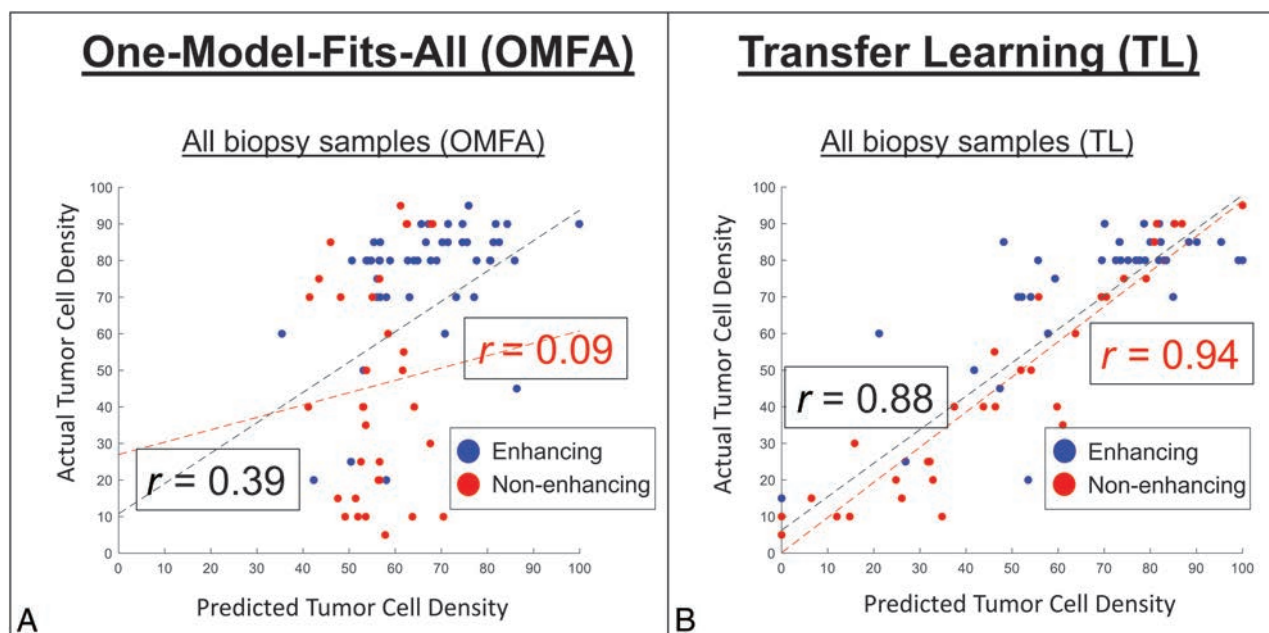


FIG 1. Transfer learning improves predictive performance for quantifying TCD. Scatterplots show the correlations between actual (y-axis) versus-model-predicted (x-axis) tumor cell densities using multivariable modeling (rCBV, T1 + C, MD, and FA) and the generalized (A) OMFA versus the individualized (B) TL approaches. Blue and red dots denote biopsy samples from enhancing ($n = 49$) and nonenhancing ($n = 33$) regions, respectively. Regression lines and Pearson correlations (r) are shown for all 82 samples (black lines and text) versus only the 33 nonenhancing samples (red lines and text). Correlations using TL are significantly higher compared with the generalized OMFA approach.

learning models consistently improved correlation coefficients and mean error rates compared with corresponding generalized OMFA models. Figure 1 shows the scatterplots for actual-versus-predicted TCD using the highest performing TL model, which incorporated rCBV, T1 + C, FA, and MD as model predictors. After LOOCV, this model achieved a Pearson correlation of $r = 0.88$ ($P < .001$) across all samples ($n = 82$), which further increased among nonenhancing T2/FLAIR samples alone ($r = 0.94$, $P < .001$, $n = 33$). By comparison, the generalized OMFA approach, using the same model predictors, achieved much lower correlation coefficients for all samples ($r = 0.39$, $n = 82$) and nonenhancing samples alone ($r = 0.09$, $n = 33$). As shown in Fig 2, the TL model can be used to generate color overlay maps of predicted TCD that correspond with actual TCD from spatially matched biopsies throughout different nonenhancing regions in the same GBM tumor.

DISCUSSION

In this study, we correlated a panel of MR imaging features with regional tumor cell density using image-guided biopsies and spatially matched MR imaging measurements. In particular, the advanced MR imaging features (ie, rCBV, MD, FA) have been widely published for their potential to characterize TCD within the nonenhancing tumor segment of GBM. On univariate analysis, we found that rCBV was the only advanced MR imaging feature to significantly correlate with TCD after correcting for multiple comparisons ($P = .01$) (besides the conventional MR imaging feature T1 + C). This low-moderate positive correlation ($r = 0.33$, $P < .001$) remains concordant with other published studies on rCBV,^{18–20} which have all consistently reported positive correlations with TCD. In contrast, our analysis showed no significant correlation for MD. The correlation for FA ($r = -0.24$)

showed a P value of .06 after correcting for multiple comparisons, which trends toward significance. These results are not entirely discordant with the literature because past studies have lacked general consensus on how MD and FA correlate with TCD. For instance, Stadlbauer et al¹¹ and Price et al⁵ reported negative correlations between FA and TCD, while Beppu et al²¹ reported positive correlations. Similarly, Ellingson et al⁹ and Chang et al¹⁶ reported negative correlations between MD and TCD, while Stadlbauer et al¹¹ reported positive correlations.

We hypothesized that the correlations observed in our study (as well as in the literature) may be impacted by interpatient variability in how MR imaging signal relates to TCD. To gain insight to this variability, we analyzed individualized plots of MR imaging signal versus tumor content within our cohort. In keeping with trends in the literature, rCBV correlations were highly consistent with regard to direction, with 92.5% of patients showing positive correlations. We did, however, observe a wide range of correlation strengths (range, $r = +0.07$ to $+0.95$), which explains the low-moderate group correlation. In contrast to rCBV, we observed highly variable correlations for both FA (range, $r = -0.75$ to $+0.78$) and MD (range, $r = -0.96$ to $+0.78$), with conflicting directions across patients. These discrepancies echo the discordance among studies in the literature and underscore the challenge of using a one-model-fits-all approach to generalize heterogeneity across patients.

TL addresses this challenge by estimating models for each patient by iteratively identifying patient similarity and leveraging it for robust model building using a Bayesian framework.³³ Our results strongly suggest that TL should prioritize rCBV, given its high interpatient consistency and statistically significant correlations in univariate analysis. This assertion is supported further by the consistency of reported rCBV correlations in the litera-

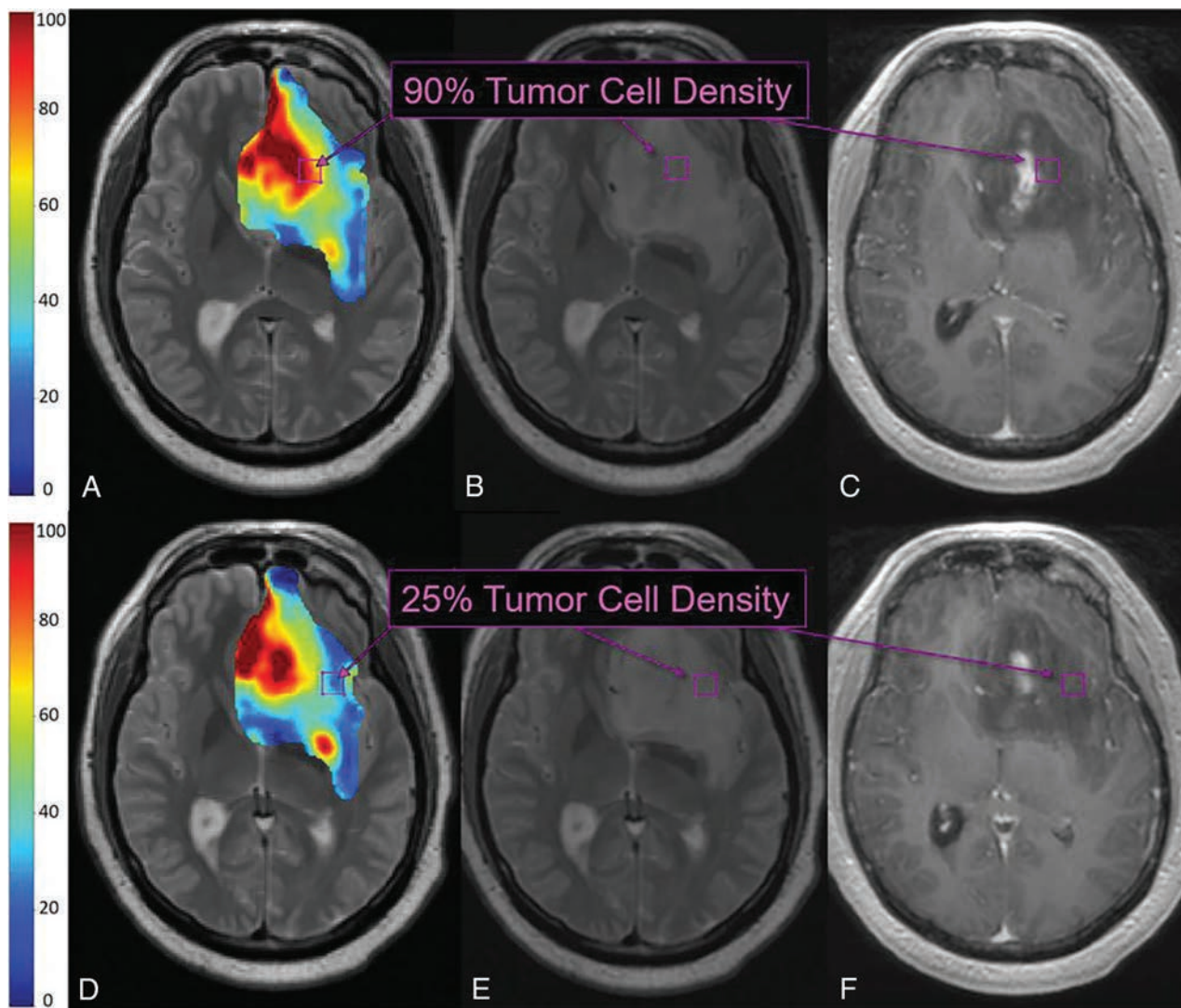


FIG 2. TL maps and multiple biopsies in a 71-year-old patient with primary GBM. TL-based color map overlay on a T2-weighted image (A) shows predicted regional TCD ranging from 0% to 100% (blue to red) throughout the segmented tumor region (based on the T2-weighted signal abnormality). Histologic analysis of the top biopsy (purple boxes B and C) yielded 90% TCD, corresponding to red regions of high TL-predicted TCD (purple box, A). TL-based color map (D) from a more caudal T2-weighted slice shows blue regions of low TL-predicted TCD (blue/green, purple box), corresponding to 25% TCD on histologic analysis of the bottom biopsy (purple boxes, E and F).

ture.^{18–20} The application of TL to an rCBV-based model predictor significantly improved correlation ($r = 0.53$) compared with the one-model-fits-all approach ($r = 0.27$). TL further improved performance when combining rCBV with other MR imaging features in a multivariate fashion ($r = 0.88$), particularly for the nonenhancing T2/FLAIR samples ($r = 0.94$). This represents a substantial increase in performance compared with the conventional one-model-fits-all approach in our study ($r = 0.30$) (Table 2) and those previously published.^{16,22}

Of note, the TL method presented here requires MR imaging and histologic input from at least 2 image-localized biopsies (per patient) to make predictive inferences for the remaining “unknown” (ie, unbiopsied) regions throughout each patient’s tumor. Our analysis shows that these patient-specific inputs dramatically increase predictive performance for quantifying regional TCD on an individualized basis. While retrospective in nature, these results offer proof of concept that TL can help prospectively guide surgical biopsy and/or resection

in a patient-specific manner. As part of our intraoperative workflow, we are currently integrating real-time neuropathologists’ estimates of TCD (adding ~2–3 minutes of analysis per sample) from frozen surgical specimens to support prospective TL-based neurosurgical guidance. These real-time estimates allow active updating of the TL model intraoperatively, accomplished in <5 minutes given standard computing hardware, to guide surgical targeting for the remaining unresected tumor regions. Future prospective studies in a larger cohort of patients will also allow us to evaluate how the tissue-sampling methodology (eg, number and distribution of biopsy locations) in individual patients might be optimized to improve predictive accuracy and model uncertainty. Additionally, individualized TL-based models can also guide dosimetric radiation planning in the postoperative setting. By delineating regional populations of residual nonenhancing tumor in the otherwise nonspecific T2/FLAIR segment, individualized TL-based maps will facilitate more nuanced radiation-planning

strategies to prescribe higher doses with increasing TCD while sparing the dose to normal nontumoral brain.

We recognize several limitations to this study. First, like all other previously published reports, our study lacks a dedicated validation set. In fact, the conventional approach in the literature has been to report correlation coefficients from training data alone, which are prone to overfitting.^{3,5,9,11,15-22} By comparison, our study is the first to use more rigorous cross-validation testing (through LOOCV) to offset potential risks of overfitting, whereby each biopsy sample in our cohort is treated as an “unseen” or unknown case to test predictive performance.³ While cross-validation strengthens our confidence in these initial findings, prospective validation in future studies will ultimately be needed. Second, we have used neuropathologists’ estimates of TCD as the benchmark measure of tumor content. We believe that this represents a more clinically relevant metric compared with total cell density, which can comprise both tumoral and nontumoral components (eg, astrocytes, microglia).^{9,16}

Nonetheless, we are currently pursuing automated quantification of cellular density in our histologic samples.¹⁶ This type of standardization will help facilitate TL implementation across different institutions in the future. Finally, we recognize that image distortions and brain shift following craniotomy could lead to misregistration errors. To compensate, neurosurgeons used small craniotomy sizes to minimize brain shift and also visually validated stereotactic image location with intracranial neuroanatomic landmarks to help correct for random brain shifts. Rigid-body coregistration of multiparametric imaging also helped reduce possible geometric distortions.^{2,3,12,18} Overall, our experience suggests that combined misregistration is approximately 1–2 mm from both brain shift and registration techniques, which is similar to that from previous studies using stereotactic needle biopsy.¹¹ To help minimize the effects of these potential misregistration errors, we selected larger ROI sizes relative to the expected biopsy tissue volumes. Thus, any minor shifts in the recorded biopsy locations (at the time of tissue sampling) would, in all likelihood, remain colocalized to the specified ROI.

CONCLUSIONS

We present an MR imaging–based transfer learning approach that optimizes individualized models of TCD and extent for patients with GBM. These models show particularly high predictive performance for the nonenhancing infiltrative tumor segment that is problematic to the diagnosis and treatment of GBM. Particularly, relevant clinical applications include surgical guidance for the extent of resection and dosimetric radiation targeting of nonenhancing residual tumor during postoperative adjuvant care.

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REFERENCES

1. Sarkaria JN, Hu LS, Parney IF, et al. Is the blood-brain barrier really disrupted in all glioblastomas? A critical assessment of existing clinical data. *Neuro Oncol* 2018;20:184–91 [CrossRef Medline](#)
2. Barajas RF Jr, Hodgson JG, Chang JS, et al. Glioblastoma multiforme regional genetic and cellular expression patterns: influence on anatomic and physiologic MR imaging. *Radiology* 2010;254:564–76 [CrossRef Medline](#)
3. Hu LS, Ning S, Eschbacher JM, et al. Multi-parametric MRI and texture analysis to visualize spatial histologic heterogeneity and tumor extent in glioblastoma. *PLoS One* 2015;10:e0141506 [CrossRef Medline](#)
4. Baldock AL, Ahn S, Rockne R1, et al. Patient-specific metrics of invasiveness reveal significant prognostic benefit of resection in a predictable subset of gliomas. *PLoS One* 2014;9:e99057 [CrossRef Medline](#)
5. Price SJ, Jena R, Burnet NG, et al. Improved delineation of glioma margins and regions of infiltration with the use of diffusion tensor imaging: an image-guided biopsy study. *AJNR Am J Neuroradiol* 2006;27:1969–74 [Medline](#)
6. Hu LS, Ning S, Eschbacher JM, et al. Radiogenomics to characterize regional genetic heterogeneity in glioblastoma. *Neuro Oncol* 2017; 19:128–37 [CrossRef Medline](#)
7. Corwin D, Holdsworth C, Rockne RC, et al. Toward patient-specific, biologically optimized radiation therapy plans for the treatment of glioblastoma. *PLoS One* 2013;8:e79115 [CrossRef Medline](#)
8. Pafundi DH, Laack NN, Youland RS, et al. Biopsy validation of 18F-DOPA PET and biodistribution in gliomas for neurosurgical planning and radiotherapy target delineation: results of a prospective pilot study. *Neuro Oncol* 2013;15:1058–67 [CrossRef Medline](#)
9. Ellingson BM, Malkin MG, Rand SD, et al. Validation of functional diffusion maps (fDMs) as a biomarker for human glioma cellularity. *J Magn Reson Imaging* 2010;31:538–48 [CrossRef Medline](#)
10. Mohsen LA, Shi V, Jena R., et al. Diffusion tensor invasive phenotypes can predict progression-free survival in glioblastomas. *Br J Neurosurg* 2013;27:436–41 [CrossRef Medline](#)
11. Stadlbauer A, Ganslandt O, Buslei R. et al. Gliomas: histopathologic evaluation of changes in directionality and magnitude of water diffusion at diffusion-tensor MR imaging. *Radiology* 2006;240:803–10 [CrossRef Medline](#)
12. Hu LS, Eschbacher JM, Dueck AC, et al. Correlations between perfusion MR imaging cerebral blood volume, microvessel quantification, and clinical outcome using stereotactic analysis in recurrent high-grade glioma. *AJNR Am J Neuroradiol* 2012;33:69–76 [CrossRef Medline](#)
13. Hu LS, Baxter LC, Smith KA, et al. Relative cerebral blood volume values to differentiate high-grade glioma recurrence from posttreatment

- radiation effect: direct correlation between image-guided tissue histopathology and localized dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging measurements. *AJNR Am J Neuroradiol* 2009;30:552–58 [CrossRef Medline](#)
14. Hu LS, Eschbacher JM, Heiserman JE, et al. Reevaluating the imaging definition of tumor progression: perfusion MRI quantifies recurrent glioblastoma tumor fraction, pseudoprogression, and radiation necrosis to predict survival. *Neuro Oncol* 2012;14:919–30 [CrossRef Medline](#)
 15. LaViolette PS, Mickevicius NJ, Cochran EJ, et al. Precise ex vivo histological validation of heightened cellularity and diffusion-restricted necrosis in regions of dark apparent diffusion coefficient in 7 cases of high-grade glioma. *Neuro Oncol* 2014;16:1599–1606 [CrossRef Medline](#)
 16. Chang PD, Malone HR, Bowden SG, et al. A multiparametric model for mapping cellularity in glioblastoma using radiographically localized biopsies. *AJNR Am J Neuroradiol* 2017;38:890–98 [CrossRef Medline](#)
 17. Eidel O, Neumann JO, Burth S, et al. Automatic analysis of cellularity in glioblastoma and correlation with ADC using trajectory analysis and automatic nuclei counting. *PLoS One* 2016;11:e0160250 [CrossRef Medline](#)
 18. Barajas RF Jr, Phillips JJ, Parvataneni R, et al. Regional variation in histopathologic features of tumor specimens from treatment-naïve glioblastoma correlates with anatomic and physiologic MR imaging. *Neuro Oncol* 2012;14:942–54 [CrossRef Medline](#)
 19. Sadeghi N, D'Haene N, Decaestecker C, et al. Apparent diffusion coefficient and cerebral blood volume in brain gliomas: relation to tumor cell density and tumor microvessel density based on stereotactic biopsies. *AJNR Am J Neuroradiol* 2008;29:476–82 [CrossRef Medline](#)
 20. Price SJ, Green HA, Dean AF, et al. Correlation of MR relative cerebral blood volume measurements with cellular density and proliferation in high-grade gliomas: an image-guided biopsy study. *AJNR Am J Neuroradiol* 2011;32:501–06 [CrossRef Medline](#)
 21. Beppu T, Inoue T, Shibata Y, et al. Fractional anisotropy value by diffusion tensor magnetic resonance imaging as a predictor of cell density and proliferation activity of glioblastomas. *Surg Neurol* 2005;63:56–61; discussion 61 [CrossRef Medline](#)
 22. Durst CR, Raghavan P, Shaffrey ME, et al. Multimodal MR imaging model to predict tumor infiltration in patients with gliomas. *Neuroradiology* 2014;56:107–15 [CrossRef Medline](#)
 23. Semmineh NB, Xu J, Skinner JT, et al. Assessing tumor cytoarchitecture using multiecho DSC-MRI derived measures of the transverse relaxivity at tracer equilibrium (TRATE). *Magn Reson Med* 2015;74:772–84 [CrossRef Medline](#)
 24. Lowekamp BC, Chen DT, Ibáñez L, et al. The design of simple eITK. *Front Neuroinform* 2013;7:45 [CrossRef](#)
 25. Sethian JA. *Level Set Methods and Fast Marching Methods: Evolving Interfaces in Computational Geometry, Fluid Mechanics, Computer Vision, and Materials Science*. New York: Cambridge University Press, 1999
 26. Tustison NJ, Avants BB, Cook PA, et al. N4ITK: improved N3 bias correction. *IEEE Trans Med Imaging* 2010;29:1310–20 [CrossRef Medline](#)
 27. Mitchell JR, Jones C, Karlik SJ, et al. MR multispectral analysis of multiple sclerosis lesions. *J Magn Reson Imaging* 1997; 7:499–511 [CrossRef Medline](#)
 28. Hu LS, Kelm Z, Korfiatis P, et al. Impact of software modeling on the accuracy of perfusion MRI in glioma. *AJNR Am J Neuroradiol* 2015; 36:2242–49 [CrossRef Medline](#)
 29. Boxerman JL, Schmainda KM, Weisskoff RM. Relative cerebral blood volume maps corrected for contrast agent extravasation significantly correlate with glioma tumor grade, whereas uncorrected maps do not. *AJNR Am J Neuroradiol* 2006;27:859–67 [Medline](#)
 30. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society Series B (Methodological)* 1995;57:289–300 [CrossRef](#)
 31. Weiss K, Khoshgoftaar TM, Wang D. A survey of transfer learning. *J Big Data* 2016;3:9
 32. Pan SJ, Yang Q. A survey on transfer learning. *IEEE Trans Knowl Data Eng* 2009;22:1345–59
 33. Zou N, Baydogan M, Zhu Y, et al. A transfer learning approach for predictive modeling of degenerate biological systems. *Technometrics* 2015;57:362–73 [CrossRef Medline](#)
 34. Brown R, Zlatescu M, Sijben A, et al. The use of magnetic resonance imaging to noninvasively detect genetic signatures in oligodendroglioma. *Clin Cancer Res* 2008;14:2357–62 [CrossRef Medline](#)
 35. Dalrymple SJ, Parisi JE, Roche PC, et al. Changes in proliferating cell nuclear antigen expression in glioblastoma multiforme cells along a stereotactic biopsy trajectory. *Neurosurgery* 1994;35:1036–44; discussion 1044–55 [CrossRef Medline](#)

Neuroimaging-Based Classification Algorithm for Predicting 1p/19q-Codeletion Status in *IDH*-Mutant Lower Grade Gliomas

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ABSTRACT

BACKGROUND AND PURPOSE: *Isocitrate dehydrogenase* (*IDH*)-mutant lower grade gliomas are classified as oligodendrogliomas or diffuse astrocytomas based on 1p/19q-codeletion status. We aimed to test and validate neuroradiologists' performances in predicting the codeletion status of *IDH*-mutant lower grade gliomas based on simple neuroimaging metrics.

MATERIALS AND METHODS: One hundred two *IDH*-mutant lower grade gliomas with preoperative MR imaging and known 1p/19q status from The Cancer Genome Atlas composed a training dataset. Two neuroradiologists in consensus analyzed the training dataset for various imaging features: tumor texture, margins, cortical infiltration, T2-FLAIR mismatch, tumor cyst, T2* susceptibility, hydrocephalus, midline shift, maximum dimension, primary lobe, necrosis, enhancement, edema, and gliomatosis. Statistical analysis of the training data produced a multivariate classification model for codeletion prediction based on a subset of MR imaging features and patient age. To validate the classification model, 2 different independent neuroradiologists analyzed a separate cohort of 106 institutional *IDH*-mutant lower grade gliomas.

RESULTS: Training dataset analysis produced a 2-step classification algorithm with 86.3% codeletion prediction accuracy, based on the following: 1) the presence of the T2-FLAIR mismatch sign, which was 100% predictive of noncodeleted lower grade gliomas, ($n = 21$); and 2) a logistic regression model based on texture, patient age, T2* susceptibility, primary lobe, and hydrocephalus. Independent validation of the classification algorithm rendered codeletion prediction accuracies of 81.1% and 79.2% in 2 independent readers. The metrics used in the algorithm were associated with moderate-substantial interreader agreement ($\kappa = 0.56-0.79$).

CONCLUSIONS: We have validated a classification algorithm based on simple, reproducible neuroimaging metrics and patient age that demonstrates a moderate prediction accuracy of 1p/19q-codeletion status among *IDH*-mutant lower grade gliomas.

ABBREVIATIONS: *IDH* = *isocitrate dehydrogenase*; *IDH*mut-Code = 1p/19q-codeleted *IDH*-mutant LGGs, oligodendrogliomas; *IDH*mut-Noncode = noncodeleted *IDH*-mutant LGGs, astrocytomas; LGG = lower grade glioma; MLR = multivariate logistic regression; PPV = positive predictive value; TCGA = The Cancer Genome Atlas; TCIA = The Cancer Imaging Archive; WHO = World Health Organization

The revised World Health Organization (WHO) 2016 classification of diffuse gliomas integrates *isocitrate dehydrogenase* (*IDH*) gene status and whole-arm codeletion of chromosome arms 1p and 19q with histologic findings to classify grades II and III diffuse lower grade gliomas (LGGs).^{1,2} More than 80% of LGGs are *IDH*-mutant; of those, 37%–50% carry the 1p/19q

codeletion.^{3,4} The 1p/19q-codeleted *IDH*-mutant LGGs (oligodendrogliomas; *IDH*mut-Code) show better overall survival compared with noncodeleted *IDH*-mutant LGGs (astrocytomas; *IDH*mut-Noncode) and are more sensitive to adjuvant chemotherapy with procarbazine, lomustine, and vincristine.⁵⁻⁷

The integration of genomic data in the updated WHO classification of LGGs has accelerated efforts to noninvasively predict genetic signatures of diffuse gliomas using neuroimaging techniques. While numerous studies have identified neuroimaging features that correlate with 1p/19q-codeletion status in LGG subtypes,⁸⁻²⁸ many were performed before the 2016 WHO update,

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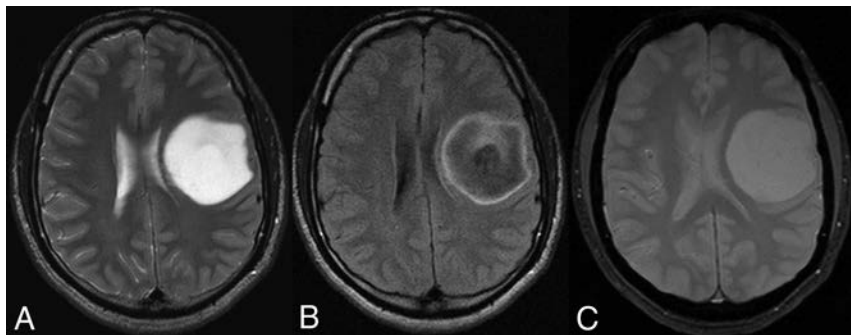


FIG 1. A 38-year-old man with a left frontal lobe diffuse astrocytoma, *IDH*-mutant and 1p/19q-noncodeleted, showing characteristic imaging features. **A**, On T2WI, the mass is homogeneously hyperintense, sharply margined, and without significant cortical infiltration. **B**, FLAIR sequence shows central suppression of signal compared with the T2WI, except for a peripheral rim (ie, T2-FLAIR mismatch sign). **C**, T2*WI shows lack of susceptibility blooming.

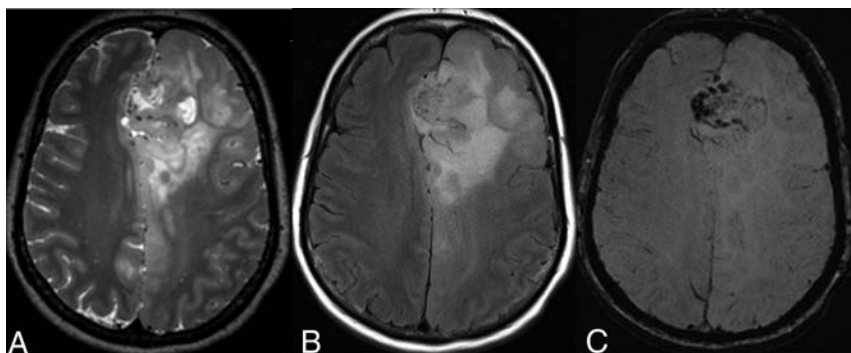


FIG 2. A 54-year-old woman with a left frontal lobe oligodendroglioma, *IDH*-mutant and 1p/19q-codeleted, showing characteristic imaging features. **A** and **B**, T2WI and FLAIR demonstrate a heterogeneous and poorly margined mass with significant cortical infiltration and no T2-FLAIR mismatch sign. **C**, T2*WI shows regions of striking susceptibility blooming.

affecting their patient-selection process (ie, no accounting for *IDH* status). Moreover, these studies have applied variable imaging metrics and neuroimaging analysis, rendering it difficult to assess the relative and combined diagnostic performance of the various neuroimaging metrics reported to be associated with 1p/19q-codeletion status. Finally, simple metrics extrinsic to the glioma (eg, hydrocephalus, midline shift) have not been tested. The purpose of our study was to test and validate the combined accuracy of simple neuroimaging features to predict 1p/19q-codeletion status among cohorts of *IDH*-mutant LGGs.

MATERIALS AND METHODS

This was a Health Insurance Portability and Accountability Act-compliant retrospective study conducted with the University of Virginia Health System institutional review board approval.

The study consisted of 2 phases. First, analysis of a training dataset yielded a multivariate classification algorithm for predicting 1p/19q-codeletion status. Second, the classification algorithm was validated using a separate dataset of cases and separate neuroradiologist readers.

Training Dataset Analysis

The cases composing the training dataset were accrued from The Cancer Imaging Archive (TCIA), an LGG on-line data base.²⁹ TCIA data base houses MR imaging data for 199 LGGs, with molecular data (including *IDH* and 1p/19q statuses) available

through The Cancer Genome Atlas (TCGA). The inclusion criteria were the following: 1) LGG with histopathologic assessment and grade, 2) LGG with an *IDH* mutation, 3) LGG with known 1p/19q-codeletion status, and 4) preoperative MR imaging (or MR imaging after a small-needle biopsy) containing imaging sequences relevant to the below-described neuroimaging classification. *IDH* wild-type glioma ($n = 42$), cases with incomplete molecular/pathologic data ($n = 2$), and cases with insufficient MR imaging data ($n = 53$) were excluded from the study, rendering 102 *IDH*-mutant LGGs included in the training dataset.

Two neuroradiologists, with 5 and 13 years of experience, blinded to the 1p/19q-codeletion status, analyzed the MR images from the training dataset in consensus. They measured 14 neuroimaging metrics: 1) primary lobe: yes/no centered on frontal lobe; 2) texture: more or less than 75% of the tumor showing homogeneous signal intensity on T1WI/T2WI; 3) margins: more or less than 75% of the tumor showing sharp/circumscribed margins; 4) T2-FLAIR mismatch sign: the presence or absence of complete/near-complete hyperintense signal on T2WI and relatively hypointense signal on FLAIR except for a hyperintense peripheral rim¹⁹; 5) T2* susceptibility blooming: present or absent; 6) contrast enhancement: present or absent; 7) cysts: present or absent; 8) necrosis: present or absent; 9) maximum tumor diameter (centimeter); 10) cortical infiltration: present or absent; 11) peritumoral edema: present or absent; 12) gliomatosis: yes/no involvement of ≥ 3 lobes; 13) midline shift (centimeter); and 14) hydrocephalus: present or absent. Figures 1 and 2 show the characteristic imaging appearance of *IDH*mut-Noncodel and *IDH*mut-Codel LGGs, respectively, including a description of several of the above imaging metrics.

Univariate and multivariate logistic regression analysis of the MR imaging characteristics and patient age for predicting the 1p/19q-codeletion status was undertaken. On the basis of these results, a classification algorithm for 1p/19q prediction was developed.

Validation Analysis

To validate the classification algorithm developed with the training dataset, two new neuroradiologists analyzed a separate institutional cohort of *IDH*-mutant LGGs. The same selection criteria used for the training dataset were applied, and 106 *IDH*-mutant LGGs consecutively accrued from an institutional neuro-oncology/neuroradiology data base between 2010 and 2017 composed the validation cohort. The neuroradiologists (reader A with 3

years of experience, reader B with 19 years of experience), blinded to the 1p/19q-codeletion status, independently reviewed the MR images of these cases. The readers analyzed the MR imaging metrics relevant to the classification model with the same criteria used for the training dataset. Interreader agreement for the neuroimaging metrics and independent reader performance in predicting 1p/19q-codeletion status were determined.

Neuropathology

For TCIA/TCGA cohort, histopathologic assignment and molecular classification were derived from supplemental material in Ceccarelli et al,³⁰ in 2016, and included somatic mutation analysis of *IDH1* or *IDH2* from whole-exome sequencing and codeletion of chromosome arms 1p and 19q from the SNP Array 6.0 (Affymetrix, Santa Clara, California).

For the validation cohort, the *IDH* and 1p/19q statuses were retrieved from the electronic medical record. Both markers were tested in the Clinical Laboratory Improvement Amendments–certified molecular pathology laboratory at our institution. *IDH* mutation status was first determined by immunohistochemistry using an *IDH1* R132H mutant-specific clinically validated antibody (DIA-H09; Dianova GmbH, Hamburg, Germany).^{31,32} In immunohistochemistry cases negative for *IDH1* R132H mutation, *IDH* mutation status was assessed by the clinically validated DNA pyrosequencing assay.³³ 1p/19q status was determined by fluorescence in situ hybridization on paraffin-embedded tissue, using human probes localizing 1p, 1q, 19p, and 19q (Locus Specific Identifier 1p36/1q25 and 19p13/19q13 Dual-Color Probes; Vysis, Downers Grove, Illinois).

Statistical Analysis

The following is an abbreviated description of the statistical methodology; a full description is included in the On-line Appendix.

Training Dataset. Univariate logistic regression analysis of the 14 MR imaging characteristics and patient age for predicting 1p/19q-codeletion status was undertaken for the TCIA/TCGA–derived training dataset. Because the presence of the T2-FLAIR mismatch sign showed 100% positive predictive value (PPV) for the *IDH*mut-Noncodel molecular subtype (see Results below), these cases were segregated from the cohort. A multivariate logistic regression using the remaining aforementioned predictor variables was applied in a 2-step analytic process to the remaining cases in the cohort (either negative for the T2-FLAIR mismatch sign or had no T2-FLAIR match sign information available). First, a full model was constructed with the goal of identifying predictor variables that contribute unique information about 1p/19q-codeletion status based on a set of type III Wald χ^2 tests at the $\alpha = .10$ threshold. Second, a reduced model was constructed using only the unique predictors of 1p/19q-codeletion status. The regression equation of the reduced multivariate model was then used to compute the predicted probability for codeletion status, and these predicted probabilities were used to derive a classification algorithm rule. The predicted probability threshold for the classification rule of the algorithm was derived by identifying the predicted probability threshold that produced the largest Youden J statistic ($J = \text{Diagnostic Sensitivity} + \text{Diagnostic Specificity} - 1$).³⁴

Validation Dataset. Interreader agreement for readers A and B

was evaluated via the unweighted κ statistic sign. Cases that were deemed by the independent readers to be positive for the T2-FLAIR mismatch sign were included as “true-negatives” (ie, 1p/19q noncodeleted), and the training set–derived reduced multivariate logistic regression model equation was applied to the reader data in cases negative for T2-FLAIR mismatch. Cases could be classified as either 1p/19q codeleted or noncodeleted based on whether the predicted probability was greater than, equal to, or less than the established classification algorithm predicted probability threshold, respectively. The overall diagnostic classification performance was assessed per reader.

Statistical Software. The statistical software package Spotfire S+, Version 8.2 (TIBCO, Palo Alto, California) was used to conduct the multivariate logistic regression (MLR) analyses, and the pROC package of R (<http://www.r-project.org/>) was used to conduct the diagnostic classification performance analyses.^{35,36}

RESULTS

Training Dataset Analysis

Of the 102 patients with *IDH*-mutant LGGs in the training dataset, 51% were women ($n = 52$) and 49% were men ($n = 50$). The median age was 41 years (range, 20.0–75.0 years; interquartile range, 33.0–53.0 years). Of the 102 LGGs, 62.7% ($n = 64$) were *IDH*mut-Noncodel and 37.3% ($n = 38$) were *IDH*mut-Codel, 57.8% ($n = 59$) were WHO grade II, and 42.2% ($n = 43$) were WHO grade III.

Univariate Analyses. Univariate logistic regression analyses showed that several metrics were significantly associated with 1p/19q-codeletion status, including texture (OR, 12.33; 95% CI, 4.66–31.58; $P < .001$), T2* susceptibility blooming (OR, 6.92; 95% CI, 2.04–23.49; $P = .002$), T2-FLAIR mismatch sign (OR, 22.50; 95% CI, 6.26– ∞ ; $P < .001$), location (OR, 5.68; 95% CI, 2.08–15.44; $P = .001$), midline shift (OR, 4.27; 95% CI, 1.49–12.23; $P = .027$), and patient age (OR, 3.38; 95% CI, 1.71–6.71; $P < .001$) (Table 1). Notably, the T2-FLAIR mismatch sign showed PPV = 100% and negative predictive value = 44% for the *IDH*mut-Noncodel subtype. In 100% of cases ($n = 21$) in which the T2-FLAIR mismatch sign was present, the glioma was 1p/19q-noncodeleted. Therefore, the cases in which the T2-FLAIR mismatch sign was present were segregated from the cohort, and a multivariate logistic regression analysis was undertaken in the remaining cases ($n = 81$).

Multivariate Analyses. On the basis of a full multivariate logistic regression model analysis, tumor texture ($P < .001$), patient age ($P = .010$), T2* susceptibility blooming ($P = .022$), primary lobe ($P = .039$), and hydrocephalus ($P = .052$) were determined to be uniquely associated with 1p/19q-codeletion status, and these metrics were used to create a reduced multivariate logistic regression model. A predicted probability threshold of 0.40 resulted in the largest Youden J statistic for the reduced multivariate logistic regression model. Finally, a 2-step classification algorithm was created on the basis of the following: 1) the presence of the T2-FLAIR mismatch sign; and 2) a reduced multivariate logistic regression model, with application of the Youden J statistic–derived predicted probability threshold of 0.40 (Fig 3). The 2-step classification algorithm demonstrated 86.3% accuracy in predicting the

Table 1: Univariate logistic regression analyses for predicting 1p/19q codeletion among the training dataset

Predictor	Ratio	Odds	
		Ratio (95% CI)	P Value
Maximum diameter (cm)	1st Quartile: 3rd quartile	1.33 (0.70–2.49)	.381
Margins	Irregular: sharp	1.04 (0.47–2.33)	.917
Texture	Homogeneous (<75%): homogeneous (>75%)	12.33 (4.66–31.58)	<.001 ^a
Peritumoral edema	Yes: no	1.42 (0.62–3.23)	.973
Hydrocephalus	No: yes	2.32 (0.88–6.11)	.089
Midline shift (cm) ^b	1st Quartile: 3rd quartile	4.27 (1.49–12.23)	.027 ^a
Enhancement	Yes: no	1.28 (0.57–2.86)	.555
Necrosis	Yes: no	2.18 (0.61–7.69)	.228
T2* blooming	Yes: no	6.92 (2.04–23.49)	.002 ^a
Cortical infiltration	Yes: no	2.02 (0.67–6.10)	.212
Cyst	No: yes	1.18 (0.48–2.91)	.715
T2 FLAIR mismatch sign ^c	No: yes	22.50 (6.26–∞)	<.001 ^a
Gliomatosis	Yes: no	1.13 (0.18–7.08)	.896
Primary lobe	Frontal: nonfrontal	5.68 (2.08–15.44)	.001 ^a
Age	3rd Quartile: 1st quartile	3.38 (1.71–6.71)	<.001 ^a
Sex	Female: male	1.55 (0.69–3.50)	.283

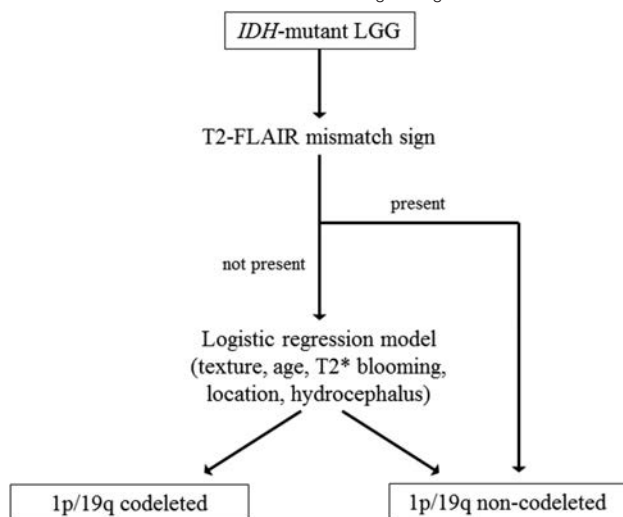
^a Significant.^b Analyzed as a restricted cubic spline function of the predictor.^c Median unbiased estimate derived with exact logistic regression.

FIG 3. Classification algorithm for 1p/19q-codeletion status in *IDH*-mutant LGGs, derived from an analysis of the TCGA/TCIA training cohort. The first step of the algorithm is an assessment of the T2-FLAIR mismatch sign; when present, it indicates, with high certainty, the *IDH*-mutant 1p/19q-noncodeleted subtype. When the T2-FLAIR mismatch sign is absent (or unavailable), a multivariate logistic regression model based on tumor texture, patient age, T2* blooming, tumor location, and hydrocephalus is applied. The equation for the logistic regression model is the following: $p \text{ codeleted} = \exp[(X\beta) / (1 + \exp(X\beta))]$, where $X\beta = -4.8834 + 2.7842 \times (\text{texture} < 75\% \text{ homogeneous}) + 0.0587 \times (\text{patient age}) + 3.1948 \times (\text{T2* susceptibility blooming present}) + 1.6646 \times (\text{primary lobe} = \text{frontal}) - 3.4496 \times (\text{hydrocephalus} = \text{present})$. A predicted probability threshold of 0.40 was established for the logistic regression model, based on the Youden J statistic. Cases were classified as either 1p/19q codeleted or non-codeleted based on whether their predicted probability was $\geq$ or $<$ 0.40, respectively.

1p/19q-codeletion status among the *IDH*-mutant LGGs in the training dataset (Table 2).

Validation Analysis

The validation dataset accrued from our institution was composed of 106 patients with *IDH*-mutant LGGs, of which 50% were

female ($n = 53$). The median age was 38.5 years (range, 17.0–70.0 years; interquartile range, 32.0–50.8 years). Of the 106 LGGs, 47.2% ($n = 50$) were *IDH*mut-Noncodel, 52.8% ($n = 56$) were *IDH*mut-Codel, 70.8% ($n = 75$) were WHO grade II, and 29.2% ($n = 31$) were WHO grade III.

Readers A and B demonstrated moderate interreader agreement with respect to the T2-FLAIR mismatch sign ($\kappa = 0.56$; 95% CI, 0.34–0.77) and substantial interreader agreement with respect to tumor texture ($\kappa = 0.69$; 95% CI, 0.56–0.83), T2* blooming ($\kappa = 0.74$; 95% CI, 0.58–0.90), primary lobe ($\kappa = 0.79$; 95% CI, 0.68–0.89), and hydrocephalus ($\kappa = 0.72$; 95% CI, 0.51–0.93).

The performance of the 2-step classification algorithm (Fig 3) was assessed using the independently collected data

from readers A and B. Reader A identified the T2-FLAIR mismatch sign in 19 cases; thus, the remaining 87 cases were assessed by applying the reduced logistic regression model based on texture, patient age, T2* susceptibility blooming, primary lobe, and hydrocephalus. Reader B identified the T2-FLAIR mismatch sign in 16 cases, with the remaining 90 cases assessed by applying the reduced logistic regression model. The 2-step classification algorithm for predicting 1p/19q-codeletion status had 81.1% accuracy for reader A and 79.2% accuracy for reader B (Table 3). Notably, the T2-FLAIR mismatch sign demonstrated PPV = 100% for predicting the *IDH*mut-Noncodel subtype for both independent readers.

DISCUSSION

Prior studies have reported multiple morphologic imaging features in LGGs that were associated with 1p/19q-codeletion status.^{8–28} *IDH*mut-Codel LGGs commonly localize to the frontal lobe and typically have indistinct borders, calcification, and tumor heterogeneity. *IDH*mut-Noncodel LGGs are more typically homogeneous, circumscribed, lack calcification, and more frequently localize to the insula and temporal lobe. Before the 2016 WHO classification update, studies assessing neuroimaging associations with 1p/19q-codeletion status frequently limited their analysis to histologically defined oligodendrogliomas or oligoastrocytomas.^{8–15} The impact of excluding diffuse astrocytomas from these earlier studies is unknown. Although recent studies have adopted the 2016 WHO classification scheme, many have limited their analyses to select MR imaging sequences, select morphologic imaging features, or single-institution datasets without training/validation methodology.^{20,23,26,28}

Four recent studies have used training/validation methodology for analyzing imaging features associated with 1p/19q-codeletion status.^{19,24,25,27} Park et al,²⁴ in 2018, analyzed the neuroimaging features of a discovery set of 175 LGGs and a validation set of 40 LGGs and reported that mixed restricted diffusion and pial invasion were associated with 1p/19q codeletion among *IDH*1-

mutant LGGs. Limitations to their methodology included single-institution analysis, lack of T2-FLAIR mismatch sign assessment, and lack of *IDH2* testing. Kanazawa et al,²⁷ in 2018, analyzed a discovery cohort ($n = 45$) and validation cohort ($n = 52$) of LGGs and found that when at least 3 of the following imaging features were present—calcification, paramagnetic susceptibility, indistinct tumor border, and cystic component—there was >95% specificity for 1p/19q codeletion. Limitations to their methodology included a lack of interreader agreement determination, mostly nonradiologist readers, lack of T2-FLAIR mismatch sign assessment, and overlap between calcification and paramagnetic susceptibility. Patel et al,¹⁹ in 2017, assessed LGG MR imaging features in training ($n = 125$) and validation ($n = 60$) datasets and were the first to report 100% PPV of the T2-FLAIR mismatch sign for predicting the *IDH*mut-Noncodelel molecular subtype. Limitations to their methodology included the small number of imaging metrics tested ($n = 4$).

Notably, Broen et al,²⁸ in 2018, confirmed the 100% PPV for the T2-FLAIR mismatch sign in predicting *IDH*-mutant non-codeleted astrocytomas in a multi-institution cohort of LGGs ($n = 154$), though they did not use a training/validation methodology. Finally, Lasocki et al,²⁵ in 2018, analyzed the MR imaging features of an LGG cohort comprising 69 patients ($n = 10$ in the training cohort, $n = 59$ in the validation cohort). They found 100% PPV of >50% T2-FLAIR mismatch for lack of 1p/19q codeletion and high specificity of calcification for underlying 1p/19q codeletion. Limitations to their methodology included low cohort size (only 10 patients used for training), inclusion of cases with unknown *IDH* status, and single-institution analysis. None of the above described studies used completely different readers for their training and validation analyses.

In our study, we strictly adhered to the molecular classification of diffuse LGGs defined in the 2016 WHO update and excluded cases without relevant molecular data. We excluded *IDH* wild-type LGGs because our aim was to determine imaging features associated with each of the 2 subgroups among *IDH*-mutant LGGs, as defined by their 1p/19q-codeletion status. The TCGA/TCIA data base was selected as our training dataset because it had the highest likelihood for generalizability: Cases were accrued from multiple institutions, MR imaging examinations were performed on a variety of scanners with marked variability in imag-

ing quality, and the molecular data were reliable and comprehensive. To further explore the generalizability and reproducibility of our results, we used a large-validation cohort and completely different readers for the training and validation analyses. Our neuroimaging metrics are simple, mostly binary, and can be easily deduced from routine neuroimaging sequences. Unique to our study, we assessed simple extrinsic morphologic features such as hydrocephalus and midline shift, as well as patient age. Aside from Lasocki et al,²⁵ no prior study assessed the utility of T2-FLAIR mismatch in a multivariate model for predicting 1p/19q codeletion.

Our classification algorithm achieved good accuracy (86.3%) for predicting the codeletion status among the TCGA/TCIA *IDH*-mutant LGGs, and the validation analysis showed comparable accuracy (81.1% and 79.2% for readers A and B). In addition, we revalidated the high PPV of the T2-FLAIR mismatch sign for predicting the *IDH*mut-Noncodelel subtype (PPV = 100% in both training and validation analyses). We also report a novel association between hydrocephalus and midline shift with codeletion status. We found tumor heterogeneity, frontal lobe location, and T2* susceptibility blooming to be significant predictors of the presence of 1p/19q-codeletion status, concordant with prior studies. However, in contrast to prior studies, tumor margin was not a useful discriminatory feature for determining codeletion status in our study.^{10,17} This could be partly due to differences in the cohorts chosen for analysis or may reflect the subjective nature of this imaging metric.

Although we did not include *IDH* wild-type LGGs in our analysis, prediction of *IDH* status is critical to a neuroimaging-based classification of LGGs. This topic has been extensively studied in recent years, including with the use of conventional neuroimaging metrics,^{37,38} advanced methods such as MR spectroscopic detection of 2-hydroxyglutarate (an oncometabolite that accumulates in *IDH*-mutant gliomas),³⁹ and machine learning techniques.⁴⁰ Our work may complement neuroimaging-based methods for *IDH* prediction and contribute to a comprehensive prediction of molecular status in LGGs.

Our study has limitations. We followed a retrospective design, and prospective validation of our results would be desirable. The training and validation cohorts had differing frequencies of 1p/19q codeletions and WHO grades, which may have affected our results. The moderate accuracy achieved by our classification algorithm for predicting codeletion status underlines the fact that molecular testing of surgical specimens will remain the criterion standard for LGG classification in the foreseeable future. However, prediction by neuroimaging may be useful for patient counseling in the preoperative setting, in cases in which biopsy or resection is challenging or pathologic tissue is insufficient for accurate rendering of molecular results, and in cases of laboratory error or misinterpretation (eg, misinterpretation of flu-

Table 2: Training dataset classification summary for predicting 1p/19q codeletion based on the classification algorithm in Fig 3^a

Classification Algorithm Prediction	Molecular Status	
	1p/19q Codeleted	1p/19q Noncodeleted
1p/19q Codeleted	34	10
1p/19q Noncodeleted	4	54

^a Overall prediction accuracy was 86.3%.

Table 3: Validation dataset classification summary for predicting 1p/19q codeletion with 2 independent readers based on the classification algorithm in Fig 3^a

Reader A Prediction	Molecular Status		Reader B Prediction	Molecular Status	
	1p/19q Codeleted	1p/19q Noncodeleted		1p/19q Codeleted	1p/19q Noncodeleted
1p/19q Codeleted	48	12	1p/19q Codeleted	48	15
1p/19q Noncodeleted	8	38	1p/19q Noncodeleted	7	36

^a Overall prediction accuracy was 81.1% for reader A and 79.2% for reader B.

orescence in situ hybridization–based 1p/19q-codeletion results in the setting of chromosomal polysomy or partial chromosome arm deletions).^{41–43}

CONCLUSIONS

A 2-step classification algorithm based on the T2-FLAIR mismatch sign and a multivariate logistic regression model using tumor texture, patient age, T2* blooming, location, and hydrocephalus demonstrates an overall moderate prediction accuracy for 1p/19q-codeletion status in *IDH*-mutant LGGs. We validated the high PPV of the T2-FLAIR mismatch sign for predicting the *IDH*mut-Noncodel LGG subtype and report novel associations between midline shift/hydrocephalus and the *IDH*mut-Noncodel LGG subtype.

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REFERENCES

- Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol* 2016;131:803–20 CrossRef Medline
- Appin CL, Brat DJ. Molecular genetics of gliomas. *Cancer J* 2014;20:66–72 CrossRef Medline
- Yan H, Parsons DW, Jin G, et al. *IDH1* and *IDH2* mutations in gliomas. *N Engl J Med* 2009;360:765–73 CrossRef Medline
- Brat DJ, Verhaak RG, Aldape KD, et al; Cancer Genome Atlas Research Network. Comprehensive, integrative genomic analysis of diffuse lower-grade gliomas. *N Engl J Med* 2015;372:2481–98 CrossRef Medline
- van den Bent MJ, Brandes AA, Taphoorn MJ, et al. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. *J Clin Oncol* 2013;31:344–50 CrossRef Medline
- Chamberlain MC, Born D. Prognostic significance of relative 1p/19q codeletion in oligodendroglial tumors. *J Neurooncol* 2015;125:249–51 CrossRef Medline
- van den Bent MJ. Chemotherapy for low-grade glioma: when, for whom, which regimen? *Curr Opin Neurol* 2015;28:633–938 CrossRef Medline
- Zlatescu MC, TehraniYazdi A, Sasaki H, et al. Tumor location and growth pattern correlate with genetic signature in oligodendroglial neoplasms. *Cancer Res* 2001;61:6713–15 Medline
- Megyesi JF, Kachur E, Lee DH, et al. Imaging correlates of molecular signatures in oligodendrogliomas. *Clin Cancer Res* 2004;10:4303–06 CrossRef Medline
- Jenkinson MD, du Plessis DG, Smith TS, et al. Histological growth patterns and genotype in oligodendroglial tumours: correlation with MRI features. *Brain* 2006;129(Pt 7):1884–91 CrossRef Medline
- Brown R, Zlatescu M, Sijben A, et al. The use of magnetic resonance imaging to noninvasively detect genetic signatures in oligodendroglioma. *Clin Cancer Res* 2008;14:2357–62 CrossRef Medline
- Sherman JH, Prevedello DM, Shah L, et al. MR imaging characteristics of oligodendroglial tumors with assessment of 1p/19q deletion status. *Acta Neurochir (Wien)* 2010;152:1827–34 CrossRef Medline
- Kim JW, Park CK, Park SH, et al. Relationship between radiological characteristics and combined 1p and 19q deletion in World Health Organization grade III oligodendroglial tumours. *J Neurol Neurosurg Psychiatry* 2011;82:224–27 CrossRef Medline
- Fellah S, Caudal D, De Paula AM, et al. Multimodal MR imaging (diffusion, perfusion, and spectroscopy): is it possible to distinguish oligodendroglial tumor grade and 1p/19q codeletion in the pretherapeutic diagnosis? *AJNR Am J Neuroradiol* 2013;34:1326–33 CrossRef Medline
- Chawla S, Krejza J, Vossough A, et al. Differentiation between oligodendroglioma genotypes using dynamic susceptibility contrast perfusion-weighted imaging and proton MR spectroscopy. *AJNR Am J Neuroradiol* 2013;34:1542–49 CrossRef Medline
- Smits M. Imaging of oligodendroglioma. *Br J Radiol* 2016;89:20150857 CrossRef Medline
- Johnson DR, Diehn FE, Giannini C, et al. Genetically defined oligodendroglioma is characterized by indistinct tumor borders at MRI. *AJNR Am J Neuroradiol* 2017;38:678–84 CrossRef Medline
- Darlix A, Deverdun J, Menjot de Champfleury N, et al. *IDH* mutation and 1p19q codeletion distinguish two radiological patterns of diffuse low-grade gliomas. *J Neurooncol* 2017;133:37–45 CrossRef Medline
- Patel SH, Poisson LM, Brat DJ, et al. T2-FLAIR mismatch, an imaging biomarker for *IDH* and 1p/19q status in lower-grade gliomas: a TCGA/TCIA project. *Clin Cancer Res* 2017;23:6078–85 CrossRef Medline
- Yoon HJ, Ahn KJ, Lee S, et al. Differential diagnosis of oligodendroglial and astrocytic tumors using imaging results: the added value of perfusion MR imaging. *Neuroradiology* 2017;59:665–75 CrossRef Medline
- Akkus Z, Ali I, Sedlář J, et al. Predicting deletion of chromosomal arms 1p/19q in low-grade gliomas from MR images using machine intelligence. *J Digit Imaging* 2017;30:469–76 CrossRef Medline
- Smits M, van den Bent MJ. Imaging correlates of adult glioma genotypes. *Radiology* 2017;284:316–31 CrossRef Medline
- Delfanti RL, Piccioni DE, Handwerker J, et al. Imaging correlates for the 2016 update on WHO classification of grade II/III gliomas: implications for *IDH*, 1p/19q and *ATRX* status. *J Neurooncol* 2017;135:601–09 CrossRef Medline
- Park YW, Han K, Ahn SS, et al. Prediction of *IDH1*-mutation and 1p/19q-codeletion status using preoperative MR imaging phenotypes in lower grade gliomas. *AJNR Am J Neuroradiol* 2018;39:37–42 CrossRef Medline
- Lasocki A, Gaillard F, Gorelik A, et al. MRI features can predict 1p/19q status in intracranial gliomas. *AJNR Am J Neuroradiol* 2018;39:687–92 CrossRef Medline
- Park YW, Han K, Ahn SS, et al. Whole-tumor histogram and texture analyses of DTI for evaluation of *IDH1*-mutation and 1p/19q-codeletion status in World Health Organization grade II gliomas. *AJNR Am J Neuroradiol* 2018;39:693–98 CrossRef Medline
- Kanazawa T, Fujiwara H, Takahashi H, et al. H. Imaging scoring systems for preoperative molecular diagnoses of lower-grade gliomas. *Neurosurg Rev* 2018 Apr 26. [Epub ahead of print] CrossRef Medline
- Broen MP, Smits M, Wijnenga MM, et al. The T2-FLAIR mismatch sign as an imaging marker for non-enhancing *IDH*-mutant, 1p/19q-intact lower-grade glioma: a validation study. *Neuro Oncol* 2018;20:1393–99 CrossRef Medline
- Pedano N, Flanders AE, Scarpace L, et al. Radiology Data from The Cancer Genome Atlas Low Grade (TCGA-LGG) collection. The Cancer Imaging Archive. <http://doi.org/10.7937/K9/TCIA.2016.L4LTD3TK>. Accessed January 10, 2019
- Ceccarelli M, Barthel FP, Malta TM, et al. Molecular profiling reveals biologically discrete subsets and pathways of progression in diffuse glioma. *Cell* 2016;164:550–63 CrossRef Medline
- Capper D, Weissert S, Balss J, et al. Characterization of R132H mutation-specific *IDH1* antibody binding in brain tumors. *Brain Pathol* 2010;20:245–54 CrossRef Medline
- Capper D, Zentgraf H, Balss J, et al. Monoclonal antibody specific for

- IDH1 R132H mutation.** *Acta Neuropathol* 2009;118:599–601 [CrossRef](#) [Medline](#)
33. Felsberg J, Wolter M, Seul H, et al. **Rapid and sensitive assessment of the IDH1 and IDH2 mutation status in cerebral gliomas based on DNA pyrosequencing.** *Acta Neuropathol* 2010;119:501–07 [CrossRef](#) [Medline](#)
 34. Youden WJ. **Index for rating diagnostic tests.** *Cancer* 1950;3:32–35 [CrossRef](#)
 35. Robin X, Turck N, Hainard A, et al. **pROC: an open-source package for R and S+ to analyze and compare ROC curves.** *BMC Bioinformatics* 2011;12:77 [CrossRef](#) [Medline](#)
 36. R Development Core Team. *R: A Language and Environment for Statistical Computing.* Vienna; R Foundation for Statistical Computing; 2017
 37. Qi S, Yu L, Li H, et al. **Isocitrate dehydrogenase mutation is associated with tumor location and magnetic resonance imaging characteristics in astrocytic neoplasms.** *Oncol Lett* 2014;7:1895–902 [CrossRef](#) [Medline](#)
 38. Metellus P, Coulibaly B, Colin C, et al. **Absence of IDH mutation identifies a novel radiologic and molecular subtype of WHO grade II gliomas with dismal prognosis.** *Acta Neuropathol* 2010;120:719–29 [CrossRef](#) [Medline](#)
 39. Choi C, Ganji SK, DeBerardinis RJ, et al. **2-hydroxyglutarate detection by magnetic resonance spectroscopy in IDH-mutated patients with gliomas.** *Nat Med* 2012;18:624–29 [CrossRef](#) [Medline](#)
 40. Chang K, Bai HX, Zhou H, et al. **Residual convolutional neural network for determination of IDH status in low- and high-grade gliomas from MR imaging.** *Clin Cancer Res* 2018;24:1073–81 [CrossRef](#) [Medline](#)
 41. Patel KS, Carter BS, Chen CC. **Role of biopsies in the management of intracranial gliomas.** *Prog Neurol Surg* 2018;30:232–43 [CrossRef](#) [Medline](#)
 42. Horbinski C, Miller CR, Perry A. **Gone FISHing: clinical lessons learned in brain tumor molecular diagnostics over the last decade.** *Brain Pathol* 2011;21:57–73 [CrossRef](#) [Medline](#)
 43. Riemenschneider MJ, Jeuken JW, Wesseling P, et al. **Molecular diagnostics of gliomas: state of the art.** *Acta Neuropathol* 2010;120:567–84 [CrossRef](#) [Medline](#)

Preoperative MR Imaging to Differentiate Chordoid Meningiomas from Other Meningioma Histologic Subtypes

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ABSTRACT

BACKGROUND AND PURPOSE: Chordoid meningiomas are uncommon WHO grade II primary intracranial neoplasms that possess unique chordoid histology and follow an aggressive clinical course. Our aim was to assess the utility of qualitative MR imaging features and quantitative apparent diffusion coefficient values as distinguishing preoperative MR imaging metrics to identify and differentiate chordoid histology from other meningioma histologic subtypes.

MATERIALS AND METHODS: Twenty-one patients with meningiomas with chordoid histology, which included both chordoid meningiomas (>50% chordoid histology) and meningiomas with focal chordoid histology (<50% chordoid histology) with available preoperative MR imaging examinations, including diffusion-weighted imaging, were identified. Qualitative imaging features and quantitative ADC values were compared between meningiomas with chordoid histology and 42 nonchordoid meningiomas (29 WHO grade I, eleven WHO grade II, and 2 WHO grade III).

RESULTS: The median ADC ($10^{-3}\text{mm}^2/\text{s}$) of meningiomas with chordoid histology was significantly higher than nonchordoid meningiomas (1.16 versus 0.92, $P < .001$), as was the median normalized ADC (1.60 versus 1.19, $P < .001$). In subgroup analysis, the median and normalized ADC values of chordoid meningiomas ($n = 11$) were significantly higher than those in meningiomas with focal chordoid histology ($n = 10$, $P < .001$ and $P < .001$, respectively) or nonchordoid meningiomas ($n = 42$, $P < .001$ and <0.001 , respectively). Median and normalized ADC values were not significantly different between the meningiomas with focal chordoid histology and nonchordoid meningiomas ($P = .816$ and $.301$, respectively). Among the qualitative imaging features, only DWI signal intensity was significantly associated with meningiomas with chordoid histology diagnosis.

CONCLUSIONS: ADC values are higher in chordoid compared with nonchordoid meningiomas and may be used to discriminate the degree of chordoid histology in meningiomas. While qualitative MR imaging features do not strongly discriminate chordoid from nonchordoid meningiomas, DWI may allow preoperative identification of chordoid meningiomas.

ABBREVIATIONS: IQR = interquartile range; MCH = meningiomas with chordoid histology; nADC = normalized ADC

Chordoid meningiomas are a rare subtype of atypical, WHO grade II meningioma.¹ By histopathology, chordoid menin-

giomas are composed of spindled-to-epithelioid cells with eosinophilic cytoplasm arranged in chains and cords within a basophilic extracellular matrix. This myxoid stroma is rich in acidic mucin and stains with mucicarmine, periodic-acid-Schiff, and Alcian blue. Chordoid meningiomas are associated with higher rates of recurrence than benign WHO grade I meningiomas and have thus been designated as a grade II variant in the WHO classification, even in those examples lacking increased mitotic activity, brain invasion, or other atypical criteria.²⁻⁵ Thus, preoperative imaging identification of chordoid meningiomas could provide

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valuable information to guide surgical planning, adjuvant therapy, and patient counseling.

Several studies have sought to define imaging features that can reliably distinguish low- and high-grade meningiomas. In that regard, features such as larger size and irregular shape are associated with a higher meningioma grade.⁶⁻⁹ Although sensitive, these associations have poor specificity and are thus unreliable for identifying atypical and anaplastic meningiomas.¹⁰ Investigators have addressed these limitations by analyzing advanced MR imaging with quantitative metrics, including diffusion, perfusion, and MR spectroscopy.¹¹⁻¹⁷ To date, the most promising MR imaging feature for differentiating WHO grades in meningiomas is the apparent diffusion coefficient, a measure of the degree of diffusion of water molecules within tissue.^{11,12} Prior meningioma studies have revealed a significant correlation between whole-tumor ADC histogram metrics and tumor histology and corresponding WHO grade.^{18,19} However, only 1 study, which was limited to 4 patients, has specifically addressed the utility of ADC in identifying chordoid meningiomas on preoperative imaging.¹³

Given the relative paucity of imaging studies focused on chordoid meningiomas and the unmet need to identify high-grade meningiomas preoperatively, our study assessed whether qualitative or quantitative MR imaging features such as ADC can be used as preoperative MR imaging metrics to differentiate chordoid meningiomas from other meningioma subtypes. Our data revealed that ADC can delineate chordoid meningiomas from other meningioma histologies and can also identify the degree of chordoid histology within an individual meningioma.

MATERIALS AND METHODS

Patient Population and Study Information

We identified 24 patients who underwent resection for meningiomas with chordoid histology at our institution from 2000 to 2018. All resection specimens were re-reviewed by an expert neuropathologist (D.A.S.) to confirm the presence and extent of chordoid histology. Chordoid meningiomas (>50% chordoid histology, $n = 11$) were considered separately from meningiomas with focal chordoid histology (<50% chordoid histology, $n = 10$), but for some analyses, these groups were combined as meningiomas with chordoid histology (MCH, $n = 21$). A cohort of 42 patients with histologically confirmed nonchordoid meningioma were randomly selected from a consecutive institutional cohort of patients with meningiomas for comparison using a random number generator. Clinical variables, including patient age, sex, and meningioma grade, were extracted from the medical record. Only patients with preoperative MR imaging examinations with available diffusion-weighted imaging and complete clinical records were included in the analysis. Patients who underwent preoperative meningioma embolization before MR imaging were excluded. This retrospective study was approved by the institutional review board.

MR Imaging Protocol

MR imaging was performed within a week before surgical resection using a 1.5T or 3T MR imaging scanner. While the acquired MR imaging pulse sequences varied during the course of the study, at a minimum, the standard neuronavigation MR imaging

protocol consisted of the following pulse sequences encompassing the entire brain: precontrast T1 and T2, T2 FLAIR, DWI (b-values, 0 and 1000 s/mm²), and gadolinium-enhanced 3D echo-spoiled gradient-echo T1-weighted images.

MR Imaging Analysis

A board-certified neuroradiologist (J.E.V.-M.) evaluated MR images for qualitative imaging features, including lesion location, focality, size, T1/T2/DWI signal intensity, the presence of a dural tail or CSF cleft sign, bony involvement, parenchymal edema, tumor location, dural venous sinus involvement, arterial narrowing, and the presence of sunburst vessels using a clinical PACS. Signal intensity was characterized relative to gray matter for T1- and T2-weighted imaging and relative to brain for DWI. ADC maps were exported to MIM Software (MIM Software, Cleveland, Ohio), in which meningiomas were contoured by a board-certified radiation oncologist with expertise in tumors of the central nervous system (D.R.R.). All contours were initially defined around the tumor on gadolinium-enhanced T1 images and individually verified to ensure that they accurately preserved meningioma borders. The contoured ROIs from gadolinium-enhanced T1 images were automatically coregistered with corresponding ADC maps to obtain whole-tumor mean ADC values. Control ADC values were measured from contralateral normal-appearing white matter. Normalized ADC (nADC) was calculated by dividing the meningioma ADC value by the respective control ADC value.

Data Analysis

All statistical analyses were performed in STATA 15.0 (StataCorp, College Station, Texas). Differences in overall ADC and nADC values between MCH and nonchordoid meningiomas were compared using Wilcoxon rank sum tests. Additional subgroup analysis was performed to investigate the difference in overall ADC and nADC values among chordoid meningiomas, meningiomas with focal chordoid histology, and nonchordoid meningiomas. Previously published cutoff values of ADC ≥ 1.4 and nADC ≥ 1.9 for identifying the chordoid histology were evaluated.¹³ Subsequently, a receiver operating characteristic analysis was performed to define optimal cutoff values for the ADC and nADC. Univariate logistic and exact logistic regressions were performed to assess the predictive value of selected imaging features in preoperative chordoid meningioma diagnosis.

RESULTS

Of the 24 identified patients with MCH, 21 met the inclusion criteria and were compared with 42 patients with nonchordoid meningiomas, which included 29 WHO grade I, eleven WHO grade II, and 2 WHO grade III meningiomas. Among the 10 meningiomas with focal chordoid features, the predominant meningioma histology included 6 WHO grade I, three WHO grade II, and WHO grade III. Approximately 70% of both MCHs and nonchordoid meningiomas were supratentorial. Similarly, both histologic groups predominantly presented as solitary lesions instead of as multifocal tumors. The proportions of MCHs and nonchordoid meningiomas observed to have a dural tail, bony involvement, a cystic component, CSF cleft sign, dural venous sinus involvement, arterial narrowing, sunburst vessels, irregular mar-

Univariate analysis of qualitative MR imaging features for chordoid meningioma

Predictor Variables	Chordoid Meningioma (N = 21)	
	OR (95% CI)	P Value
Supratentorial location	1.43 (0.43–4.75)	.555
Multifocality	4.06 (0.87–19.04)	.075
T1 hyperintensity	1.34 (0.46–3.91)	.590
T1+ marked CE ^a	6.49 (0.93 to +inf)	.061
T2 hyperintensity	2.91 (0.90–9.40)	.074
ADC hyperintensity	4.29 (1.31–13.98)	.016 ^b
Presence of dural tail ^a	0.50 (0–19.50)	.667
Bony involvement	3.10 (0.86–8.06)	.090
Cystic/necrotic change	2.31 (0.59–9.11)	.231
Sunburst vessels	1.00 (0.29–3.42)	1.000
Venous involvement ^a	1.57 (0.21–10.40)	.859
Arterial narrowing	0.48 (0.05–4.54)	.518
CSF cleft	0.44 (0.14–1.40)	.165
Parenchymal edema	1.10 (0.38–3.24)	.856
Irregular margins ^a	6.05 (0.88–69.7)	.072

Note:—CE indicates contrast enhancement; inf, infinity.

^a Exact logistic regression.

^b Significant.

gins, and parenchymal edema on imaging were 95% versus 100%, 52% versus 26%, 24% versus 12%, 62% versus 79%, 14% versus 10%, 5% versus 9.5%, 24% versus 24%, 24% versus 5%, and 62% versus 60%, respectively. T1 signal hyperintensity was observed in approximately 62% of MCHs and 55% of nonchordoid meningiomas. T2 signal hyperintensity was observed in 76% of MCHs and 52% of nonchordoid meningiomas. Marked T1 contrast enhancement was observed in 100% of MCHs and 81% of nonchordoid meningiomas. Qualitative facilitated diffusion (hyperintensity on ADC with hypointensity on DWI) was seen in 48% of MCHs and 18% of nonchordoid meningiomas. On univariate logistic and exact logistic regressions, only ADC hyperintensity was found to be significantly associated with MCH diagnosis ($P = .016$) (Table).

Intratumoral ADC values ($10^{-3}\text{mm}^2/\text{s}$) in MCHs ranged from 0.75 to 1.86, and the corresponding nADC values ranged from 1.11 to 2.49 (Figs 1 and 2). In nonchordoid meningiomas, the intratumoral ADC values ranged from 0.79 to 1.09, and the corresponding nADC values ranged from 1.01 to 1.42 (Fig 3). The median ADC of all MCHs (1.16; interquartile range [IQR] = 0.60) was significantly higher than that in nonchordoid meningiomas (0.92, IQR = 0.12,

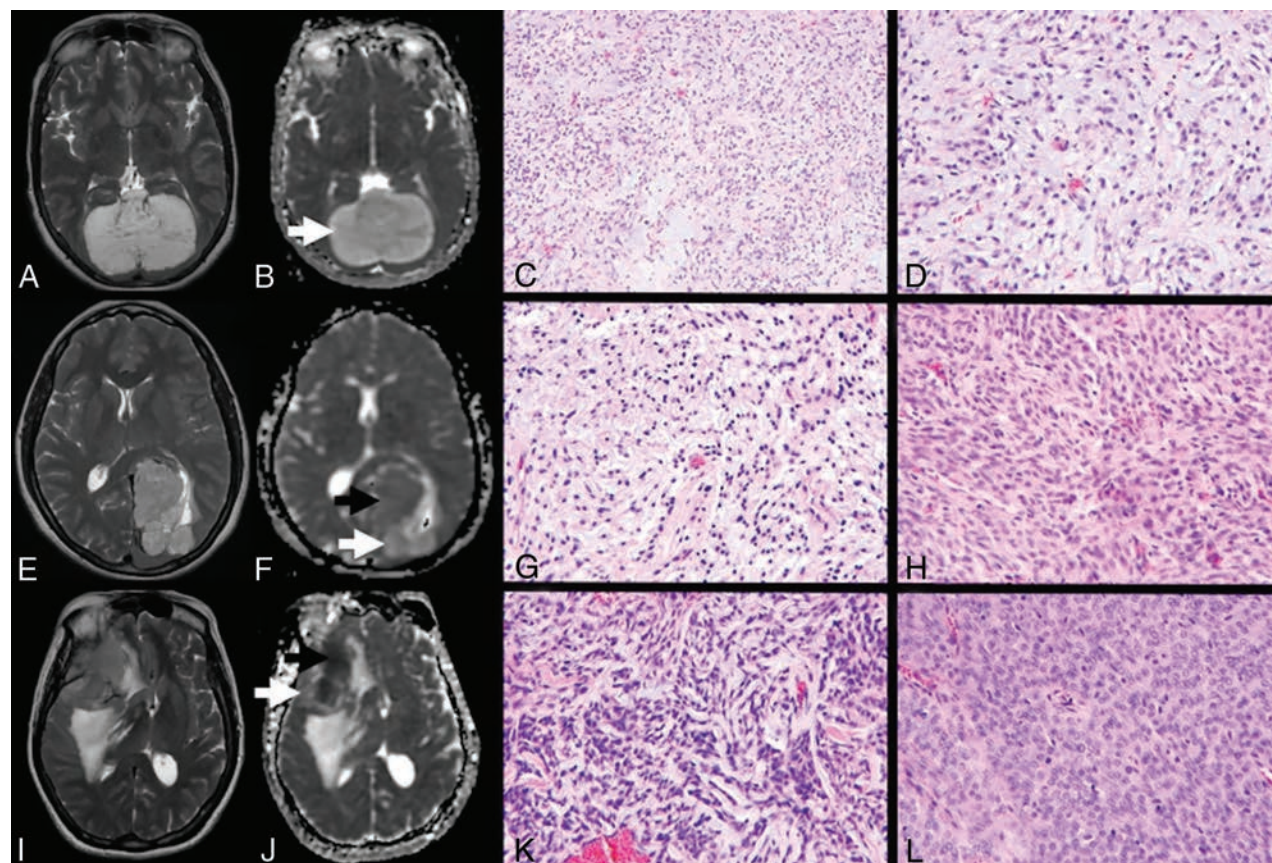


FIG 1. Meningiomas with chordoid histology. A–D, Chordoid meningioma. Axial T2-weighted image (A) demonstrates a T2 hyperintense falctentorial meningioma with facilitated diffusion on the ADC map (B, *white arrow*). Hematoxylin-eosin (H&E) stained sections at 20× (C) and 40× (D) magnification demonstrate chains and clusters of epithelioid cells in a basophilic myxoid stroma characteristic of chordoid meningioma. E–H, Meningiomas with focal chordoid features. Axial T2-weighted image (E) demonstrates a T2-hyperintense left posterior parasagittal meningioma. The corresponding ADC map (F) demonstrates a dominant area of signal isointensity (*black arrow*) with focal facilitated diffusion (*white arrow*). H&E-stained sections at 40× magnification demonstrate regions of chordoid (G) and conventional meningothelial (H) histology. I–L, Anaplastic meningioma with focal chordoid features. Axial T2-weighted image (I) demonstrates a heterogeneous right sphenoid wing meningioma. The corresponding ADC map (J) demonstrates regions of reduced diffusion (*black arrow*), suggesting increased tumoral cellularity, with a small focus of facilitated diffusion (*white arrow*). H&E-stained sections at 40× magnification demonstrate focal regions of chordoid histology (K), with a predominant component of anaplastic meningioma lacking chordoid features (L).

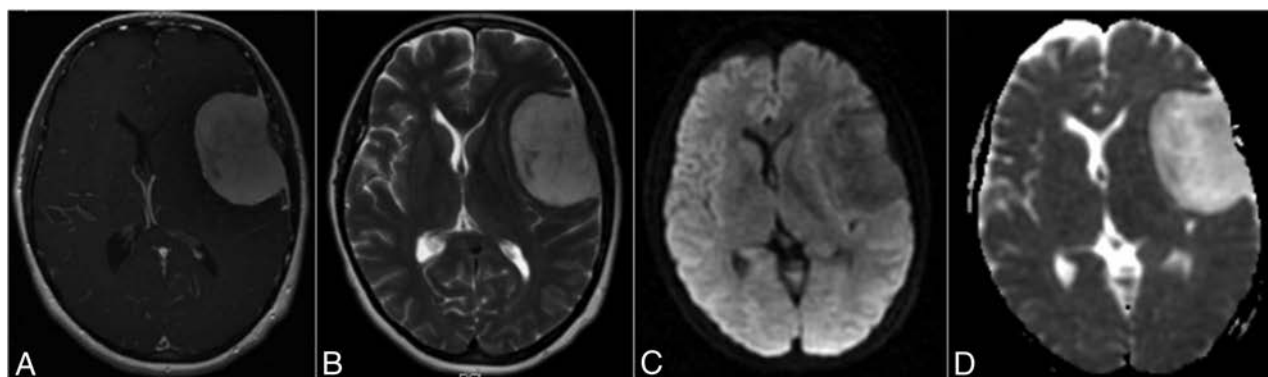


FIG 2. Left frontal chordoid meningioma. *A*, Postcontrast T1-weighted image of a 5.5×3.6 cm chordoid meningioma shows clear enhancement with areas of nonenhancement. *B*, T2-weighted image shows moderate-to-hyperintense signal. *C*, DWI shows hypointense signal. *D*, A corresponding ADC map demonstrates marked hyperintense signals from the tumor with resulting ADC and nADC values of $1.84 \times 10^{-3} \text{mm}^2/\text{s}$ and 2.36, respectively.

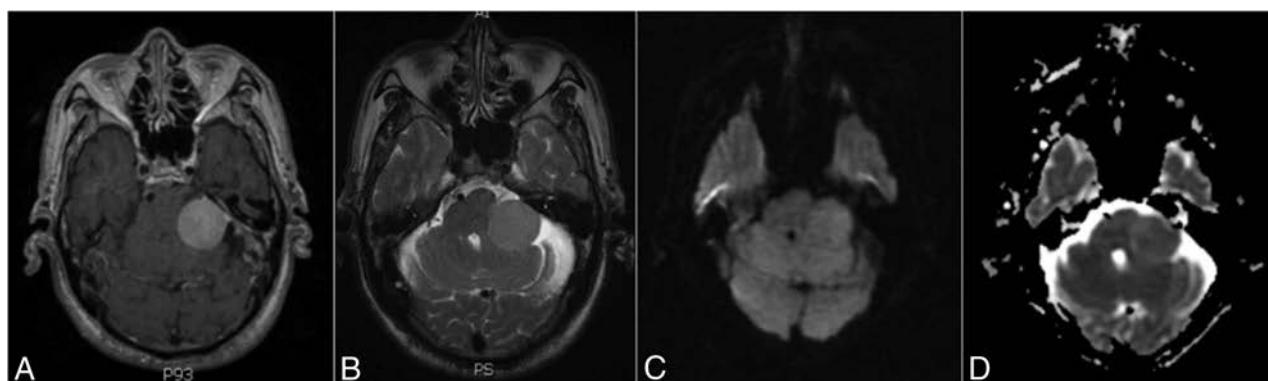


FIG 3. Left cerebellopontine angle nonchordoid meningioma, WHO grade I. *A*, Postcontrast T1-weighted image shows homogeneous enhancement in the 3.0×2.8 cm nonchordoid meningioma. *B*, T2-weighted image shows moderately intense signals. *C*, DWI shows isointense signals. *D*, A corresponding ADC map demonstrates isointense signal with resulting ADC and nADC values of $0.94 \times 10^{-3} \text{mm}^2/\text{s}$ and 1.26, respectively.

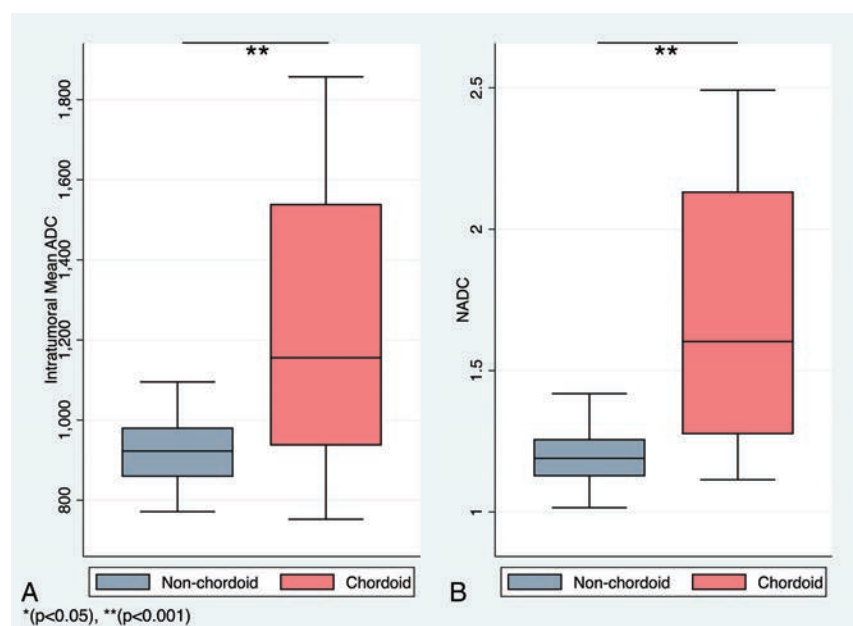


FIG 4. Distribution of ADC and nADC values between chordoid and nonchordoid meningiomas. Boxplots of ADC ($\times 10^{-6} \text{mm}^2/\text{s}$) (*A*) and nADC (*B*) values of nonchordoid (gray) and chordoid meningiomas (red).

$P < .001$) (Fig 4A). Similarly, the median nADC of MCHs (1.60, IQR = 0.86) was significantly higher than that of the nonchordoid meningiomas (1.19, IQR = 0.13, $P < .001$) (Fig 4B). Subgroup analysis revealed a significant difference in the median ADC between chordoid meningioma (1.54, IQR = 0.24, $n = 11$) and meningiomas with focal chordoid features (0.93, IQR = 0.07, $n = 10$, $P < .001$) (Fig 5A). The median nADC of chordoid meningioma (2.13, IQR = 0.41) was also significantly higher than that in meningiomas with focal chordoid features (1.30, IQR = 0.20, $P < .001$) (Fig 5B). Consistently, chordoid meningiomas had significantly higher median ADC compared with nonchordoid meningiomas (0.92, $P < .001$), while the median ADC in meningiomas with focal chordoid features was not significantly different from that in nonchordoid meningiomas ($P = .816$) (Fig 6A). Furthermore, the median nADC values were significantly higher in chor-

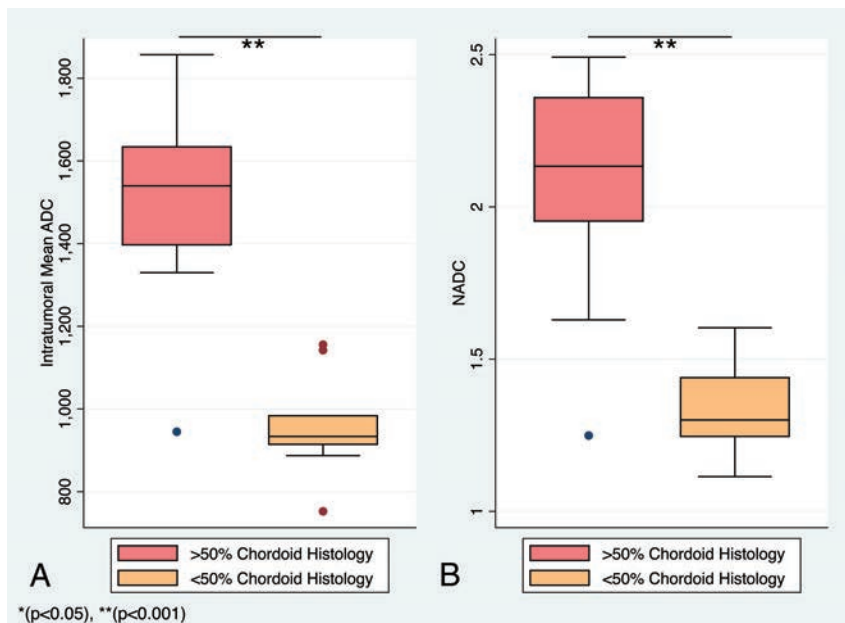


FIG 5. Distribution of ADC and nADC values by an intratumoral proportion of chordoid histology. Boxplots of ADC ($\times 10^{-6} \text{mm}^2/\text{s}$) (A) and nADC (B) values of chordoid meningiomas (red) and meningiomas with focal chordoid features (orange).

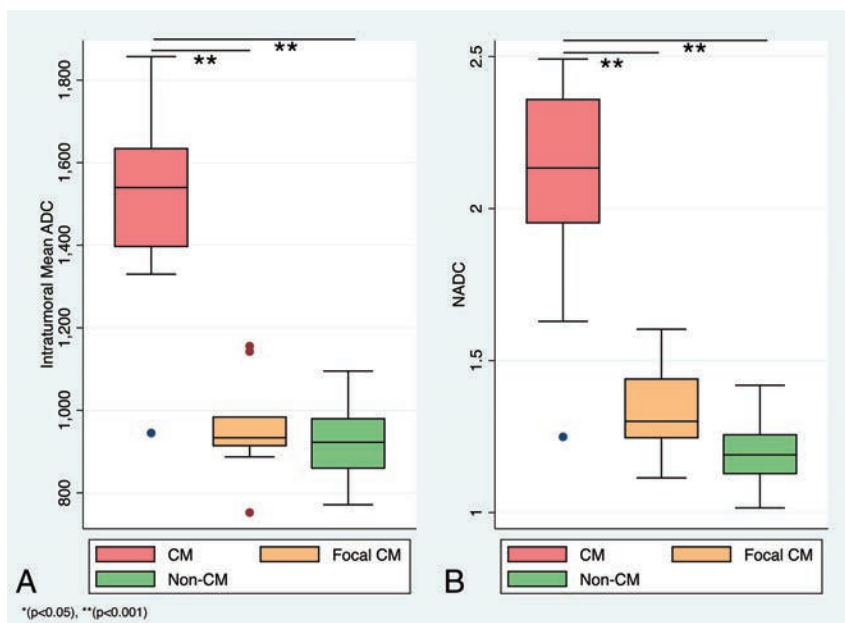


FIG 6. ADC and nADC values among chordoid meningioma, meningiomas with focal chordoid histology, and nonchordoid meningiomas. Boxplots of ADC ($\times 10^{-6} \text{mm}^2/\text{s}$) (A) and nADC (B) values of chordoid meningiomas (red), meningiomas with focal chordoid features (orange), and nonchordoid meningiomas (green).

doid meningiomas versus nonchordoid meningiomas ($1.19, P < .001$) (Fig 6B). There was no statistically significant difference in median nADC values between meningiomas with focal chordoid features and nonchordoid meningiomas ($P = .301$).

The median ADC ($1.16, \text{IQR} = 0.60$) and nADC ($1.60, \text{IQR} = 0.86$) of MCH WHO grade II tumors were significantly higher than the median ADC ($0.89, \text{IQR} = 0.22, P = .005$) and nADC ($1.21, \text{IQR} = 0.15, P = .001$) of nonchordoid WHO grade II meningiomas. Similarly, the median ADC and nADC of MCHs

were significantly elevated compared with the median ADC ($0.86, \text{IQR} = 0.04, P = .038$) and nADC ($1.15, \text{IQR} = 0.14, P = .038$) of WHO grade III meningiomas.

The overall diagnostic accuracy of the previously defined cutoff value of $\text{ADC} \geq 1.39 \times 10^{-3} \text{mm}^2/\text{s}$ to identify chordoid meningioma on preoperative imaging was 96.8%, with a sensitivity and specificity of 96.3% and 100%, respectively.¹³ The overall diagnostic accuracy of the previously defined cutoff value of $\text{nADC} \geq 1.9$ was 96.8%, with a sensitivity and specificity of 96.3% and 100%, respectively. On receiver operating characteristic analysis, cutoff values at $\text{ADC} \geq 1.33 \times 10^{-3} \text{mm}^2/\text{s}$ and $\text{nADC} \geq 1.63$ were identified with resulting identical overall accuracy, sensitivity, and specificity of 96.8%, 96.3%, and 100%, respectively.

DISCUSSION

We found that both ADC and nADC values are significantly higher in MCHs compared with nonchordoid meningiomas. Moreover, our data reveal that chordoid meningiomas have significantly higher ADC and nADC values than either meningiomas with focal chordoid features or nonchordoid meningiomas. This finding remains true at a qualitative level, at which high ADC signal intensity and corresponding low DWI signal intensity are enriched in the MCH group.

Typically, WHO grade II and III meningiomas have greater intratumoral cellularity, increased tissue density, and decreased extracellular space, all of which are thought to contribute to decreased free water diffusion.^{11,12} Despite their WHO grade II classification, chordoid meningiomas have been found to have elevated ADC values.¹³ Increased water diffusivity within chordoid meningiomas is believed to be linked to an extracellular network composed of hyaluronic acid and chondroitin sulfate-rich mucoid matrix, which

can be observed on microscopic evaluation and is unique to the chordoid subtype of meningioma.⁴ Most interesting, several studies have found associations between elevated ADC values and other types of tumors that are enriched with myxoid stroma, such as myxoid soft-tissue tumors, chordomas, and chondrosarcomas.^{14,15} Overall, our findings coincide with those reported in the only other investigation of DWI in chordoid meningioma.¹³ The overall mean ADC and nADC values for MCHs in our study were lower compared with those found in the previous study ($1.62 \pm 0.33 \times 10^{-3} \text{mm}^2/\text{s}$ and

2.22 ± 0.47, respectively). However, the mean ADC and nADC values of the chordoid meningioma group in our study are similar to the mean values of the previous study. Given that ADC values were studied in only 4 chordoid meningiomas in the previous report, it is possible that all the chordoid meningiomas in that sample were of chordoid-predominant histology. Nonetheless, their previously defined ADC and nADC cutoff values of $1.39 \times 10^{-3} \text{ mm}^2/\text{s}$ and 1.93 had the same diagnostic accuracy as the defined cutoff values of our study with identically high sensitivity and specificity.

While there have been prior clinicopathologic studies on the proportion of chordoid meningioma histology,^{4,5} our study is the first to investigate imaging features associated with chordoid meningiomas on the basis of the relative proportion of chordoid histology. Mean ADC and nADC values were highest in chordoid meningiomas, consistent with the theorized greater water diffusivity in meningiomas with >50% chordoid composition. Indeed, chordoid meningiomas had ADC and nADC values that were significantly increased compared with both meningiomas with focal chordoid features and nonchordoid meningiomas. In contrast, the mean ADC and nADC values were not significantly different between meningiomas with focal chordoid histology and nonchordoid meningiomas. With <50% chordoid histology, the degree of water diffusivity in meningiomas with focal chordoid histology seems to be principally driven by the prevailing histology within the tumor. These findings highlight not only the heterogeneity of meningioma histology but also the potential limitation of ADC in identifying meningiomas with <50% chordoid histology.

Qualitative assessment of ADC hyperintensity proved useful in distinguishing MCH from nonchordoid meningiomas. ADC hyperintensity with corresponding DWI hypointensity was observed in a greater proportion of MCHs than in nonchordoid meningiomas and was significantly associated with approximately 4 times the odds of chordoid meningioma diagnosis. Our findings support the utility of qualitative assessment of DWI sequences in identifying MCHs, which is more feasible in routine clinical practice compared with quantitative ADC analysis. Otherwise, most qualitative imaging features were not significantly associated with MCH diagnosis. Of note, while chordoid meningioma histology is rich with mucoid matrix that is typically associated with increased T2 signal, especially in other tumors such as chordomas or chondrosarcomas,^{4,15} T2 signal hyperintensity did not achieve statistical significance in this study. Overall, the scarcity of statistically significant qualitative imaging features associated with chordoid histology in meningioma diagnosis further highlights the importance of quantitative metrics like DWI in preoperative meningioma diagnosis.

There are several limitations to our study. As a retrospective study, our data were limited not only by the availability of suitable preoperative imaging including DWI but also by the rarity of chordoid meningioma. Despite the small number of cases in our study, it is the largest study of its kind to date. Another limitation may be in the measurement of ADC values. While our study did not use 2 independent extractions of ADC values to assess interobserver reliability, all of the contours were individually assessed to guarantee precise adherence to meningioma borders while avoiding areas of signal loss that could alter quantifications. Consistently, all contours were derived from postcontrast imaging and further cross-referenced with T1/T2 sequences for accurate coverage of the meningioma area. Last,

because contours of the whole tumor were used, there is greater reproducibility as opposed to simply using a single-slice ROI within the tumor. Using whole-tumor data allows more accurate representation of the total diffusion profile that may vary within the microarchitecture of a single tumor, as demonstrated by prior ADC histogram analyses on meningiomas.¹⁸ Most interesting, using whole-tumor measurements and histogram analysis may also better quantify morphologic imaging metrics such as signal intensity for predicting tumor histology, as shown by some studies.^{20,21}

CONCLUSIONS

Our study demonstrates statistically significant elevations of ADC and nADC values in chordoid meningiomas compared with meningiomas with focal chordoid features and nonchordoid meningiomas. Our study also reveals that quantitative ADC may have additional utility in classifying the proportion of intratumoral chordoid histology on preoperative imaging. Cutoff values of $\text{ADC} \geq 1.33 \times 10^{-3} \text{ mm}^2/\text{s}$ and $\text{nADC} \geq 1.63$ can be used to help identify potential chordoid meningiomas on preoperative imaging with considerable diagnostic accuracy. Preoperative identification of chordoid meningiomas could provide valuable information to guide subsequent surgical planning, adjuvant therapy, and patient counseling.

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REFERENCES

1. Louis DN, Perry A, Reifenberger G, et al. **The 2016 World Health Organization classification of tumors of the central nervous system: a summary.** *Acta Neuropathol* 2016;131:803–20
2. Kepes JJ, Chen WY, Connors MH, et al. **“Chordoid” meningeal tumors in young individuals with peritumoral lymphoplasmacellular infiltrates causing systemic manifestations of the Castleman syndrome: a report of seven cases.** *Cancer* 1988;62:391–406 [CrossRef Medline](#)
3. Yang Y, Li D, Cao XY, et al. **Clinical features, treatment, and prognostic factors of chordoid meningioma: radiological and pathological features in 60 cases of chordoid meningioma.** *World Neurosurg* 2016;93:198–207 [CrossRef Medline](#)
4. Couce ME, Aker FV, Scheithauer BW. **Chordoid meningioma: a clinicopathologic study of 42 cases.** *Am J Surg Pathol* 2000;24:899–905 [CrossRef Medline](#)
5. Epari S, Sharma MC, Sarkar C, et al. **Chordoid meningioma, an uncommon variant of meningioma: a clinicopathologic study of 12 cases.** *J Neurooncol* 2006;78:263–69 [CrossRef Medline](#)
6. Carpeggiani P, Crisi G, Trevisan C. **MRI of intracranial meningiomas: correlations with histology and physical consistency.** *Neuroradiology* 1993;35:532–36 [CrossRef Medline](#)
7. Zimmerman RD, Fleming CA, Saint-louis LA, et al. **Magnetic resonance imaging of meningiomas.** *AJNR Am J Neuroradiol* 1985;6:149–57 [Medline](#)
8. Coroller TP, Bi WL, Huynh E, et al. **Radiographic prediction of meningioma grade by semantic and radiomic features.** *PLoS One* 2017;12:e0187908 [CrossRef Medline](#)
9. Nakasu S, Nakasu Y, Nakajima M, et al. **Preoperative identification of meningiomas that are highly likely to recur.** *J Neurosurg* 1999;90:455–62 [Medline](#)
10. Watts J, Box G, Galvin A, et al. **Magnetic resonance imaging of meningiomas: a pictorial review.** *Insights Imaging* 2014;5:113–22 [CrossRef Medline](#)
11. Filippi CG, Edgar MA, Uluğ AM, et al. **Appearance of meningiomas on diffusion-weighted images: correlating diffusion constants with histopathologic findings.** *AJNR Am J Neuroradiol* 2001;22:65–72 [Medline](#)
12. Nagar VA, Ye JR, Ng WH, et al. **Diffusion-weighted MR imaging:**

- diagnosing atypical or malignant meningiomas and detecting tumor dedifferentiation. *AJNR Am J Neuroradiol* 2008;29:1147–52 [CrossRef Medline](#)
13. Pond JB, Morgan TG, Hatanpaa KJ, et al. Chordoid meningioma: differentiating a rare World Health Organization grade II tumor from other meningioma histologic subtypes using MRI. *AJNR Am J Neuroradiol* 2015;36:1253–58 [CrossRef Medline](#)
 14. Nagata S, Nishimura H, Uchida M, et al. Diffusion-weighted imaging of soft tissue tumors: usefulness of the apparent diffusion coefficient for differential diagnosis. *Radiat Med* 2008;26:287–95 [CrossRef Medline](#)
 15. Yeom KW, Lober RM, Mobley BC, et al. Diffusion-weighted MRI: distinction of skull base chordoma from chondrosarcoma. *AJNR Am J Neuroradiol* 2013;34:1056–61, S1 [CrossRef Medline](#)
 16. Yang S, Law M, Zagzag D, et al. Dynamic contrast-enhanced perfusion MR imaging measurements of endothelial permeability: differentiation between atypical and typical meningiomas. *AJNR Am J Neuroradiol* 2003;24:1554–59 [Medline](#)
 17. Zhang H, Rödiger LA, Shen T, et al. Perfusion MR imaging for differentiation of benign and malignant meningiomas. *Neuroradiology* 2008;50:525–30 [CrossRef Medline](#)
 18. Gühr GA, Horvath-Rizea D, Garnov N, et al. Diffusion profiling via a histogram approach distinguishes low-grade from high-grade meningiomas, can reflect the respective proliferative potential and progesterone receptor status. *Mol Imaging Biol* 2018;20:632–40 [CrossRef Medline](#)
 19. Schob S, Surov A, Wienke A, et al. Correlation between aquaporin 4 expression and different DWI parameters in grade I meningioma. *Mol Imaging Biol* 2017;19:138–42 [CrossRef Medline](#)
 20. Schob S, Frydrychowicz C, Gawlitza M, et al. Signal intensities in preoperative MRI do not reflect proliferative activity in meningioma. *Transl Oncol* 2016;9:274–79 [CrossRef Medline](#)
 21. Gühr GA, Horvath-Rizea D, Kohlhof-Meinecke P, et al. Histogram profiling of postcontrast T1-weighted MRI gives valuable insights into tumor biology and enables prediction of growth kinetics and prognosis in meningiomas. *Transl Oncol* 2018;11:957–61 [CrossRef Medline](#)

Improved Detection of Subtle Mesial Temporal Sclerosis: Validation of a Commercially Available Software for Automated Segmentation of Hippocampal Volume

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ABSTRACT

BACKGROUND AND PURPOSE: Identification of mesial temporal sclerosis is critical in the evaluation of individuals with temporal lobe epilepsy. Our aim was to assess the performance of FDA-approved software measures of hippocampal volume to identify mesial temporal sclerosis in patients with medically refractory temporal lobe epilepsy compared with the initial clinical interpretation of a neuroradiologist.

MATERIALS AND METHODS: Preoperative MRIs of 75 consecutive patients who underwent a temporal resection for temporal lobe epilepsy from 2011 to 2016 were retrospectively reviewed, and 71 were analyzed using Neuroreader, a commercially available automated segmentation and volumetric analysis package. Volume measures, including hippocampal volume as a percentage of total intracranial volume and the Neuroreader Index, were calculated. Radiologic interpretations of the MR imaging and pathology from subsequent resections were classified as either mesial temporal sclerosis or other, including normal findings. These measures of hippocampal volume were evaluated by receiver operating characteristic curves on the basis of pathologic confirmation of mesial temporal sclerosis in the resected temporal lobe. Sensitivity and specificity were calculated for each method and compared by means of the McNemar test using the optimal threshold as determined by the Youden J point.

RESULTS: Optimized thresholds of hippocampal percentage of a structural volume relative to total intracranial volume ($<0.19\%$) and the Neuroreader Index (≤ -3.8) were selected to optimize sensitivity and specificity (89%/71% and 89%/78%, respectively) for the identification of mesial temporal sclerosis in temporal lobe epilepsy compared with the initial clinical interpretation of the neuroradiologist (50% and 87%). Automated measures of hippocampal volume predicted mesial temporal sclerosis more accurately than radiologic interpretation (McNemar test, $P < .0001$).

CONCLUSIONS: Commercially available automated segmentation and volume analysis of the hippocampus accurately identifies mesial temporal sclerosis and performs significantly better than the interpretation of the radiologist.

ABBREVIATIONS: EEG = electroencephalography; MTS = mesial temporal sclerosis; NRI = Neuroreader Index; %Vol = percentage of a structural volume relative to total intracranial volume

Mesial temporal lobe epilepsy is one of the most common forms of epilepsy.¹ Temporal lobectomies for resection of an epileptogenic lesion are effective in reducing or even eliminating seizures and/or reducing the number of medications required for seizure management.^{2,3} Seizure semiology and scalp electroencephalography (EEG) remain critical for defining seizure onset. Concordant scalp EEG demonstrating a unilateral mesial temporal onset with unilateral mesial temporal sclerosis (MTS) predicts

postresection seizure freedom in up to 78% of patients.⁴ In the absence of an identifiable abnormality on MR imaging, invasive monitoring with surgical placement of intracranial electrodes is often necessary to confirm the localization of seizures measured by scalp EEG. In these instances, nonlesional MR imaging and intracranial monitoring demonstrating a mesial temporal seizure focus predict postresection seizure freedom in approximately 76% of patients.⁵ The presence of a positive MR imaging finding with concordant scalp EEG may be equivalent to more invasive monitoring for the localization of seizure and concordant EEG and MR imaging demonstrating MTS are considered sufficient to proceed directly to surgical resection.⁶ Thus, sensitive identification of MTS is critical to identify patients who may benefit from a resection.

Radiologically, mesial temporal sclerosis is suggested by the recognition of volume loss and T2 signal hyperintensity. This sub-

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jective interpretation can be difficult, especially with underlying diffuse cerebral volume loss as is commonly present in elderly individuals or in individuals with prior brain injury from trauma or infection, for example. Furthermore, although radiographically defined MTS relies on the presence of T2 signal abnormality, it is well-established that pathologically defined lesional MTS is discovered in cases in which the radiographic findings are very subtle and resection is primarily directed by invasive monitoring and seizure semiology. Reliable, objective tools to quantify volume loss, accounting for age and sex, would help overcome inter-observer variability and false-negative reporting, which can lead to delay or failure to identify an epileptogenic lesion potentially amenable to surgical intervention.

Neuroreader (Brainreader, Horsens, Denmark) calculates volumes and volumetric indices of specified brain regions, including hippocampal formations, on the basis of high-resolution T1-weighted MR imaging of the brain, using a variety of age- and sex-variable templates and normative data bases.⁷ MR imaging-based estimates of volume correlate with the interpretation of radiologists in a study of hippocampal volume loss in Alzheimer disease but perform better than radiologists when the clinical manifestations (and presumably the pathology) are more subtle.⁸ A different commercially available software platform, NeuroQuant (CorTech Labs, San Diego, California) was shown to be equivalent to the identification of hippocampal volume asymmetry by a radiologist.⁹ Manual estimation of hippocampal volumes failed to routinely identify a distinguishing threshold to identify abnormal hippocampi in epilepsy, and is time-prohibitive.^{10,11} The predictive value of imaging-based hippocampal volume estimation before epilepsy surgery has, however, been established using a variety of research-based automated techniques,^{12–18} but not with a clinically applicable or standardized solution. Validation of a clinically integrated method is necessary for implementation into routine practice. We chose this software on the basis of its FDA-approved status, robust and automated registration, and availability of normative comparison adjusted for age and sex.

We propose that automated volumetric analysis of MR imaging using the Neuroreader will correctly identify MTS by detecting hippocampal volume loss. The purpose of this study was to assess the performance of automated MR imaging-based measures of hippocampal volume to identify MTS in patients with medically refractory temporal lobe epilepsy compared with the interpretation of a neuroradiologist and to establish normative values to validate the method for clinical application.

MATERIALS AND METHODS

This study was approved by the University of Pittsburgh institutional review board. Informed consent was not required by the institutional review board given the retrospective nature of the study and the use of data acquired as part of an ongoing quality-assurance initiative.

Study Population

In this retrospective study, all subjects were adults (older than 18 years of age) who had undergone temporal lobectomy between 2011 and 2016 for treatment of epilepsy following consensus recommendation of the operation by the University of Pittsburgh

Medical Center Multidisciplinary Epilepsy Patient Management team. Seventy-five consecutive patients were identified during this time period. Preoperative evaluations included a detailed history, physical examination performed by a neurologist specialized in epilepsy care, scalp EEG, and 3T epilepsy protocol MR imaging in all patients. Magnetoencephalography, ictal single-photon emission CT, positron-emission tomography, and/or evaluation in an inpatient epilepsy-monitoring unit, including intracranial EEG monitoring, were added when indicated for seizure localization. Review of the clinical record was performed to obtain age, sex, and side of the operation. Four subjects were excluded for lack of imaging suitable for volumetric analysis.

Pathologic Reference Standard

Pathology reports of the resections were reviewed by a board-certified neuropathologist (C.A.W.) with >25 years of experience, and findings were classified as normal, MTS, or other (non-MTS lesion, including low-grade tumors, cavernous malformations, and dysplasia), with the reviewer blinded to the volumetric results. MTS was identified by the following criterion: discrete hippocampal damage consisting of neuronal loss and astrogliosis predominantly in the CA1 region but potentially including the end folium (CA4) and subiculum.

MR Imaging and Analysis

All included subjects had at least 1 clinical epilepsy protocol MR imaging performed, including an isotropic T1-weighted sequence acquired in either axial or coronal planes. The specific parameters varied slightly during 6 years (Discovery MR750w or Optima MR450w, BRAVO [GE Healthcare, Milwaukee, Wisconsin]: 1.5T–3T 3D fast spoiled gradient (FSPGR) BRAVO [GE Healthcare]; TR, 9.8–10.9 ms; TE, 4.1–4.5 ms; TI, 450 ms; flip angle, 8°–13°, NEX, 1; FOV, 250; matrix, 320 × 256–350 × 288; 1.2-mm thickness; 0.6- to 1.2-mm spacing; Tim Trio [Siemens, Erlangen, Germany]: 3T MPRAGE; TR, 2110 ms; TE, 2.6 ms; TI, 1100 ms; flip angle, 8°; NEX, 1; FOV, 75%; matrix, 256 × 192; 1.5-mm thick). All volumetric series were inspected for artifacts or large structural lesions that would interfere with the segmentation process. The volumetric sequence was then analyzed using Neuroreader.⁷ Output included measures of total intracranial and hippocampal volumes with calculation of the relative hippocampal volume as a percentage of total intracranial volume (%Vol) and the Neuroreader Index (NRI), a nonparametric index of size compared with a normative data base accounting for age and sex. If a subject had both axially and coronally acquired volumetric studies before the operation, both were analyzed and the resulting values were averaged.

Radiology reports from the relevant imaging acquired before the operation were reviewed and classified as having normal findings, MTS, or other (non-MTS lesion or equivocal abnormalities not meeting the radiologic criteria for MTS as defined by volume loss and T2 signal hyperintensity).¹⁹ All MR imaging studies were interpreted by 1 of 12 Certificate of Added Qualification–certified academic neuroradiologists as part of routine clinical practice, to reflect real-world comparison of the software with radiologic interpretation. The volumetric T1 sequence was used along with all other routine clinical pulse sequences in the radiologic assess-

ment. The interpretation of a radiologist was considered positive for MTS if MTS was offered as the most likely diagnosis in the radiology report.

Statistical Analysis

The reference standard was pathologic interpretation of either MTS or non-MTS (including other pathologies or normal findings). Receiver operating characteristic curves were generated for the hippocampal NRI and %Vol for both sides of the operation and contralateral brain. Area under the curve and Youden J point were calculated for each measure. Sensitivity, specificity, and accuracy based on a threshold value determined by the Youden J

point were then compared with the radiologic interpretation using the nonparametric McNemar test. All statistics were performed with SPSS Statistics for Windows, Version 24.0 (IBM, Armonk, New York).

RESULTS

Seventy-five subjects underwent temporal lobectomy during the study period. Four subjects were excluded for inadequate imaging. Twenty-six subjects had pathologic findings consistent with MTS, while 45 subjects had either normal findings or demonstrated other pathology. Basic demographics, incidences of non-MTS pathologies, and other features comparing the 2 groups are presented in Table 1. There were no significant differences between relevant demographics between the groups classified as MTS versus non-MTS. Minor variations in the T1 volumetric imaging acquisition parameters did not differ between the 2 groups.

Table 1: Demographics and details of the operation, pathology, and imaging evaluation

	MTS (n = 26)	Normal or Other Findings (n = 45)
Age at operation (mean) (SD) (yr)	43.7 (12.9)	42.0 (13.1)
Female sex (No.) (%)	14 (54%)	18 (40%)
Left temporal lobectomy (No.) (%)	14 (54%)	23 (51.1%)
Normal pathologic findings (No.) (%)	0 (0%)	23 (51.1%)
Other pathology (No.) (%)		
Low-grade glioma	0 (0%)	7 (15.5%)
Dysplasia	1 (3.8%)	3 (6.7%)
Cavernous malformation	0 (0%)	3 (6.7%)
Gliosis or old infarct	0 (0%)	4 (8.9%)
Volumetric T1 acquisition (No.) (%)		
Axial only	6 (23%)	8 (17.8%)
Coronal only	6 (23%)	10 (22.2%)
Both	14 (54%)	27 (60%)

Receiver Operating Characteristic Curves for Identification of MTS

Hippocampal %Vol classified the presence or absence of ipsilateral MTS with an area under the curve of 0.818 ($P < 0.001$); contralateral %Vol was not significantly correlated with MTS status (area under the curve = 0.602, $P = .151$). The NRI of the hippocampus classified the presence or absence of ipsilateral MTS with an area under the curve = 0.800 ($P < 0.001$); the contralateral NRI was not significantly correlated with MTS status (area under the curve = 0.560, $P = .399$). Receiver operating characteristic curves are demonstrated in Fig 1.

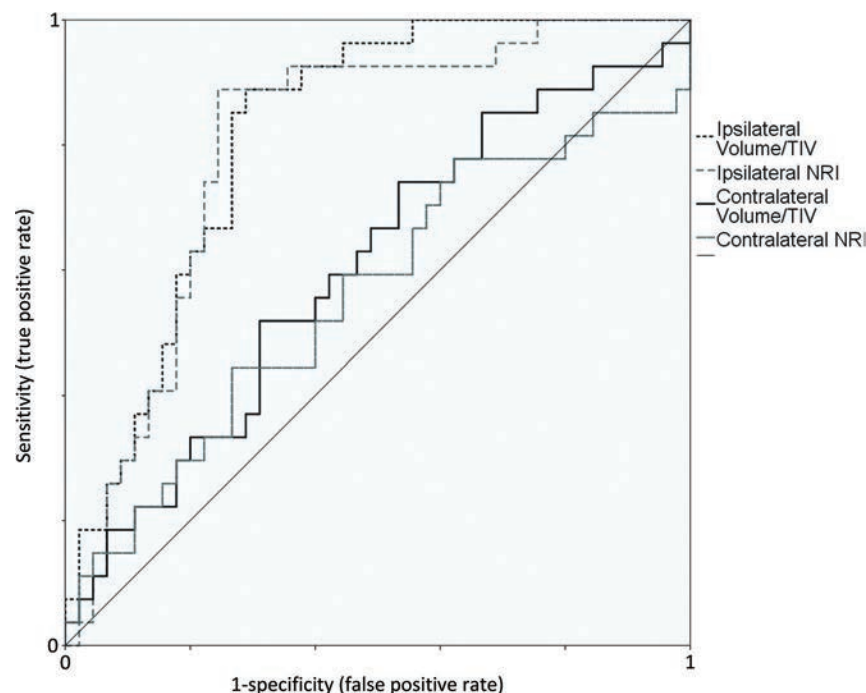


FIG 1. Receiver operating characteristic curve for mesial temporal sclerosis. The volume of the hippocampi corrected for total intracranial volume and the Neuroreader Index, a nonparametric comparative statistic derived from age- and sex-adjusted normative data, were calculated and evaluated for their ability to classify patients with pathology-proven mesial temporal sclerosis. Receiver operating characteristic curves from ipsilateral and contralateral hippocampal volume measures relative to the subsequent side of surgery are presented. Note that contralateral volumes appear skewed away from the 45° diagonal.

Comparison of Automated Segmentation Measures and Radiology Reporting

The Youden J point identified ideal thresholds for hippocampal NRI ≤ -3.80 and %Vol $< 0.19\%$ (Table 2). Pair-wise comparisons with the McNemar nonparametric test demonstrated that automated volumetric techniques performed significantly better than the interpretation of a radiologist for classification of MTS; there was no significant difference between the 2 automated volumetric measures, NRI or %Vol. Figure 2 presents 3 examples of left mesial temporal sclerosis, the corresponding clinical read, and the results from Neuroreader volumetric analysis.

DISCUSSION

Objective identification of hippocampal volume loss is associated with improved outcome from an epilepsy operation.¹² We used a commercially available software platform to demonstrate that automated volumetric measurements of preoperative brain MR imaging accurately predict pathologic evidence of MTS in TLE. Because MTS is one of the most

common lesions identified in this population before an operation, automated methods may be useful adjuncts to help radiologists more confidently identify lesions potentially amenable to surgical resection. Identification of epileptogenic lesions such as MTS can alter the treatment course for individuals with medically intractable epilepsy, prompting a more in-depth evaluation at a center dedicated to epilepsy surgery, informing a plan to confirm a seizure origin, and potentially avoiding more aggressive invasive diagnostic tests before the operation.⁶ Indeed, intracranial seizure monitoring is associated with a significant risk because up to 9%

of patients will experience surgical complications associated with their procedure, such as hemorrhage, infection, or CSF leak.²⁰

Hippocampal volume as a percentage of total intracranial volume and the NRI, a proprietary nonparametric index derived from comparison with normative databases accounting for age and sex, accurately identified MTS on the basis of preoperative imaging. Of note, the NRI did not perform significantly better than the %Vol measure, suggesting that the effect of age and sex did not substantially confound predictions when using this software in this population. Alternatively, the registration and segmentation strategy used by the software, in which best-fit templates are identified before registration, may help to pre-emptively account for age- and sex-related volume differences. A larger analysis of older patients would be helpful to further understand the specific contribution of accounting for these factors. Others have suggested using asymmetry indices. We found these measures to be inferior to individual volumes, potentially due to contralateral temporal lobe volume loss that has been described with MTS²¹; indeed, Fig 1 demonstrates that the contralateral temporal lobe volume was slightly skewed away from the 45°

Table 2: Comparison of Neuroreader measures with radiologist interpretation for detection of MTS

	SENS	SPEC	ACCUR	AUC	P	P, McNemar ^a
%Vol <0.193	89%	71%	77%	0.818	<0.001	<0.001
NRI ≤ -3.807	89%	76%	81%	0.800	<0.001	<0.001
Radiologist	50%	87%	73%	NA	NA	NA

Note:—SENS indicates sensitivity; SPEC, specificity; ACCUR, accuracy; NA, nonapplicable; AUC, area under the curve.

^aThe McNemar nonparametric test demonstrates significant differences using the provided thresholds compared with the interpretation of a radiologist for detection of mesial temporal sclerosis.

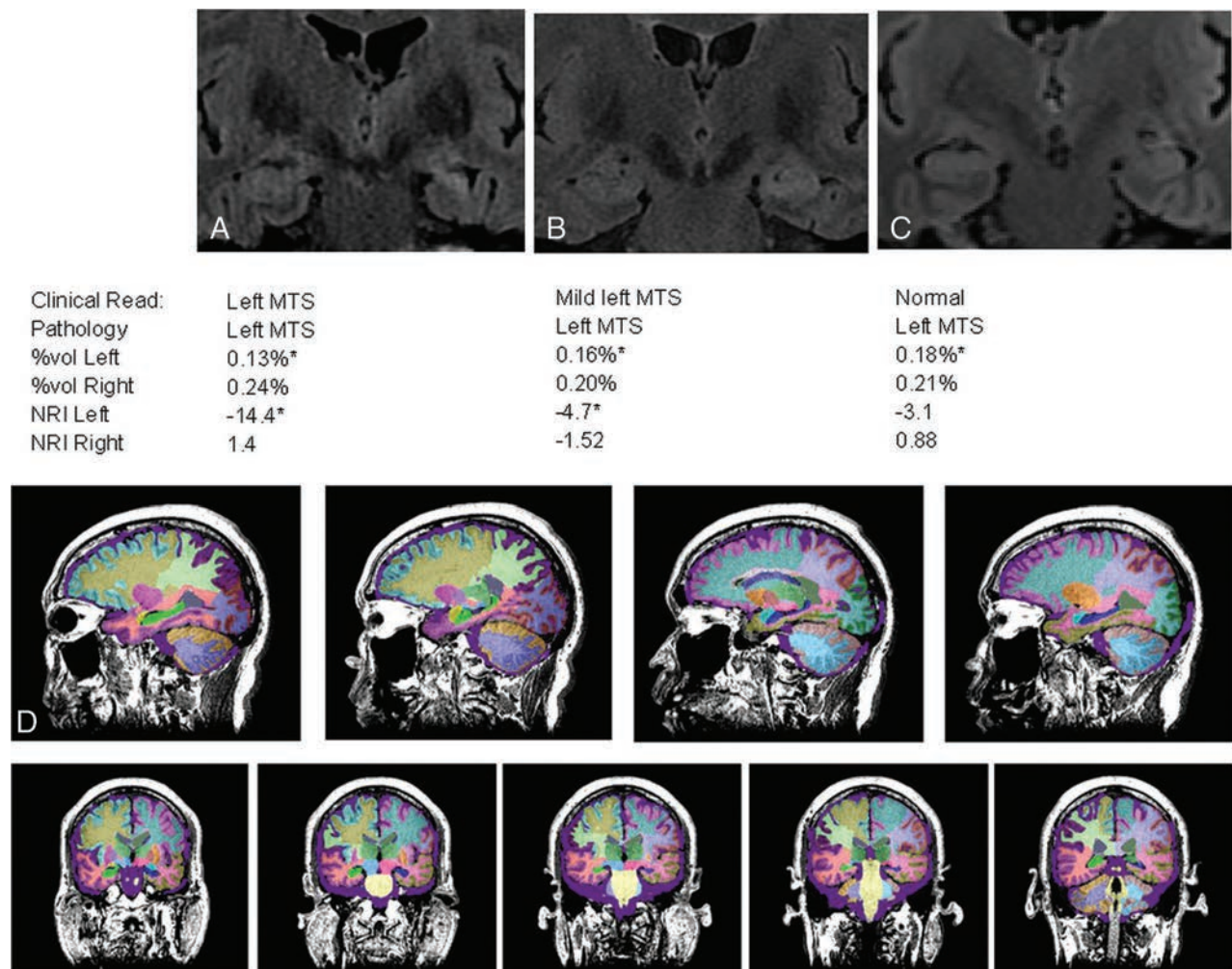


FIG 2. Volumetric analysis. A–C, Three patients with left mesial temporal sclerosis of varying conspicuity on MR imaging. Clinical reads and volumetric measures of the abnormal left and normal right hippocampal formations are presented below the images. D, Representative registration and segmentation. Hippocampal volumes are denoted by bright green (right) and dark blue (left) in a patient with left mesial temporal sclerosis.

angle line on the receiver operating characteristic curve, which would potentially degrade the sensitivity of asymmetry indices.

T2 signal intensity in the hippocampal formation is a traditional hallmark of mesial temporal sclerosis, but it was not specifically taken into consideration regarding the volumetric-based classification of disease. Although this approach goes against the traditional interpretation of MTS, we believe that overt MTS characterized by asymmetric volume loss and T2 hyperintensity is usually evident to the interpreting neuroradiologist and the primary added value of volumetric analysis would be to identify more subtle manifestations of MTS, which may not have substantial signal abnormality, thereby increasing sensitivity. Indeed, many of the discordant analyses between the radiologist and the automated volumetric analysis were in the context of false-negative radiology reporting. Conversely, non-MTS pathology such as tumors or focal cortical dysplasia is likely more evident to the radiologist, and false-positives potentially generated by automated segmentation would have little impact.

The incidence of MTS in this cohort (26/71, 37%) is not dissimilar to the report of Cohen-Gadol et al²² of 28% in a cohort of 399 patients without lesions, and the report of Tassi et al²³ of approximately 46% (mixed and isolated hippocampal sclerosis). Aggressive intracranial EEG monitoring using depth electrodes and grids has become more common, identifying more subtle, lateralizing temporal lobe epilepsy than before. Furthermore, there is growing recognition of mesial temporal lobe epilepsy amenable to resection, but without specific histopathology.²⁴ The number of cases with normal pathologic findings in this cohort may, in part, reflect nonsclerotic temporal lobe epilepsy, while other normal pathologic findings may simply reflect a damaged or incomplete specimen that pathology could not reliably interpret as anything but normal. Last, there is likely some degree of institutional bias to the overall makeup of the patients included in this cohort, given that different subspecialty services such as oncologic surgery may be involved with resection of more obvious tumor-related seizure onset, and thus were not captured in this cohort.

Inclusion of all temporal lobe resections meant that a small proportion of the studied individuals had mesial temporal involvement of tumors, cavernous malformations, or dysplasia; most important, these were not generally misclassified by volumetric analysis (2 of 18). In one of these cases, an oligodendroglioma was correctly identified by the radiologist irrespective of the volume measure. The single case that was classified incorrectly by both the radiologist and Neuroreader as MTS was diagnosed as a cortical dysplasia by pathology. Thus, it is in this mixed setting that we suggest that the software would best complement interpretation of the radiologist and contribute to greater value of imaging interpretation.

Volumetric analysis of brain regions, particularly the hippocampus, is not new. From manual, semimanual, automated, and machine learning algorithms, the value of volumetric measures of regional brain structures has been recognized in many studies, including in the fields of epilepsy, dementia, and traumatic brain injury.^{11,16–18,25,26} However, many of these approaches use software or processes that are not FDA-approved or require a prohibitive amount of time to complete, rendering them difficult to incorporate into routine clinical practice or replicate at

different sites. The relative merits of accuracy for each of these methods could be debated; however, there is clear value in the consistency and availability of a methodology to assist in traditional interpretation, and these data validate the use of volumetric analysis in this clinical context and establish normative values for clinical implementation. Future studies to determine which commercial applications perform best or most reliably for specific populations and indications would provide helpful guidance.

A limitation of this study was the retrospective nature of analysis, including only those individuals who had undergone temporal lobectomy. Future investigation requiring greater numbers of participants will better address the role of prospective volumetric analysis in epilepsy evaluations, including patients with bitemporal seizure onset, and the contribution to prognostication of surgical outcome. Our study did not directly assess the benefit of prospective interpretation when using the volumetric software. MR imaging interpretation was also made by a group of radiologists rather than a single reader, likely increasing variability but reflecting typical real-world workflow. A comprehensive review of the MRIs was not performed because we wanted to demonstrate the contribution of volumetric analysis to the true clinical read. Last, we did not consider the side of the operation or handedness of the individuals in developing our thresholds, assuming that a single-volume threshold could be applied to both the left and the right hippocampal formations in the general population, which is predominantly right-handed. Previous studies have shown that there are no significant differences between the left and right hippocampal volumes in right-handed individuals,²⁷ though a small-but-statistically significant difference was reported for left-handed individuals. A variety of scanners and volumetric protocols was included in the analysis, but without bias toward one group or the other. The software is built to robustly analyze data across platforms for consistent clinical application.

Future investigation should focus on directly comparing the performance of the volumetric software alone with the performance of a radiologist using the volumetric software in a prospective manner. We propose that the interpretation of a radiologist would be complemented by automated hippocampal volumetric measures for optimal diagnostic accuracy. While the radiologist will likely best identify obvious lesions such as advanced MTS, a cavernous malformation, cortical dysplasia, or tumor, accuracy for identification of subtle mesial temporal sclerosis will be increased given the improved sensitivity provided by the volumetric analysis. We predict that radiologists will experience increased confidence in their interpretations when using this software and describing normal study findings or subtle manifestations of mesial temporal sclerosis based on the thresholds and parameters presented above. The slightly lower specificity of the volumetric analysis is acceptable and may, in some way, be mitigated by the radiologists. In addition, the decision to proceed with an operation takes into account many other data, including scalp and intracranial EEG analysis, seizure semiology, and neurocognitive testing as well as other imaging modalities such as PET, ictal/interictal SPECT, and magnetoencephalography.

CONCLUSIONS

Automated segmentation and volumetric analysis using Neuroreader perform significantly better than subjective evaluation by a radiologist for preoperative identification of MTS in patients with mesial temporal lobe epilepsy. On the basis of this dataset, we propose that hippocampal %Vol of $\leq 0.19\%$ or NRI of ≤ -3.8 , should be considered strongly suggestive of MTS.

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REFERENCES

1. Siegel AM. Presurgical evaluation and surgical treatment of medically refractory epilepsy. *Neurosurg Rev* 2004;27:1–18, discussion 19–21 Medline
2. Miller JW, Hakimian S. Surgical treatment of epilepsy. *Continuum (Minneapolis)* 2013;19(3 Epilepsy):730–42 CrossRef Medline
3. Kwan P, Sperling MR. Refractory seizures: try additional antiepileptic drugs (after two have failed) or go directly to early surgery evaluation? *Epilepsia* 2009;50(Suppl 8):57–62 CrossRef Medline
4. Patariaia E, Lurger S, Serles W, et al. Ictal scalp EEG in unilateral mesial temporal lobe epilepsy. *Epilepsia* 1998;39:608–14 CrossRef Medline
5. Lee RW, Hoogs MM, Burkholder DB, et al. Outcome of intracranial electroencephalography monitoring and surgery in magnetic resonance imaging-negative temporal lobe epilepsy. *Epilepsy Res* 2014;108:937–44 CrossRef Medline
6. Diehl B, Lüders HO. Temporal lobe epilepsy: when are invasive recordings needed? *Epilepsia* 2000;41(Suppl 3):S61–74 Medline
7. Ahdidan J, Raji CA, DeYoe EA, et al. Quantitative neuroimaging software for clinical assessment of hippocampal volumes on MR imaging. *J Alzheimers Dis* 2016;49:723–32 CrossRef Medline
8. Boutet C, Chupin M, Colliot O, et al. Is radiological evaluation as good as computer-based volumetry to assess hippocampal atrophy in Alzheimer's disease? *Neuroradiology* 2012;54:1321–30 CrossRef Medline
9. Azab M, Carone M, Ying SH, et al. Mesial temporal sclerosis: accuracy of NeuroQuant versus neuroradiologist. *AJNR Am J Neuroradiol* 2015;36:1400–06 CrossRef Medline
10. Hanamiya M, Korogi Y, Kakeda S, et al. Partial loss of hippocampal striation in medial temporal lobe epilepsy: pilot evaluation with high-spatial-resolution T2-weighted MR imaging at 3.0 T. *Radiology* 2009;251:873–81 CrossRef Medline
11. Germeyan SC, Kalikhman D, Jones L, et al. Automated versus manual hippocampal segmentation in preoperative and postoperative patients with epilepsy. *Epilepsia* 2014;55:1374–79 CrossRef Medline
12. Jack CR Jr, Sharbrough FW, Cascino GD, et al. Magnetic resonance image-based hippocampal volumetry: correlation with outcome after temporal lobectomy. *Ann Neurol* 1992;31:138–46 CrossRef Medline
13. Jardim AP, Corso JT, Garcia MT, et al. Hippocampal atrophy on MRI is predictive of histopathological patterns and surgical prognosis in mesial temporal lobe epilepsy with hippocampal sclerosis. *Epilepsy Res* 2016;128:169–75 CrossRef Medline
14. Barnes J, Boyes RG, Lewis EB, et al. Automatic calculation of hippocampal atrophy rates using a hippocampal template and the boundary shift integral. *Neurobiol Aging* 2007;28:1657–63 CrossRef Medline
15. Barnes J, Foster J, Boyes RG, et al. A comparison of methods for the automated calculation of volumes and atrophy rates in the hippocampus. *Neuroimage* 2008;40:1655–71 CrossRef Medline
16. Hosseini MP, Nazem-Zadeh MR, Pompili D, et al. Comparative performance evaluation of automated segmentation methods of hippocampus from magnetic resonance images of temporal lobe epilepsy patients. *Med Phys* 2016;43:538 CrossRef Medline
17. Rudie JD, Colby JB, Salamon N. Machine learning classification of mesial temporal sclerosis in epilepsy patients. *Epilepsy Res* 2015;117:63–69 CrossRef Medline
18. Winston GP, Cardoso MJ, Williams EJ, et al. Automated hippocampal segmentation in patients with epilepsy: available free online. *Epilepsia* 2013;54:2166–73 CrossRef Medline
19. Howe KL, Dimitri D, Heyn C, et al. Histologically confirmed hippocampal structural features revealed by 3T MR imaging: potential to increase diagnostic specificity of mesial temporal sclerosis. *AJNR Am J Neuroradiol* 2010;31:1682–89 CrossRef Medline
20. Schmidt RF, Wu C, Lang MJ, et al. Complications of subdural and depth electrodes in 269 patients undergoing 317 procedures for invasive monitoring in epilepsy. *Epilepsia* 2016;57:1697–708 CrossRef Medline
21. Cascino GD. Temporal lobe epilepsy: more than hippocampal pathology. *Epilepsy Curr* 2005;5:187–89 CrossRef Medline
22. Cohen-Gadol AA, Wilhelm BG, Collignon F, et al. Long-term outcome of epilepsy surgery among 399 patients with nonlesional seizure foci including mesial temporal lobe sclerosis. *J Neurosurg* 2006;104:513–24 Medline
23. Tassi L, Meroni A, Deleo F, et al. Temporal lobe epilepsy: neuro-pathological and clinical correlations in 243 surgically treated patients. *Epileptic Disord* 2009;11:281–92 CrossRef Medline
24. Usui N, Baba K, Matsuda K, et al. Mesial temporal lobe epilepsy with no specific histological abnormality: a distinct surgically remediable syndrome. *Epilepsy Behav* 2013;29:542–47 CrossRef Medline
25. Akhondi-Asl A, Jafari-Khouzani K, Elisevich K, et al. Hippocampal volumetry for lateralization of temporal lobe epilepsy: automated versus manual methods. *Neuroimage* 2011;54(Suppl 1):S218–26 CrossRef Medline
26. Raji CA, Merrill DA, Barrio JR, et al. Progressive focal gray matter volume loss in a former high school football player: a possible magnetic resonance imaging volumetric signature for chronic traumatic encephalopathy. *Am J Geriatr Psychiatry* 2016;24:784–90 CrossRef Medline
27. Szabo CA, Xiong J, Lancaster JL, et al. Amygdalar and hippocampal volumetry in control participants: differences regarding handedness. *AJNR Am J Neuroradiol* 2001;22:1342–45 Medline

A Serial 10-Year Follow-Up Study of Atrophied Brain Lesion Volume and Disability Progression in Patients with Relapsing-Relmitting MS

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ABSTRACT

BACKGROUND AND PURPOSE: Disappearance of T2 lesions into CSF spaces is frequently observed in patients with MS. Our aim was to investigate temporal changes of cumulative atrophied brain T2 lesion volume and 10-year confirmed disability progression.

MATERIALS AND METHODS: We studied 176 patients with relapsing-remitting MS who underwent MR imaging at baseline, 6 months, and then yearly for 10 years. Occurrence of new/enlarging T2 lesions, changes in T2 lesion volume, and whole-brain, cortical and ventricle volumes were assessed yearly between baseline and 10 years. Atrophied T2 lesion volume was calculated by combining baseline lesion masks with follow-up CSF partial volume maps. Ten-year confirmed disability progression was confirmed after 48 weeks. ANCOVA detected MR imaging outcome differences in stable ($n = 76$) and confirmed disability progression ($n = 100$) groups at different time points; hierarchic regression determined the unique additive variance explained by atrophied T2 lesion volume regarding the association with confirmed disability progression, in addition to other MR imaging metrics. Cox regression investigated the association of early MR imaging outcome changes and time to development of confirmed disability progression.

RESULTS: The separation of stable-versus-confirmed disability progression groups became significant even in the first 6 months for atrophied T2 lesion volume (140% difference, Cohen $d = 0.54$, $P = .004$) and remained significant across all time points ($P \leq .007$). The hierarchic model, including all other MR imaging outcomes during 10 years predicting confirmed disability progression, improved significantly after adding atrophied T2 lesion volume ($R^2 = 0.27$, R^2 change 0.11, $P = .009$). In Cox regression, atrophied T2 lesion volume in 0–6 months (hazard ratio = 4.23, $P = .04$) and 0–12 months (hazard ratio = 2.41, $P = .022$) was the only significant MR imaging predictor of time to confirmed disability progression.

CONCLUSIONS: Atrophied T2 lesion volume is a robust and early marker of disability progression in relapsing-remitting MS.

ABBREVIATIONS: CDP = confirmed disability progression; EDSS = Expanded Disability Status Scale; LV = lesion volume; PBVC = percentage brain volume change; PCVC = percentage cortical volume change; PVVC = percentage ventricles volume change; RRMS = relapsing-remitting MS

For decades, appearance or accumulation of new or enlarging brain lesions or changes in lesion volume (LV) on MR imaging have been used as primary end points in Phase II clinical trials and as secondary end points in Phase III trials in multiple sclerosis.^{1–3} However, lesion activity and accumulation correlate poorly with

clinical evolution in the mid- to long-term^{1,4–8}; thus, measurement of brain atrophy has been introduced as a meaningful indicator of neurodegeneration and clinical disease progression in patients with MS.^{9–12} However, there is a further need to investigate and develop new MR imaging outcomes that can detect early changes associated with mid- to long-term disease progression in patients with MS.

One such newly proposed surrogate imaging biomarker of disease progression is the rate of brain lesion loss due to atrophy (atrophied T2-LV), which represents areas of lesional tissue

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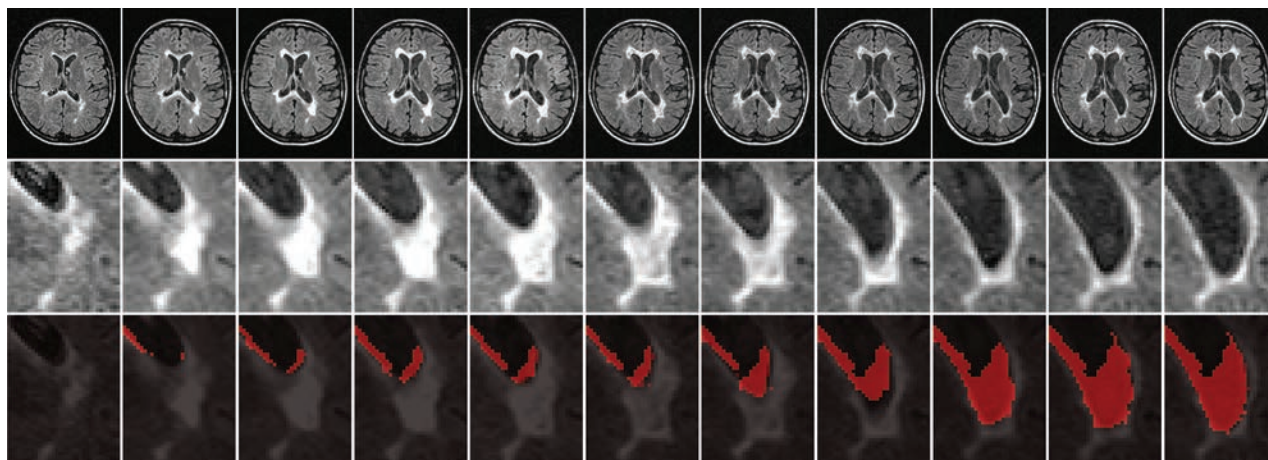


FIGURE. Representative example of a serially enlarging and then atrophying lesion. The *upper* row shows raw T2-FLAIR images from baseline to 10-year follow-up in 1-year increments, and the *middle* row provides an enlarged view of the relevant lesion. In the *lower* row, cumulative atrophied lesion volume is shown for the same area, in which red voxels indicate regions that were lesions at any prior time point and are CSF at the current time point.

having been replaced by CSF at subsequent time points, either through direct transformation or by displacement due to substantial atrophy-related local movement (Figure).^{13,14} The MS lesions at a closer distance to the inner and outer surfaces of the brain (located around ventricles or the subpial region of the cortex) are particularly vulnerable to disease pathology, likely in part due to the vicinity of CSF-mediated factors.¹⁵ It has been previously reported that the accumulation of atrophied brain T2-LV occurs mostly in the periventricular region but also, to some degree, in the cortical portions of the brain.¹³ Thus, it can be hypothesized that atrophied T2-LV measures the most vulnerable portion of lesion tissue shrinkage/destruction across time in these areas. Dwyer et al¹³ investigated the independent predictive value of atrophied T2-LV for the development of clinical disability in 174 patients with MS and 18 patients with clinically isolated syndrome and found that atrophied T2-LV was higher in patients with progressive MS, compared with those with relapsing-remitting (RR) MS or clinically isolated syndrome subtypes and explained significant additional variance in predicting disability, even when controlling for both new/enlarging lesion activity and whole-brain atrophy.

In this study, we aimed to investigate temporal changes of atrophied T2-LV and disease progression, using a well-established cohort of patients with early RRMS who participated in a previous clinical trial,¹⁶ and its long-term open-label 10-year extension,^{8,17,18} using serial MR imaging.

MATERIALS AND METHODS

Patient Population

This study of atrophied T2-LV in RRMS used a patient cohort in the 10-year Avonex-Steroid-Azathioprine (ASA) study from the Charles University, Prague, Czech Republic, in which clinical and MR imaging outcomes were previously reported.⁸ In the ASA study, 181 patients with early RRMS were initially enrolled into the 2-year double-blind, placebo-controlled phase¹⁶ and subsequently in its 5-year^{17,18} and 10-year⁸ open-label extensions. At the 10-year follow-up, 176 (97.2%) of the initial 181 patients were assessed.⁸ Two patients died (1 due to ovarian cancer and 1 due to

myocardial infarction), and 3 moved outside the area.⁸ The treatment characteristics of the studied cohort are reported in the On-line Appendix.

As previously reported,⁸ all patients were clinically assessed using the Expanded Disability Status Scale (EDSS) every 2 months during the first year and then every 3 months until year 10. MR imaging assessments were performed at baseline, 6 months, and yearly intervals at least 14 days after the last administration of any steroid treatment.

The study was approved by the Medical Ethics Committees, and all patients gave their written informed consent.

MR Imaging Acquisition and Analysis

All MR imaging assessments were performed using the same Gyroscan Intera 1.5T scanner (Philips Medical Systems, Best, the Netherlands), which did not undergo major hardware upgrades during a 10-year period. Axial brain images were obtained using nongapped FLAIR with a 1.5-mm thickness and axial 3D T1-weighted images with a 1-mm slice thickness.

The image analysis for this study included calculation of atrophied T2-LV, as previously described.¹³ Briefly, the acquired images were preprocessed with N4¹⁹ to remove spatially varying intensity inhomogeneities, standardized using a piecewise histogram-matching technique,²⁰ and linearly aligned to the baseline space using the FMRIB Linear Image Registration Tool (FLIRT; <http://www.fmrib.ox.ac.uk/fsl/fslwiki/FLIRT>).²¹ 3D-T1 images were then inpainted using FSL's Lesion Filling Tool (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/lesion_filling) to mitigate the impact of hypointense lesions on segmentation.²² To calculate atrophied T2-LV, we overlaid rigidly aligned follow-up FSL SIENAX CSF maps (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/SIENA>) on baseline T2 lesion masks. Voxelwise follow-up CSF partial volume was then integrated over the baseline lesion regions to determine the total volume of periventricular and the nonperiventricular lesion tissue subsequently replaced by CSF (Figure).¹³ The reliability of the atrophied T2-LV measurement was previously reported.¹³

T2 lesion and whole-brain, cortical, and ventricle brain volume analyses are described in the On-line Appendix.

Table 1: Demographic and clinical characteristics at baseline and during the follow-up in 176 patients with MS, according to the confirmed disability progression status at the 10-year follow-up

	Total Study Cohort (N = 176)	Stable Group (n = 76)	CDP Group (n = 100)	P Value ^a
Female sex (No.) (%)	137 (77.8)	57 (75)	80 (80)	.429
Age at baseline (mean) (SD) (yr)	30.7 (7.9)	28.7 (7.1)	31.8 (7.9)	.008 ^b
Disease duration at baseline (mean) (SD) (yr)	4.9 (5.2)	4.0 (3.2)	5.7 (6.2)	.02
EDSS at baseline (median) (IQR)	2.0 (1.0–2.5)	2.0 (1.0–2.0)	2.0 (1.5–2.0)	.093
EDSS at follow-up (median) (IQR)	3.0 (2.0–4.0)	2.0 (1.5–2.5)	4.0 (3.0–5.0)	<.001 ^b
EDSS absolute change during follow-up (median) (IQR)	1.3 (0–2) 1.0	0.13 (0–0.5) 0	2.2 (1.5–3) 2.0	<.001 ^b
No. of relapses between baseline and follow-up (mean) (SD)	5.2 (3.8) 5	4.6 (3.9)	5.8 (3.7)	.048
Annual relapse rate during the follow-up (mean) (SD)	0.5 (0.4)	0.5 (0.4)	0.6 (0.4)	.048
Relapse-free from baseline to follow-up (No.) (%)	7 (4)	5 (6.6)	2 (2)	.124
Treatment status at follow-up (No.) (%)				
Remained on IM interferon β -1a	74 (42)	45 (59.2)	29 (29)	<.001 ^b
Switched to other DMTs	79 (44.9)	23 (30.3)	56 (56)	
Discontinued DMT	23 (13.1)	8 (10.5)	15 (15)	
Time on interferon β -1a IM (mean) (SD) (mo)	87.3 (99.5)	91.3 (16.6)	84.1 (24.4)	.022

Note:—IQR indicates interquartile range; IM, intramuscular; DMT, disease-modifying treatment.

^a P values represent the stable-vs-CDP group comparisons and were derived using the Student *t* test, χ^2 test, and Mann-Whitney rank sum test, as appropriate.

^b Significant P values < .05.

Statistical Analysis

Statistical analysis was conducted using SPSS (Version 23.0; IBM, Armonk, New York). Demographic and clinical characteristics were compared between patients with MS with a 10-year stable disease course and those with confirmed disability progression (CDP) using the Student *t* test, χ^2 test, and Mann-Whitney rank sum test. ANCOVA adjusted for age, sex, and treatment change was used to compare MR imaging changes among the study groups during 10 years. Variables were checked for normality both visually and using Shapiro-Wilk tests.

The CDP (confirmed after 48 weeks) was defined as any 1.0-point sustained increase in the EDSS score in patients who had a baseline EDSS score of ≥ 1.0 or any ≥ 1.5 -point increase in patients who had a score of 0.⁸ To facilitate survival analysis, we designated the time to event as the time in months between baseline and the point of disability progression (confirmed after 48 weeks). Patients who did not show disability progression were censored at the 10-year mark (confirmed at 48 weeks).

To explore the association between atrophied T2-LV and other MR imaging outcomes with CDP, we used both univariate and multivariable logistic regression analyses. To determine the unique additive variance explained by atrophied T2-LV in association with CDP in addition to other MR imaging metrics, we used a full hierarchic regression model, with age, sex, and MR imaging outcomes entered in the first model and atrophied T2-LV added as a second step. This nested model was compared using a likelihood ratio test. Multicollinearity was assessed using the variance inflation factor, with a variance inflation factor of < 5 being considered acceptable.

Cox regression was used to analyze the association of early MR imaging outcome changes (0–6 and 0–12 months) and time to development of CDP. The hazard ratio of models with lesion measures as the predictor represent an increase in risk of progression with 1 new/enlarging lesion or a 1-mL change in lesion volume, while models with percentage brain volume change (PBVC), percentage cortical volume change (PCVC), and percentage ventricles volume change (PVVC) as the predictors represent the increase in risk of progression with a 1% change in brain volume. Subsequently, Kaplan-Meier analysis was per-

formed when groups were classified using receiver operating characteristic curve analysis to determine cutoff points of the MR imaging variables at 80% specificity in predicting CDP (confirmed after 48 weeks). Results are reported as the cutoff point value, area under the curve, and sensitivity.

The Benjamini-Hochberg correction was used to control the false discovery rate, and corrected P values < .05 were considered significant using 2-tailed tests.²³

RESULTS

Demographic and Clinical Characteristics

Table 1 shows baseline and follow-up demographic and clinical characteristics, according to the CDP status for the 176 evaluable patients assessed at the 10-year follow-up, as previously reported.⁸ At the 10-year follow-up, 100 (56.8%) patients with MS developed CDP and 76 (43.2%) remained stable. The median time to disability progression (confirmed after 48 weeks) was 48.6 months (interquartile range, 24.2–72.9 months).

MR Imaging Characteristics at Baseline and at 10-Year Follow-Up

On-line Table 1 shows MR imaging baseline and follow-up characteristics in 176 patients with MS, according to CDP status at the 10-year follow-up. At baseline, there were no significant differences between the stable and CDP groups for T2-LV ($P = .076$), normalized whole-brain volume ($P = .523$), normalized cortical volume ($P = .879$), or normalized ventricle volume ($P = .573$). During 10 years, patients with RRMS accumulated 3.83 mL of T2-LV, 19.5 new/enlarging T2 lesions, and 1.11 mL of atrophied T2-LV. The average PBVC was -6.52% , PCVC was -7.0% , and PVVC was 42% . Atrophied T2-LV (0.68 versus 1.54 mL, $P < .001$), PBVC (-5.23% versus -7.52% , $P < .001$), PCVC (-6.22% versus -7.71% , $P = .001$), and PVVC (32.4% versus 49.7% , $P = .001$) differed between patients with MS with stable disease and those with CDP at the 10-year mark of the follow-up, whereas absolute change in T2-LV (2.89 versus 4.59 mL, $P = .190$) and accumulation of new/enlarging T2 lesions (18.67 versus 20.03 , $P = .753$) did not.

Table 2: Time course of cumulative atrophied T2 lesion volume on serial MRI in patients with MS, according to the confirmed disability progression status at the 10-year follow-up^a

Months from Baseline	No. in Stable Group	Atrophied T2-LV Stable Group (Mean) (SD)	No. of Patients with CDP	Atrophied T2-LV CDP Group (Mean) (SD)	% Difference	Cohen d	P Value ^b
6 mo	74	0.05 (0.09)	94	0.12 (0.16)	140	0.54	.004
12 mo	76	0.09 (0.14)	95	0.21 (0.30)	133	0.51	<.001
24 mo	68	0.14 (0.21)	85	0.32 (0.41)	129	0.52	<.001
36 mo	67	0.21 (0.36)	89	0.40 (0.50)	90.5	0.44	<.001
48 mo	68	0.30 (0.50)	87	0.52 (0.70)	73.3	0.36	.007
60 mo	67	0.36 (0.57)	91	0.62 (0.83)	72.2	0.37	.004
72 mo	66	0.43 (0.70)	87	0.83 (1.10)	93	0.43	<.001
84 mo	68	0.44 (0.54)	85	1.10 (1.40)	150	0.62	<.001
96 mo	67	0.52 (0.66)	87	1.36 (1.72)	162	0.64	.004
108 mo	68	0.60 (0.76)	84	1.39 (1.68)	132	0.61	<.001
120 mo	68	0.68 (0.85)	85	1.54 (1.90)	126.5	0.58	<.001

^a The volumes are presented in milliliters.

^b P values, percentage difference, and Cohen d effect size represent the CDP-vs-stable group comparisons. The follow-up changes in P values were calculated using analysis of covariance corrected for age, sex, and treatment change at each time point. The Benjamini-Hochberg correction was used to minimize the false discovery rate, and all P values < .05 were considered significant.

Table 3: Time course of whole-brain atrophy on serial MRI in patients with MS, according to the confirmed disability progression status at the 10-year follow-up

Months from Baseline	No. in Stable Group	PBVC Stable Group (Mean) (SD)	No. of Patients with CDP	PBVC CDP Group (Mean) (SD)	% Difference	Cohen d	P Value ^a
6 mo	74	-0.24 (0.80)	94	-0.34 (1.00)	47.8	0.11	.396
12 mo	76	-0.50 (0.88)	95	-0.77 (1.33)	54.0	0.27	.098
24 mo	68	-0.99 (1.13)	85	-1.49 (1.66)	50.5	0.36	.022 ^b
36 mo	67	-1.70 (1.66)	89	-2.51 (2.42)	46.8	0.38	.010 ^b
48 mo	68	-2.24 (1.76)	87	-3.50 (3.11)	55.8	0.51	<.001 ^b
60 mo	67	-2.63 (2.10)	91	-4.46 (3.80)	69.6	0.62	<.001 ^b
72 mo	66	-3.18 (2.30)	87	-5.03 (3.16)	58.2	0.68	<.001 ^b
84 mo	68	-3.92 (2.60)	85	-6.00 (3.58)	53.3	0.67	<.001 ^b
96 mo	67	-4.49 (2.81)	87	-6.30 (3.40)	40.3	0.58	<.001 ^b
108 mo	68	-4.58 (2.91)	84	-6.86 (3.64)	49.8	0.70	<.001 ^b
120 mo	68	-5.23 (3.00)	85	-7.52 (3.84)	43.8	0.55	<.001 ^b

^a P values, percentage difference, and Cohen d effect size represent the CDP-vs-stable group comparisons. The follow-up changes in P values were calculated using analysis of covariance corrected for age, sex, and treatment change at each time point. The Benjamini-Hochberg correction was used to minimize the false discovery rate, and P values < .05 were considered significant.

^b Significant P values < .05.

Serial MR Imaging Changes during 10-Year Follow-Up

On-line Tables 2 and 3 and On-line Figure A, -B show serial cumulative changes of new/enlarging T2 lesions and absolute T2-LV changes during the 10-year follow-up. No differences for accumulation of new/enlarging T2 lesions or absolute changes of T2-LV were found between stable and CDP groups at any time point of the study.

Tables 2 and 3 and On-line Figure C, -D show serial changes of PBVC and cumulative atrophied T2-LV. The separation of stable-versus-CDP groups became significant even in the first 6 months for atrophied T2-LV (140% difference, Cohen d = 0.54, $P = .004$) and remained significant across all time points (between 72.2% and 162% difference, $P \leq .007$), while the difference for PBVC became significant only at the 2-year follow-up (50.5% difference, Cohen d = 0.36, $P = .022$) and remained significant across all remaining time points (between 40.3% and 69.6% difference, $P \leq .01$).

On-line Tables 4 and 5 and On-line Figure E, -F show serial changes of PCVC and PVVC. The separation of stable-versus-CDP groups became significant only at 5 years for PCVC (31.6% difference, Cohen d = 0.44, $P = .008$) and remained significant

across the remaining time points, while the difference for PVVC became significant at the 2-year follow-up (50.8% difference, Cohen d = 0.38, $P = .025$) and remained significant across all remaining time points.

On-line Tables 6 and 7 show the time course of atrophied T2-LV and PBVC between different consecutive MR imaging time points in patients with MS, according to the CDP at the 10-year follow-up. The atrophied T2-LV was able to differentiate patients with stable MS from those who developed CDP at all time points ($P \leq .012$) except for periods of 24–36 months ($P = .190$), 36–48 months ($P = .075$), and 84–96 months ($P = .061$), whereas no significant changes were observed for PBVC, PCVC, and PVVC.

Association of Atrophied Brain T2-LV with Other MR Imaging Outcomes and Confirmed Disability Progression

In univariate regression analysis, T2-LV at baseline ($R^2 = 0.40$, $P < .001$), new/enlarging T2 lesion accumulation during 10 years ($R^2 = 0.39$, $P < .001$), PBVC loss during 10 years ($R^2 = 0.30$, $P < .001$), PVVC during 10 years ($R^2 = 0.13$, $P = .002$), PCVC during 10 years ($R^2 = 0.20$, $P < .001$), and absolute change in T2-LV

Table 4: Early MRI predictors (0–6 and 0–12 mo) of time to confirmed disability progression status using Cox regression analysis and Kaplan-Meier survival analysis^a

	Cox Regression Analysis		AUC Analysis		Kaplan-Meier Survival Analysis at 80% Specificity		
	HR	P Value	AUC	P Value	Cutoff	Sensitivity	P Value
New/enlarging T2 lesions 0–6 mo	1.01	.726	0.56	.293	3.5	0.25	.582
New/enlarging T2 lesions 0–12 mo	1.01	.435	0.59	.072	5.3	0.33	.171
T2-LV absolute change 0–6 mo	1.02	.711	0.54	.501	1.16	0.27	.415
T2-LV absolute change 0–12 mo	1.03	.567	0.57	.190	1.41	0.32	.188
Atrophied T2-LV 0–6 mo	4.23	.04 ^b	0.61	.022 ^b	0.09	0.40	.017 ^b
Atrophied T2-LV 0–12 mo	2.41	.022 ^b	0.61	.022 ^b	0.18	0.36	.076
PBVC 0–6 mo	0.89	.431	0.54	.366	−0.83	0.29	.128
PBVC 0–12 mo	0.85	.105	0.55	.379	−1.38	0.21	.704
PVVC 0–6 mo	1.01	.419	0.52	.707	13.46	0.22	.482
PVVC 0–12 mo	1.07	.375	0.53	.451	16.29	0.26	.487
PCVC 0–6 mo	0.92	.123	0.55	.272	−2.28	0.31	.152
PCVC 0–12 mo	0.92	.115	0.62	.011 ^b	−2.47	0.39	.091

Note:—HR indicates hazard ratio; AUC, area under the curve.

^a Cox regression and Kaplan-Meier analyses were used to analyze the association of early MRI outcome changes (0–6 and 0–12 mo) and time to development of CDP. The Benjamini-Hochberg correction was used to minimize the false discovery rate, and *P* values < .05 were considered significant.

^b Significant *P* value < .05.

during 10 years ($R^2 = 0.25$, $P < .001$) were associated with cumulative atrophied T2-LV during 10 years. In a multivariable stepwise regression model, T2-LV at baseline, new/enlarging T2 lesion accumulation during 10 years, and PBVC during 10 years were associated with atrophied T2-LV at 10 years (overall adjusted model, $R^2 = 0.54$, $P < .001$).

In univariate logistic regression analysis, atrophied T2-LV ($R^2 = 0.21$), PBVC ($R^2 = 0.13$), PVVC ($R^2 = 0.13$), and PCVC ($R^2 = 0.07$) were each significantly associated with CDP at 10 years, while absolute T2-LV change ($R^2 = 0.012$) and accumulation of new/enlarging T2 lesions ($R^2 = 0.011$) were not. In a multivariable logistic regression model including all MR imaging measures significant in univariate analysis, the final model predicting CDP included only atrophied LV ($R^2 = 0.25$, variance inflation factor ≤ 1.7 , $P = .04$).

In the hierarchic regression model, including all MR imaging measures predicting CDP at 10 years except atrophied T2-LV, the adjusted Nagelkerke R^2 was 0.16. When we added atrophied T2-LV during 10 years to the model, the model was significantly improved ($R^2 = 0.27$, R^2 change 0.11, variance inflation factor ≤ 2.5 , $P = .009$).

Early MR Imaging Outcome Predictors (0–6 and 0–12 Months) of Time to Confirmed Disability Progression

Table 4 shows the value of early MR imaging predictor measures (0–6 and 0–12 months) in predicting CDP using survival models.

In Cox regression analysis, only atrophied T2-LV showed a significant association with time to CDP in 0–6 months (hazard ratio = 4.23, $P = .04$) and 0–12 months (hazard ratio = 2.41, $P = .022$), while no significant changes were observed for new/enlarging T2 lesions and absolute change in T2-LV, PBVC, PCVC, or PVVC.

By means of Kaplan-Meier survival analysis based on cutoff points at 80% specificity in predicting CDP, only increased atrophied T2-LV in 0–6 months showed a significant association with time to CDP (cutoff = 0.09 mL, $P = .017$), while this association did not remain significant for 0–12 months after correction for multiple comparisons (cutoff = 0.18 mL, $P = .076$).

DISCUSSION

The main study findings are that cumulative atrophied T2-LV showed a robust association with development of 10-year CDP and that this association was maintained across all time points with an effect size similar to that of whole-brain, cortical, and central atrophy. In addition, atrophied T2-LV was associated with the development of 10-year CDP for most consecutive time points, which was not the case for whole-brain, cortical, and central atrophy. Atrophied T2-LV was the only MR imaging predictor that showed an association with time to CDP after only 6 months of follow-up, whereas it took 2 years for whole-brain and central atrophy and 5 years for cortical atrophy to show a comparable effect. Finally, we extended preliminary findings from a recent study that showed that atrophied T2-LV can significantly add to the prediction of midterm disability, even when accounting for the accumulation of new and enlarging T2 lesions and T2-LV and development of whole-brain, cortical, and central atrophy.¹³

An overall increase in T2-LV stems from a combination of the development of new lesions and the enlargement of pre-existing ones. Reductions with time are also possible following either complete resolution or shrinkage of lesions due to beneficial processes of remyelination and repair.^{24–26} However, accumulation of lesions in patients with MS shows a limited association with disease progression because new and old lesions alike may be partially or entirely destroyed by atrophy. This phenomenon may account for some of the commonly observed plateauing of the lesion burden and ultimate decline in the most advanced disease stages.^{1,5,6,9,12,26,27} In the current study, we found that all conventional MR imaging measures were similarly associated with the cumulative atrophied T2-LV, including baseline T2-LV, accumulation of new/enlarging T2 lesions, change in T2-LV, and development of whole brain, cortical, and central atrophy. These findings confirm that although atrophied T2-LV is influenced by both ongoing lesion accrual and brain atrophy, it appears to provide unique or complementary information beyond these individual MR imaging outcomes because these conventional outcomes combined explained only about 54% of the variance in the atrophied T2-LV. The lesion loss due to atrophy was less visually

apparent than the accumulation or enlargement of new lesions (Figure) but was similar to that of brain atrophy. In terms of magnitude, although change in atrophied T2-LV represented only about 30% of the change in total T2-LV, its relation to long-term CDP was much stronger. In addition, in line with the results from the previous study in which we found that the rate of atrophied and new T2-LV accumulation was similar in patients with RRMS but almost double in patients with progressive MS,¹³ atrophied T2-LV accumulation in the current study was accelerated from years 5 to 10 of follow-up, whereas accumulation of total T2-LV decelerate in the same time period (On-line Figure, Tables 2 and 3, and On-line Tables 5 and 6). This temporal evolution profile makes this MR imaging outcome of particular interest for use in monitoring the transition from relapsing to progressive forms of MS.

At 10 years, the cumulative atrophied T2-LV was 1.54 mL in the CDP and 0.68 mL in patients with stable MS, which represents a 126.5% difference with an effect size of 0.58. This was similar to the PBVC, PCVC, and PVVC between baseline and 10 years. However, the development of brain atrophy was not associated in the first 2 years of follow-up with the development of 10-year CDP, while atrophied T2-LV showed robust differences already at 6, 12, and 24 months of follow-up. In addition, when between-serial-time-point changes were examined with 10-year CDP, the atrophied T2-LV was significantly associated with nearly all consecutive time points, except for 24–36, 36–48, and 84–96 months, while the PBVC, PCVC, and PVVC were associated with neither one. These findings make atrophied T2-LV a potentially more attractive MR imaging outcome for clinical monitoring on a year-to-year basis in comparison with the development of brain atrophy or lesion accrual. In line with numerous previous studies, accumulation of new and enlarging T2 lesions and T2-LV was not associated with long-term CDP.^{1,4–8,28}

Because atrophied T2-LV is a product of both inflammation (in the form of lesion accrual) and neurodegeneration (in the form of brain atrophy development), this MR imaging measure may add more value in predicting CDP than other MR imaging measures reflecting only a single aspect of pathophysiologic progression, as previously reported.¹³ In a multivariable model exploring the association with 10-year CDP status, only atrophied T2-LV was retained and explained 25% of the variance, while in the hierarchic regression model that included all MR imaging measures significant in univariate analyses, atrophied T2-LV significantly improved the explained variance by 11%, which was highly significant ($P = .009$).

Establishing an MR imaging outcome that can early and reliably define which individual patients with MS will develop CDP during the long term has remained elusive in MS research for many years.^{2,6,9–12,18,24–27,29,30} The results of the Cox regression analysis in the present study suggest that atrophied T2-LV could be a good candidate for such an endeavor. In the first 6 months of follow-up, the risk of time to conversion to CDP was already 4.23 times higher for each milliliter of atrophied T2-LV increase in CDP compared with patients with stable MS, and 2.41 times higher in 0–12 months. No other MR imaging outcomes were able to predict the risk to time of CDP in the first 12 months in the present study. In the Kaplan-Meier analysis, we determined that cumulative atrophied T2-LV of 0.09 mL in the first 6 months or

0.18 mL in the first 12 months had a cutoff of 80% specificity and around 40% sensitivity to predict time to CDP, while no other MR imaging outcomes were significantly associated with time to development of CDP.

The association between atrophied T2-LV and CDP suggests that the role of lesion tissue pathologically replaced by CSF has to be further explored using more sophisticated voxelwise studies. In line with a previous study,¹³ we observed that atrophied T2-LV was most frequently located in periventricular regions and at the cortical gyri borders that atrophied to displace sulci CSF and replace parts of the lesions. In addition, because we did not use MR imaging acquisitions specifically for the detection of cortical lesions,^{31,32} the true prevalence of atrophied T2-LV in cortical regions may be largely underestimated. Therefore, atrophy-related local lesion movement into cortical sulci has to be further explored using more sophisticated voxelwise studies.

There are a number of limitations that have to be considered. There was a relatively high percentage of patients in the “stable” group in this study during 10 years. This might imply that the population consisted of patients having a more benign MS course or it might be related to the high compliance to disease-modifying therapies. The pathologic specificity of the transition of lesions to the CSF tissue has to be further explored using nonconventional MR imaging measures.^{1,10,11,26,30} A serial ultra-high-field MR imaging may also be preferred for investigating the pathophysiologic processes leading to the loss of lesions surrounded by parenchyma in cortical regions. We did not explore what portion of the atrophied T2-LV is represented by T1-hypointense black hole lesions, which have a higher rate of tissue destruction into the CSF.^{33,34} Another issue to be clarified is the effect of therapy-induced pseudodilatation on atrophied T2-LV.^{9,10,12,35}

CONCLUSIONS

Atrophied T2-LV is a robust and early marker of disease progression associated with long-term disease progression in patients with RRMS.

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REFERENCES

- Poloni G, Minagar A, Haacke EM, et al. **Recent developments in imaging of multiple sclerosis.** *Neurologist* 2011;17:185–204 CrossRef Medline
- Bar-Zohar D, Agosta F, Goldstaub D, et al. **Magnetic resonance imaging metrics and their correlation with clinical outcomes in multiple sclerosis: a review of the literature and future perspectives.** *Mult Scler* 2008;14:719–27 CrossRef Medline
- Sormani MP, Bruzzi P, Comi G, et al. **MRI metrics as surrogate markers for clinical relapse rate in relapsing-remitting MS patients.** *Neurology* 2002;58:417–21 CrossRef Medline
- O'Riordan JI, Thompson AJ, Kingsley DP, et al. **The prognostic value of brain MRI in clinically isolated syndromes of the CNS. A 10-year follow-up.** *Brain* 1998;121(Pt 3):495–503 CrossRef Medline
- Rudick RA, Lee JC, Simon J, et al. **Significance of T2 lesions in multiple sclerosis: a 13-year longitudinal study.** *Ann Neurol* 2006;60:236–42 CrossRef Medline
- Barkhof F. **The clinico-radiological paradox in multiple sclerosis revisited.** *Curr Opin Neurol* 2002;15:239–45 CrossRef Medline
- Sailer M, Losseff NA, Wang L, et al. **T1 lesion load and cerebral atrophy as a marker for clinical progression in patients with multiple sclerosis: a prospective 18 months follow-up study.** *Eur J Neurol* 2001;8:37–42 CrossRef Medline
- Zivadinov R, Uher T, Hagemeier J, et al. **A serial 10-year follow-up study of brain atrophy and disability progression in RRMS patients.** *Mult Scler* 2016;22:1709–18 CrossRef Medline
- Bermel RA, Bakshi R. **The measurement and clinical relevance of brain atrophy in multiple sclerosis.** *Lancet Neurol* 2006;5:158–70 CrossRef Medline
- De Stefano N, Airas L, Grigoriadis N, et al. **Clinical relevance of brain volume measures in multiple sclerosis.** *CNS Drugs* 2014;28:147–56 CrossRef Medline
- Miller DH, Barkhof F, Frank JA, et al. **Measurement of atrophy in multiple sclerosis: pathological basis, methodological aspects and clinical relevance.** *Brain* 2002;125:1676–95 CrossRef Medline
- Zivadinov R, Jakimovski D, Gandhi S, et al. **Clinical relevance of brain atrophy assessment in multiple sclerosis: implications for its use in a clinical routine.** *Expert Rev Neurother* 2016;16:777–93 CrossRef Medline
- Dwyer MG, Bergsland N, Ramasamy DP, et al. **Atrophied brain lesion volume: a new imaging biomarker in multiple sclerosis.** *J Neuroimaging* 2018;28:490–95 CrossRef Medline
- Zivadinov R, Bergsland N, Dwyer MG. **Atrophied brain lesion volume, a magnetic resonance imaging biomarker for monitoring neurodegenerative changes in multiple sclerosis.** *Quant Imaging Med Surg* 2018;8:979–83 CrossRef Medline
- Pardini M, Sudre CH, Prados F, et al. **Relationship of grey and white matter abnormalities with distance from the surface of the brain in multiple sclerosis.** *J Neurol Neurosurg Psychiatry* 2016;87:1212–17 CrossRef Medline
- Havrdova E, Zivadinov R, Krasensky J, et al. **Randomized study of interferon beta-1a, low-dose azathioprine, and low-dose corticosteroids in multiple sclerosis.** *Mult Scler* 2009;15:965–76 CrossRef Medline
- Horakova D, Cox JL, Havrdova E, et al. **Evolution of different MRI measures in patients with active relapsing-remitting multiple sclerosis over 2 and 5 years: a case-control study.** *J Neurol Neurosurg Psychiatry* 2008;79:407–14 CrossRef Medline
- Zivadinov R, Bergsland N, Dolezal O, et al. **Evolution of cortical and thalamus atrophy and disability progression in early relapsing-remitting MS during 5 years.** *AJNR Am J Neuroradiol* 2013;34:1931–39 CrossRef Medline
- Tustison NJ, Avants BB, Cook PA, et al. **N4ITK: improved N3 bias correction.** *IEEE Trans Med Imaging* 2010;29:1310–20 CrossRef Medline
- Nyúl LG, Udupa JK, Zhang X. **New variants of a method of MRI scale standardization.** *IEEE Trans Med Imaging* 2000;19:143–50 CrossRef Medline
- Smith SM, Jenkinson M, Woolrich MW, et al. **Advances in functional and structural MR image analysis and implementation as FSL.** *Neuroimage* 2004;23(Suppl 1):S208–19 CrossRef Medline
- Gelineau-Morel R, Tomassini V, Jenkinson M, et al. **The effect of hypointense white matter lesions on automated gray matter segmentation in multiple sclerosis.** *Hum Brain Mapp* 2012;33:2802–14 CrossRef Medline
- Benjamini Y, Drai D, Elmer G, et al. **Controlling the false discovery rate in behavior genetics research.** *Behav Brain Res* 2001;125:279–84 CrossRef Medline
- Giacomini PS, Levesque IR, Ribeiro L, et al. **Measuring demyelination and remyelination in acute multiple sclerosis lesion voxels.** *Arch Neurol* 2009;66:375–81 CrossRef Medline
- Mallik S, Samson RS, Wheeler-Kingshott CA, et al. **Imaging outcomes for trials of remyelination in multiple sclerosis.** *J Neurol Neurosurg Psychiatry* 2014;85:1396–404 CrossRef Medline
- Zivadinov R. **Can imaging techniques measure neuroprotection and remyelination in multiple sclerosis?** *Neurology* 2007;68:S72–82; discussion S91–96 CrossRef Medline
- Trapp BD, Ransohoff R, and Rudick R. **Axonal pathology in multiple sclerosis: relationship to neurologic disability.** *Curr Opin Neurol* 1999;12:295–302 CrossRef Medline
- Uher T, Vaneckova M, Sobisek L, et al. **Combining clinical and magnetic resonance imaging markers enhances prediction of 12-year disability in multiple sclerosis.** *Mult Scler* 2017;23:51–61 CrossRef Medline
- Zivadinov R, Havrdová E, Bergsland N, et al. **Thalamic atrophy is associated with development of clinically definite multiple sclerosis.** *Radiology* 2013;268:831–41 CrossRef Medline
- Zivadinov R, Stosic M, Cox JL, et al. **The place of conventional MRI and newly emerging MRI techniques in monitoring different aspects of treatment outcome.** *J Neurol* 2008;255(Suppl 1):61–74 CrossRef Medline
- Geurts JJ, Pouwels PJ, Uitdehaag BM, et al. **Intracortical lesions in multiple sclerosis: improved detection with 3D double inversion-recovery MR imaging.** *Radiology* 2005;236:254–60 CrossRef Medline
- Nielsen AS, Kinkel RP, Madigan N, et al. **Contribution of cortical lesion subtypes at 7T MRI to physical and cognitive performance in MS.** *Neurology* 2013;81:641–49 CrossRef Medline
- Yao B, Ikonomidou VN, Cantor FK, et al. **Heterogeneity of multiple sclerosis white matter lesions detected with T2*-weighted imaging at 7.0 Tesla.** *J Neuroimaging* 2015;25:799–806 CrossRef Medline
- van Walderveen MA, Barkhof F, Pouwels PJ, et al. **Neuronal damage in T1-hypointense multiple sclerosis lesions demonstrated in vivo using proton magnetic resonance spectroscopy.** *Ann Neurol* 1999;46:79–87 CrossRef Medline
- Zivadinov R, Reder AT, Filippi M, et al. **Mechanisms of action of disease-modifying agents and brain volume changes in multiple sclerosis.** *Neurology* 2008;71:136–44 CrossRef Medline

Aqueductal CSF Stroke Volume Is Increased in Patients with Idiopathic Normal Pressure Hydrocephalus and Decreases after Shunt Surgery

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ABSTRACT

BACKGROUND AND PURPOSE: Increased CSF stroke volume through the cerebral aqueduct has been proposed as a possible indicator of positive surgical outcome in patients with idiopathic normal pressure hydrocephalus; however, consensus is lacking. In this prospective study, we aimed to compare CSF flow parameters in patients with idiopathic normal pressure hydrocephalus with those in healthy controls and change after shunt surgery and to investigate whether any parameter could predict surgical outcome.

MATERIALS AND METHODS: Twenty-one patients with idiopathic normal pressure hydrocephalus and 21 age- and sex-matched healthy controls were prospectively included and examined clinically and with MR imaging of the brain. Eighteen patients were treated with shunt implantation and were re-examined clinically and with MR imaging the day before the operation and 3 months postoperatively. All MR imaging scans included a phase-contrast sequence.

RESULTS: The median aqueductal CSF stroke volume was significantly larger in patients compared with healthy controls (103.5 μ L; interquartile range, 69.8–142.8 μ L) compared with 62.5 μ L (interquartile range, 58.3–73.8 μ L; $P < .01$) and was significantly reduced 3 months after shunt surgery from 94.8 μ L (interquartile range, 81–241 μ L) to 88 μ L (interquartile range, 51.8–173.3 μ L; $P < .05$). Net flow in the caudocranial direction (retrograde) was present in 11/21 patients and in 10/21 controls. Peak flow and net flow did not differ between patients and controls. There were no correlations between any CSF flow parameters and surgical outcomes.

CONCLUSIONS: Aqueductal CSF stroke volume was increased in patients with idiopathic normal pressure hydrocephalus and decreased after shunt surgery, whereas retrograde aqueductal net flow did not seem to be specific for patients with idiopathic normal pressure hydrocephalus. On the basis of the results, the usefulness of CSF flow parameters to predict outcome after shunt surgery seem to be limited.

ABBREVIATIONS: ACSV = aqueductal CSF stroke volume; iNPH = idiopathic normal pressure hydrocephalus; IQR = interquartile range; MMSE = Mini-Mental State Examination; NPH = normal pressure hydrocephalus; PC = phase-contrast; TUG = Timed Up and Go Test

Idiopathic normal pressure hydrocephalus (iNPH) is a disease of the elderly population, presenting with a triad of gait disturbance, progressive dementia, and urinary incontinence.¹ Radiologic findings include ventriculomegaly out of proportion to sulcal enlargement and without apparent obstruction of the CSF circulation, often in combination with periventricular white mat-

ter hyperintensities and increased CSF flow through the ventricular system.^{2–4} The disease is treated by CSF diversion, in most cases in the form of a ventriculoperitoneal shunt. Shunting selection criteria vary among different centers, as well as the reported rate of clinical improvement after the operation, with a reported range of 60%–80%.^{5,6} Because shunt surgery has potentially serious risks, correctly identifying patients who may benefit from a shunt operation is of clinical importance.

Several previous studies have explored the stroke volume of CSF through the cerebral aqueduct, evaluated by phase-contrast (PC) MR imaging as a predictor of shunt surgery outcome.^{7–11} However, the aforementioned studies have presented contradicting results, and the validity of the method remains in dispute. Also, there are reports of retrograde CSF net flow in patients with iNPH,^{12–14} but few studies have included age-matched controls.

With this prospective study, we aimed to compare aqueductal CSF stroke volume (ACSV), peak flow, and net flow in patients

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Table 1: Demographics and background data in patients and controls^a

	Patients (n = 21)	Controls (n = 21)	P Value
Age (median) (range) (yr)	74 (65–81)	74 (65–82)	NS ^b
Sex (No. of men) (%)	11 (52%)	11 (52%)	NS ^c
MMSE	25 (22–27)	30 (29–30)	<.001 ^d
Urgency scale	3 (1–4)	1 (1–1)	<.001 ^d
mRS	2 (2–3)	0 (0–0)	<.001 ^d
TUG (sec)	20 (14–31)	9 (8–11)	<.001 ^d
TUG (No. of steps)	22 (18–34)	12 (11–14)	<.001 ^d
10 Meter Walk test (sec)	12 (8–17)	5 (5–6)	<.001 ^d
10 Meter Walk Test (No. of steps)	22 (16–30)	12 (11–13)	<.001 ^d
Evans index	0.35 (0.34–0.39)	0.28 (0.24–0.30)	<.001 ^d
DWMH	1 (1–3)	1 (1–2)	NS ^d
DESH (No.) (%)	14 (67%)	0 (0%)	<.001 ^c
Callosal angle	66° (60°–73°)	113° (104°–121°)	<.001 ^d
Flow void	3 (2–3)	2 (2–2)	NS ^d

Note:—DWMH indicates deep white matter hyperintensities; DESH, disproportionately enlarged subarachnoid space hydrocephalus; NS, not significant.

^a Unless indicated otherwise, data are median, with IQR in parenthesis.

^b Mann-Whitney *U* test.

^c McNemar test.

^d Wilcoxon signed rank test.

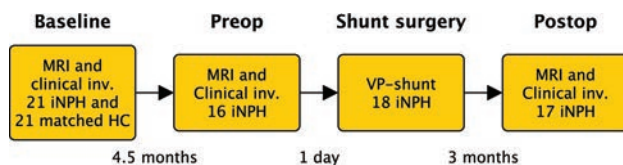


FIG 1. Timeline. MRI indicates MR imaging with the phase-contrast MR imaging sequence; Clinical inv., clinical investigation with tests of gait function, cognition, and urinary symptoms; HC, age- and sex-matched healthy controls. Preop = preoperative investigations; Postop, postoperative follow-up.

with iNPH with those in age- and sex-matched healthy controls and investigate whether any of these CSF flow parameters could function as a predictor of outcome of shunt surgery.

MATERIALS AND METHODS

Patients and Controls

Twenty-six patients with suspected iNPH were prospectively included in the study. After examination by a multidisciplinary normal pressure hydrocephalus (NPH) team consisting of a neurosurgeon, neurologist, physiotherapist, and an occupational therapist, 23 of them were diagnosed with iNPH according to the international guidelines,^{1,5} whereas 3 were considered to have other conditions. All patients had a typical progressive gait disorder in combination with cognitive dysfunction and/or urgency incontinence, and all patients had findings of enlarged lateral ventricles and tight high-convexity sulci on imaging. MR imaging of the brain and lumbar punctures were performed in the diagnostic work-up.

Twenty-three controls were randomly recruited from the Uppsala municipality using the Swedish population registry and were matched with patients with respect to sex and age (± 2 years). Exclusion criteria were previous stroke or any known neurologic disease, diabetes mellitus, history of myocardial infarction, dependence on walking aids, and any terminal disease. Antihypertensive medication, aspirin, and common pain medications were allowed. Two of the controls did not match any patient; therefore, 21 patient-control pairs were available. The controls did not differ from patients with

respect to vascular risk factors. The patients and controls are described in Table 1, and they were also included in previous studies.^{16,17} The study was approved by the local ethics committee in Uppsala, Sweden, and all patients and controls gave written informed consent for participation.

Time Scheme

Patients and controls were examined at baseline with MR imaging of the brain and clinical evaluation. Patients were also investigated preoperatively (the day before the operation) with MR imaging and 3 months postoperatively with repeat clinical examinations and MR imaging. The time between baseline and preoperative scans was a median of 4.5 months (interquartile range [IQR], 4–7.75 months; range, 2–11 months),

and time between the operation and postoperative MR imaging was 3 months (IQR, 2–4 months; range, 2–8 months; Fig 1).

The study comprised 2 parts—Part 1: baseline scans of patients were compared with those of matched healthy controls; and Part 2: baseline, preoperative, and postoperative scans of patients were compared with investigate longitudinal differences across time and the predictive values of the CSF flow parameters.

All 21 patients with iNPH were offered shunt surgery. Two patients dropped out of Part 2 of the study, and 1 died before surgery. The 18 patients still included in the study underwent shunt surgery. One of the 18 patients included in Part 2 of the study did not match any healthy control and was therefore not included in Part 1 (the patient with the highest ACSV at baseline in Fig 2B).

Baseline MR imaging was performed in all 18 patients; however, in 2 patients, the preoperative scans were missing, and in 1 patient, the postoperative flow-quantification scans were lost due to technical issues. Data of the baseline scan were used in the patient who was investigated postoperatively but with a missing preoperative investigation in the longitudinal comparison.

Four patients underwent a re-operation within 3 months: 1 related to a shunt infection, 2 with adjustments to the proximal catheter, and 1 due to bowel perforation. All patients were initially implanted with a ventriculoperitoneal shunt with a Strata valve (Medtronic, Dublin, Ireland). The patient with a bowel perforation after the first operation underwent a re-operation with a ventriculoatrial shunt. The postoperative MR imaging and follow-up visit were performed 3 months after the re-operation in these 4 patients.

Clinical Examination

The clinical examination consisted of a standard neurologic examination, the Mini-Mental State Examination (MMSE), mRS, the Timed Up and Go Test (TUG), time and number of steps required to walk 10 m at maximum pace, and the gait and balance tests from the iNPH scale.¹⁸ Tests of gait function were performed

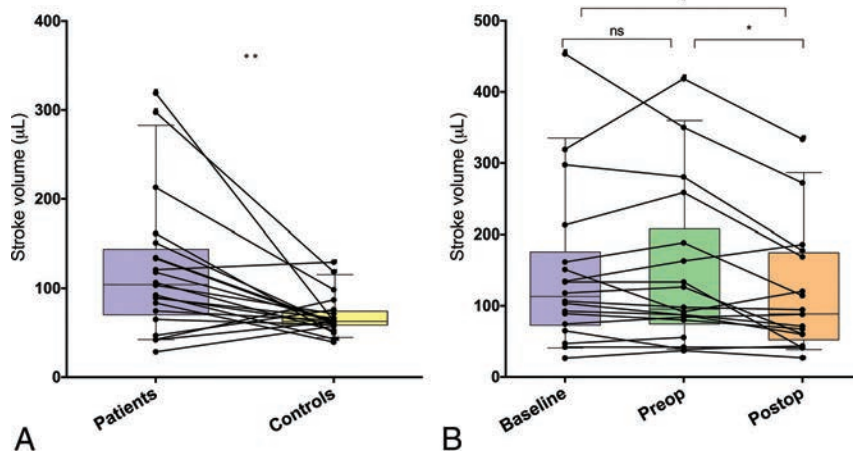


FIG 2. A, Aque ductal cerebral stroke volume in patients with iNPH and healthy controls. The lines connect each patient with a matched control. B, Aque ductal cerebral stroke volume in patients with iNPH at baseline, the day before shunt surgery (preop), and at 3 months after the operation (postop). Error bars represent 10th and 90th percentiles. The asterisk indicates $P < .05$; double asterisks, $P < .01$; NS, not significant.

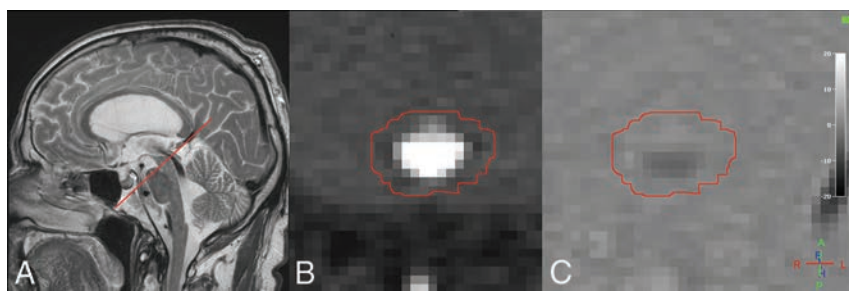


FIG 3. A, Sagittal T2-weighted turbo spin-echo image (without flow compensation) with the red line illustrating the location of the phase-contrast MR imaging scan plane. B, Transverse magnitude image through the aqueduct. The red circle illustrates the ROI drawn for flow measurements. C, Corresponding velocity (phase) image.

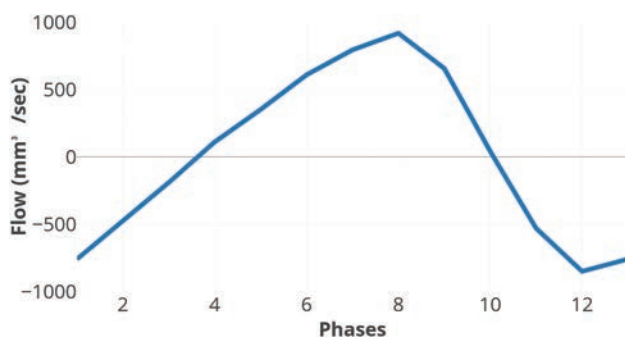


FIG 4. Aque ductal CSF flow during 1 cardiac cycle. Positive values are in the craniocaudal direction.

twice, and the mean value of the 2 trials was used in the statistical analysis. To reduce the number of variables in the correlation analyses, we created a quantitative gait variable, which was the mean of the number of steps and seconds for both the 10 Meter Walk Test and the TUG. The same examinations were repeated at postoperative follow-up. Variables used in the statistical analyses of postoperative outcome were differences in the quantitative gait variable and MMSE. Results of clinical tests from preoperative and postoperative investigations are documented On-line Table 1.

Imaging

MR imaging was performed on a 3T Achieva System (Philips Healthcare, Best, the Netherlands) using a 32-channel head coil with the patient in the supine position. Imaging parameters for the PC MR imaging were as follows: acquired voxel size = $0.59 \times 0.84 \times 4.00$ mm (reconstructed to $0.59 \times 0.59 \times 4.00$ mm), acquisition matrix = 256×179 , TR = 12 ms, TE = 7.5 ms, flip angle = 15° , retrospective cardiac gating with 12 phases using a peripheral pulse unit. The scan was positioned perpendicular to the aqueduct (Fig 3A), and the phase-correction technique provided by the vendor was applied. All patients were examined once with a velocity-encoding value of 20 cm/s. To increase accuracy and decrease the risk of velocity aliasing, we then analyzed the peak velocity of CSF and repeated the sequence with a velocity-encoding adjusted to a slightly higher value than the recorded peak velocity in each individual.

Image data were analyzed in the Q-Flow package (Philips Healthcare) software. An ROI was drawn manually (Fig 3B, -C), with the examiner blinded to clinical data, covering the perimeter of the aqueduct and adjusted, if necessary, in all phases of the sequence. ACSV, defined as the volumetric mean of the caudal and cranial flow of CSF through the

aqueduct; net flow during 1 cardiac cycle; peak velocity; and aque ductal area were calculated by the software. Positive values represent the craniocaudal direction. Quantified flow during 1 cardiac cycle is illustrated in Fig 4.

A morphologic 3D T1-weighted sequence and a T2-weighted FLAIR sequence were also included in the MR imaging protocol for descriptive purposes. In addition to aque ductal flow parameters, we measured 5 imaging features: Evans index,¹⁹ deep white matter hyperintensities according to the Fazekas visual grading scale,²⁰ disproportionately enlarged subarachnoid space hydrocephalus,⁴ callosal angle,²¹ and the presence of a flow void in the cerebral aqueduct.²² The volume of the lateral ventricles was quantified using SyntheticMR (<http://www.syntheticmr.com/>).²³

Statistical Analysis

The difference between patients and matched controls was tested with the Wilcoxon signed rank test except for age, which was tested with the Mann-Whitney U test. Differences between baseline and preoperative and postoperative investigations were tested with the Friedman test, and post hoc analysis was performed with the Wilcoxon signed rank test. Correlations were tested with the Spearman rank correlation coefficient. It has been suggested that patients with iNPH with ACSV twice as high as that in healthy

controls respond to shunting.²⁴ Therefore, differences in outcome between patients with ACSV twice as high as that in the median in controls ($>125 \mu\text{L}$) were compared with patients with ACSV of $<125 \mu\text{L}$, and the difference in outcome was tested with the Mann-Whitney U test. The level of significance was set at $P < .05$, and all analyses were performed using SPSS Statistics for Macintosh, Version 23.0 (IBM, Armonk, New York). No corrections for multiple analyses were performed.

RESULTS

The median ACSV with IQR at baseline was $62.5 \mu\text{L}$ ($58.3\text{--}73.8 \mu\text{L}$) in controls and $103.5 \mu\text{L}$ ($69.8\text{--}142.8 \mu\text{L}$) in patients ($P < .01$, Fig 2A). The aqueductal area was also significantly larger in patients than in controls ($P < .001$), but there was no difference in net flow volume or peak velocity (Table 2). The net flow was negative (caudocranial direction) in 11 of 21 patients and in 10 of 21 healthy controls.

The median ACSV was significantly reduced from $94.8 \mu\text{L}$ (IQR, $81\text{--}241 \mu\text{L}$) preoperatively to $88 \mu\text{L}$ (IQR, $51.8\text{--}73.3 \mu\text{L}$) postoperatively ($P < .05$, Fig 2B). There was also a significant difference between baseline and postoperative investigation ($P < .05$), but not between baseline and preoperative MR imaging (Fig 2). There were no longitudinal differences for net flow, peak velocity, or aqueductal area (Table 3).

In patients, ACSV correlated with peak velocity ($r = 0.78$, $P < .001$), aqueductal area ($r = 0.48$, $P < .05$), callosal angle ($r = -0.48$, $P < .05$), and flow void ($r = 0.53$, $P < .05$). There was also a correlation between peak velocity and flow void ($r = 0.56$, $P < .01$).

At baseline, ACSV correlated with the clinical variables, mRS score ($r = -0.49$, $P < .05$) and performance on quantitative gait tests ($r = -0.43$, $P < .05$). Postoperative difference in ACSV correlated with postoperative changes in the mRS score ($r = 0.62$, $P < .01$).

Table 2: Aqueductal stroke volume, peak velocity, and aqueductal area in controls and patients at baseline^a

	Healthy Controls (n = 21)	Patient Baseline (n = 21)	P Value ^b
ACSV (μL)	62.5 (58.3–73.8)	103.5 (69.8–142.8)	$<.01$
Peak velocity (mm/s)	103 (79.5–113.5)	103 (68.5–166.5)	NS
Net flow (μL)	–2.9 (–5.65–2.55)	–1.6 (–19–14)	NS
Aq area (mm^2)	18 (15.5–19)	22 (19–25)	$<.001$

Note:—Aq indicates aqueductal; NS, not significant.

^a Data are median with IQR in parentheses.

^b Wilcoxon signed rank test.

Table 3: Aqueductal stroke volume, peak velocity, and aqueductal area in patients at all assessment times^a

	Patient Baseline (n = 21)	Patient Preop (n = 16)	Patient Postop (n = 17)	P Value
ACSV (μL)	103.5 (69.8–142.8)	94.8 (81–241)	88 (51.8–173.3)	$<.05^b$
Peak velocity (mm/s)	103 (68.5–166.5)	127 (72.5–154.8)	108 (71.5–146.5)	NS
Net flow (μL)	–1.6 (–19–14)	–1.8 (–14.5–10.8)	0 (–12.5–2.1)	NS
Aq area (mm^2)	22 (19–25)	22.5 (19.3–25.8)	24 (20.5–25.5)	NS

Note:—Preop indicates preoperative; Postop, postoperative; Aq, aqueductal; NS, not significant.

^a Data are median with interquartile range in parentheses.

^b Wilcoxon signed rank test. Significant difference between baseline and postoperative investigation and between preoperative and postoperative investigation. Comparisons between baseline and preoperative measurements were all nonsignificant.

None of the CSF flow parameters at baseline correlated with the postoperative clinical outcome. Of the 18 patients in Part 2 of the study, ACSV were $>125 \mu\text{L}$ (twice as high as in controls) in 8 patients and $<125 \mu\text{L}$ in 10 patients. There were no significant differences in postoperative outcome in any clinical variable between patients with high ACSV ($>125 \mu\text{L}$) compared with patients with ACSV of $<125 \mu\text{L}$.

In controls, ACSV correlated with peak velocity ($r = 0.64$, $P < .01$), but not with aqueductal area. Also in controls, ACSV correlated with the Evans index ($r = 0.57$, $P < .01$), callosal angle ($r = -0.47$, $P < .05$), and flow void ($r = 0.47$, $P < .05$), and peak velocity correlated with callosal angle ($r = -0.52$, $P < .05$) and deep white matter hyperintensities ($r = -0.55$, $P < .05$).

There was a correlation between ACSV and quantified ventricular volume in healthy controls ($r = 0.46$, $P < .05$), but not in patients (On-line Table 2).

Nine patients (50%) improved $>10\%$ in the quantitative gait variable, and 6 patients (33%) improved ≥ 3 levels in the MMSE.

DISCUSSION

Major Findings

In this study, we found that the stroke volume through the cerebral aqueduct measured by PC MR imaging is larger in patients with iNPH than in age-matched healthy controls. Additionally, ACSV seems to be reduced following shunt surgery. However, preoperative ACSV did not correlate with clinical improvement after shunt surgery in patients with iNPH. Net flow during 1 cardiac cycle was in the caudocranial direction in half of the patients with iNPH as well as in half of the healthy controls. The strength of this study was the consecutive and prospective inclusion of patients who were investigated longitudinally before and after shunt surgery and compared with healthy controls recruited randomly from the general population.

ACSV as a Predictive Test

The usefulness of MR imaging–based assessment of CSF hydrodynamics in the selection process of patients with iNPH for surgery has been a topic of interest since Bradley et al⁷ reported a relationship between increased ACSV and favorable shunt response in 1996. Several studies have since then investigated the concept, however with conflicting results.^{8,10,25,26} Consequently, we aimed to further investigate the usefulness of PC MR imaging–derived flow parameters in the selection of patients for shunt surgery. Our results do not support the use of increased ACSV as a prognostic marker of surgical outcome. Most more recent studies

on the subject have come to similar conclusions,^{8–11} while other studies^{25,26} have presented results in favor of ACSV quantification in the process of surgical selection. Although our study alone cannot conclusively rule out the usefulness of ACSV measured by PC MR imaging as a predictor of shunt surgery outcome, it adds to an existing body of data questioning the viability of the method.

In the article published by Bradley et al,⁷ in 1996, an ACSV of $\geq 42 \mu\text{L}$ was

proposed as a marker of favorable shunting outcome. In a more recent publication, it was suggested that ACSV is highly scanner- and technique-dependent, and the author proposed that each treatment center should determine a “normal” ACSV for the scanner by examining a number of healthy elderly individuals. An ACSV twice as high as the ACSV in healthy controls was suggested as a potential marker of shunting success.²⁴ We applied this method in the present study but found no significant difference in clinical outcome between patients with an ACSV at least twice that of the controls ($>125 \mu\text{L}$) compared with patients with lower ACSVs.

Comprehensive knowledge regarding the pathophysiology of iNPH remains elusive. Impaired compliance of brain parenchyma and vasculature and white matter ischemia are some of the suggested underlying mechanisms.^{27,28} It has been suggested that a less compliant brain would hamper the Windkessel effect, resulting in increased CSF pulsatility, including ACSV.²⁹ In a study investigating the influence of morphologic and hydrodynamic features on the magnitude of ACSV, no parameters except ventricular volume and cross-sectional aqueductal area were correlated with ACSV.³⁰ These findings have been reproduced by other authors.^{10,31} In our study, there was a correlation between ACSV and the volume of the lateral ventricles measured with quantitative MR imaging in controls but not in patients. Contradicting results regarding correlation between ACSV and ventricular volume in patients with iNPH could possibly be explained by inclusion of patients with variable disease progression in different studies. Advancing disease may have more impact on ACSV than on ventricular volume. In contrast, there was a moderate negative correlation between callosal angle and ACSV, indicating that callosal angle could be more closely related to disease progress than ventricular volume. However, correlation between ACSV and any morphologic feature does not necessarily imply causation, and the etiology of increased ACSV remains unclear.

There have been reports of variability of ACSV with regard to both short- and long-term time spans. Scollato et al²⁵ published data suggesting a change of ACSV across time in unshunted patients with NPH. Repeat PC MR imaging during 24 months showed a gradual increase of ACSV, followed by a gradual decrease. The authors hypothesized that ACSV reached a peak level once brain atrophy started to set in, which, in turn, resulted in a decrease of ACSV. In the present study, there was no significant difference in ACSV between baseline and the preoperative investigation with a median time interval of 4.5 months. However, the previously described variability of ACSV across time brings further doubt regarding the method as a prognostic marker and could serve as a partial explanation for our inability to correlate preoperative ACSV with surgical outcome in our study.

At baseline, a low ACSV correlated with poor gait function and global functioning measured by the mRS. If ACSV increased with disease progression, one would expect that these correlations would be the opposite. Our findings could possibly be explained by the theories presented by Scollato et al,²⁵ who reported that ACSV is reduced in the late stages of the disease.

Elevated ACSV in Patients with iNPH

Although ACSV did not correlate with shunting outcome, significantly higher ACSV was present in the patient group. Accordingly, higher flow rates and ACSV in iNPH have been described in previously published literature.^{32–34} However, there was a considerable overlap in ACSV between patients and controls in our study, which limits the diagnostic potential of the method. To better investigate the diagnostic potential of ACSV, future studies should include control groups with patients with ventriculomegaly secondary to atrophy³⁵ and controls with differential diagnoses such as progressive supranuclear palsy and multiple system atrophy.

Reduced ACSV after Shunt Placement

Our results indicated a slight reduction in ACSV occurring after the operation. Previous publications have come to similar conclusions.^{26,36} Shunt insertion is performed to drain excess CSF from the ventricular system and act as a form of capacitance system. It seems logical that ACSV would be reduced following shunt placement; with every systolic phase, a portion of the intraventricular CSF will be diverted through the shunt rather than the cerebral aqueduct. Some authors have suggested that brain compliance increases after shunting, which could also contribute to reduced CSF pulsatility.³⁶ This finding could potentially imply that an increase in ACSV, after an initial reduction following shunt placement, may be indicative of shunt dysfunction; however, this implication should be investigated in large samples.

Retrograde Net Flow

It has been reported in several studies that the net flow in some patients with iNPH is directed caudocranially (ie, flow of CSF into the ventricles).^{12–14,34,37} This is often referred to as retrograde flow because the main production site of CSF is believed to be in the plexus choroideus.³⁸ Findings of retrograde net flow have been suggested as a technical error.³⁹ Others interpret it as an indicator of a major extraventricular source of CSF production in patients with iNPH^{12,40} that could have an important role in the pathophysiology of the disease.¹³ Representative control groups are missing in many previous studies, but 2 recent studies investigated net flow in iNPH with age-matched controls.^{13,34} Yin et al¹³ reported that retrograde net flow was more common in iNPH, while Qvarlander et al³⁴ found no difference in the direction of net flow between patients with iNPH and healthy controls. Our results were more similar to those of Qvarlander et al, with no difference between patients and controls regarding the direction of net flow. However, retrograde net flow was a common finding in our study in both patients and healthy controls. How CSF flow direction is related to age in healthy individuals should be studied further before conclusions can be drawn from results in patients with iNPH. There are also reports that retrograde net flow is reversed after shunting,¹² but we could not replicate that finding.

Limitations

There were some limiting factors concerning technical aspects of the radiologic examination. The flow curves obtained were based on 12 phases. This is comparable with earlier studies investigating ACSV, though many modern studies have used 30–40 phases.

However, an increase in temporal resolution would lead to prolonged scan times, which, in turn, would increase the risk of movement artifacts.

The cerebral aqueduct and the measured ACSV are of small magnitude in the context of phase-contrast MR imaging. This makes the measurements particularly susceptible to partial volume effects and phase-background correction methods.

We did not monitor the respiratory cycle of patients during PC MR imaging examinations. Considering that ACSV has been reported to be influenced by breathing, this could potentially lead to less accurate results.⁴¹ A potential flow-quantification method with both cardiac and respiratory triggering might provide a more precise measurement of ACSV.

Some studies have chosen to place an additional ROI in the static brain parenchyma to measure and correct for any background noise or mass brain movement that may influence flow measurements. This was not required by the manufacturer's recommendations and was not done in our study.

Measurements of net flow are associated with technical difficulties. The quantity of the value is very small and calculated from the much larger bidirectional flow. Therefore, only small variations in the bidirectional flow lead to uncertain estimation of net flow. The IQR of the net flow was large in our patients and could have influenced the results. The scan time for the PC MR imaging sequence is approximately 5–7 minutes, and flow values in an individual patient during this short investigation are not necessarily generalizable to 24 hours in the same patient.

CONCLUSIONS

Although ACSV was higher in patients with iNPH compared with healthy controls and decreased after shunt surgery in patients with iNPH, quantified flow volumes did not predict outcome after shunt surgery. In addition, there was an overlap in the magnitude of ACSV between patients and controls that limits the diagnostic potential of the method. Retrograde net flow does not seem to be specific for iNPH. On the basis of our findings and previous reports in the literature, we question the usefulness of PC MR imaging–derived flow values for decisions concerning surgical intervention in patients with iNPH.

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REFERENCES

- Adams RD, Fisher CM, Hakim S, et al. **Symptomatic occult hydrocephalus with "normal" cerebrospinal-fluid pressure: a treatable syndrome.** *N Engl J Med* 1965;273:117–26 [CrossRef Medline](#)
- Virhammar J, Laurell K, Cesarini KG, et al. **Preoperative prognostic value of MRI findings in 108 patients with idiopathic normal pressure hydrocephalus.** *AJNR Am J Neuroradiol* 2014;35:2311–18 [CrossRef Medline](#)
- Kockum K, Lilja-Lund O, Larsson EM, et al. **The idiopathic normal-pressure hydrocephalus Radscale: a radiological scale for structured evaluation.** *Eur J Neurol* 2018;25:569–76 [CrossRef Medline](#)
- Hashimoto M, Ishikawa M, Mori E, et al; Study of INPH on neurological improvement (SINPHONI). **Diagnosis of idiopathic normal pressure hydrocephalus is supported by MRI-based scheme: a prospective cohort study.** *Cerebrospinal Fluid Res* 2010;7:18 [CrossRef Medline](#)
- Sundström N, Malm J, Laurell K, et al. **Incidence and outcome of surgery for adult hydrocephalus patients in Sweden.** *Br J Neurosurg* 2017;31:21–27 [CrossRef Medline](#)
- Toma AK, Papadopoulos MC, Stapleton S, et al. **Systematic review of the outcome of shunt surgery in idiopathic normal-pressure hydrocephalus.** *Acta Neurochir (Wien)* 2013;155:1977–80 [CrossRef Medline](#)
- Bradley WG Jr, Scalzo D, Queralt J, et al. **Normal-pressure hydrocephalus: evaluation with cerebrospinal fluid flow measurements at MR imaging.** *Radiology* 1996;198:523–29 [CrossRef Medline](#)
- Kahlon B, Annertz M, Ståhlberg F, et al. **Is aqueductal stroke volume, measured with cine phase-contrast magnetic resonance imaging scans useful in predicting outcome of shunt surgery in suspected normal pressure hydrocephalus?** *Neurosurgery* 2007;60:124–29; discussion 129–30 [CrossRef Medline](#)
- Algin O, Hakyemez B, Parlak M. **The efficiency of PC-MRI in diagnosis of normal pressure hydrocephalus and prediction of shunt response.** *Acad Radiol* 2010;17:181–87 [CrossRef Medline](#)
- Ringstad G, Emblem KE, Geier O, et al. **Aqueductal stroke volume: comparisons with intracranial pressure scores in idiopathic normal pressure hydrocephalus.** *AJNR Am J Neuroradiol* 2015;36:1623–30 [CrossRef Medline](#)
- Dixon GR, Friedman JA, Luetmer PH, et al. **Use of cerebrospinal fluid flow rates measured by phase-contrast MR to predict outcome of ventriculoperitoneal shunting for idiopathic normal-pressure hydrocephalus.** *Mayo Clin Proc* 2002;77:509–14 [CrossRef Medline](#)
- Ringstad G, Emblem KE, Eide PK. **Phase-contrast magnetic resonance imaging reveals net retrograde aqueductal flow in idiopathic normal pressure hydrocephalus.** *J Neurosurg* 2016;124:1850–57 [CrossRef Medline](#)
- Yin LK, Zheng JJ, Zhao L, et al. **Reversed aqueductal cerebrospinal fluid net flow in idiopathic normal pressure hydrocephalus.** *Acta Neurol Scand* 2017;136:434–39 [CrossRef Medline](#)
- Kim DS, Choi JU, Huh R, et al. **Quantitative assessment of cerebrospinal fluid hydrodynamics using a phase-contrast cine MR image in hydrocephalus.** *Childs Nerv Syst* 1999;15:461–67 [CrossRef Medline](#)
- Relkin N, Marmarou A, Klinge P, et al. **Diagnosing idiopathic normal-pressure hydrocephalus.** *Neurosurgery* 2005;57:S4–16; discussion ii–v [Medline](#)
- Virhammar J, Laurell K, Ahlgren A, et al. **Arterial spin-labeling perfusion MR imaging demonstrates regional CBF decrease in idiopathic normal pressure hydrocephalus.** *AJNR Am J Neuroradiol* 2017;38:2081–88 [CrossRef Medline](#)
- Virhammar J, Laurell K, Ahlgren A, et al. **Idiopathic normal pressure hydrocephalus: cerebral perfusion measured with pCASL before and repeatedly after CSF removal.** *J Cereb Blood Flow Metab* 2014;34:1771–78 [CrossRef Medline](#)
- Hellström P, Klinge P, Tans J, et al. **A new scale for assessment of severity and outcome in iNPH.** *Acta Neurol Scand* 2012;126:229–37 [CrossRef Medline](#)
- Evans W. **An encephalographic ratio for estimating ventricular enlargement and cerebral atrophy.** *Arch Neurol* 1942;47:931–37 [CrossRef](#)
- Fazekas F, Chawluk JB, Alavi A, et al. **MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging.** *AJR Am J Roentgenol* 1987;149:351–56 [CrossRef Medline](#)
- Ishii K, Kanda T, Harada A, et al. **Clinical impact of the callosal angle in the diagnosis of idiopathic normal pressure hydrocephalus.** *Eur Radiol* 2008;18:2678–83 [CrossRef Medline](#)
- Bradley WG Jr, Whittemore AR, Kortman KE, et al. **Marked cerebrospinal fluid void: indicator of successful shunt in patients with suspected normal-pressure hydrocephalus.** *Radiology* 1991;178:459–66 [CrossRef Medline](#)
- Warntjes JB, Leinhard OD, West J, et al. **Rapid magnetic resonance**

- quantification on the brain: Optimization for clinical usage. *Magn Reson Med* 2008;60:320–29 [CrossRef Medline](#)
24. Bradley WG Jr. CSF flow in the brain in the context of normal pressure hydrocephalus. *AJNR Am J Neuroradiol* 2015;36:831–38 [CrossRef Medline](#)
 25. Scollato A, Tenenbaum R, Bahl G, et al. Changes in aqueductal CSF stroke volume and progression of symptoms in patients with unshunted idiopathic normal pressure hydrocephalus. *AJNR Am J Neuroradiol* 2008;29:192–97 [CrossRef Medline](#)
 26. Abbey P, Singh P, Khandelwal N, et al. Shunt surgery effects on cerebrospinal fluid flow across the aqueduct of Sylvius in patients with communicating hydrocephalus. *J Clin Neurosci* 2009;16: 514–18 [CrossRef Medline](#)
 27. Bateman GA. Vascular compliance in normal pressure hydrocephalus. *AJNR Am J Neuroradiol* 2000;21:1574–85 [Medline](#)
 28. Bradley WG, Safar FG, Furtado C, et al. Increased intracranial volume: a clue to the etiology of idiopathic normal-pressure hydrocephalus? *AJNR Am J Neuroradiol* 2004;25:1479–84 [Medline](#)
 29. Greitz D. Radiological assessment of hydrocephalus: new theories and implications for therapy. *Neurosurg Rev* 2004;27:145–65; discussion 166–67 [Medline](#)
 30. Chiang WW, Takoudis CG, Lee SH, et al. Relationship between ventricular morphology and aqueductal cerebrospinal fluid flow in healthy and communicating hydrocephalus. *Invest Radiol* 2009;44: 192–99 [CrossRef Medline](#)
 31. Qvarlander S. *Analysis of ICP Pulsatility and CSF Dynamics: The Pulsatility Curve and Effects of Postural Changes, with Implications for Idiopathic Normal Pressure Hydrocephalus* [thesis]. Umeå: Umeå University; 2013
 32. Al-Zain FT, Rademacher G, Meier U, et al. The role of cerebrospinal fluid flow study using phase contrast MR imaging in diagnosing idiopathic normal pressure hydrocephalus. *Acta Neurochir Suppl* 2008;102:119–23 [CrossRef Medline](#)
 33. Luetmer PH, Huston J, Friedman JA, et al. Measurement of cerebrospinal fluid flow at the cerebral aqueduct by use of phase-contrast magnetic resonance imaging: technique validation and utility in diagnosing idiopathic normal pressure hydrocephalus. *Neurosurgery* 2002;50:534–43; discussion 543–44 [Medline](#)
 34. Qvarlander S, Ambarki K, Wahlin A, et al. Cerebrospinal fluid and blood flow patterns in idiopathic normal pressure hydrocephalus. *Acta Neurol Scand* 2017;135:576–84 [CrossRef Medline](#)
 35. Chaarani B, Bader C, Capel C, et al. Estimation of the lateral ventricles volumes from a 2D image and its relationship with cerebrospinal fluid flow. *Biomed Res Int* 2013;2013:215989 [CrossRef Medline](#)
 36. Scollato A, Gallina P, Gautam B, et al. Changes in aqueductal CSF stroke volume in shunted patients with idiopathic normal-pressure hydrocephalus. *AJNR Am J Neuroradiol* 2009;30:1580–86 [CrossRef Medline](#)
 37. Penn RD, Basati S, Sweetman B, et al. Ventricle wall movements and cerebrospinal fluid flow in hydrocephalus. *J Neurosurg* 2011;115: 159–64 [CrossRef Medline](#)
 38. Spector R, Robert Snodgrass S, Johanson CE. A balanced view of the cerebrospinal fluid composition and functions: focus on adult humans. *Exp Neurol* 2015;273:57–68 [CrossRef Medline](#)
 39. Wagshul ME, Chen JJ, Egnor MR, et al. Amplitude and phase of cerebrospinal fluid pulsations: experimental studies and review of the literature. *J Neurosurg* 2006;104:810–19 [Medline](#)
 40. Lindstrom EK, Ringstad G, Mardal KA, et al. Cerebrospinal fluid volumetric net flow rate and direction in idiopathic normal pressure hydrocephalus. *Neuroimage Clin* 2018;20:731–41 [CrossRef Medline](#)
 41. Chen L, Beckett A, Verma A, et al. Dynamics of respiratory and cardiac CSF motion revealed with real-time simultaneous multi-slice EPI velocity phase contrast imaging. *Neuroimage* 2015;122: 281–87 [CrossRef Medline](#)

Quantitative Susceptibility Mapping to Assess Cerebral Vascular Compliance

C. Birkel, C. Langkammer, P. Sati, C. Enzinger, F. Fazekas, and S. Ropele



ABSTRACT

SUMMARY: This study explored whether autoregulatory shifts in cerebral blood volume induce susceptibility changes large enough to be depicted by quantitative susceptibility mapping. Eight healthy subjects underwent fast quantitative susceptibility mapping at 3T while lying down to slowly decrease mean arterial pressure. A linear relationship between mean arterial pressure and susceptibility was observed in cortical and subcortical structures, likely representing vessels involved in autoregulation. The slope of this relationship is assumed to indicate the extent of cerebral vascular compliance.

ABBREVIATIONS: CVC = cerebral vascular compliance; greEPI = gradient-echo echo-planar imaging; MAP = mean arterial blood pressure; QSM = quantitative susceptibility mapping; SpO₂ = peripheral capillary oxygen saturation

Quantitative susceptibility mapping (QSM) is a powerful technique to assess the magnetic susceptibility of tissue.¹ In brain tissue, this property is dominated by the diamagnetic susceptibility of water, but paramagnetic iron and diamagnetic lipids, proteins, or calcifications may cause regional susceptibility variations.² In contrast, the magnetic susceptibility of blood is dominated by the oxygenation level of hemoglobin, with a more paramagnetic susceptibility in venous vessels and a more diamagnetic susceptibility in arterial vessels.³

Cerebral autoregulation⁴ serves to maintain a constant cerebral blood flow over a wide range of mean arterial blood pressure (MAP) levels (50–150 mm Hg) to ensure an adequate supply of glucose and oxygen to the brain. This occurs by vasodilation or vasoconstriction of blood vessels with concomitant changes of intravascular blood volume.⁵ Changes in blood volume per a given change in blood pressure are viewed as indicators of cerebral vascular compliance (CVC), which reflects a main component of

vascular function.^{6,7} The capability for CVC varies across the cerebral vasculature, depending on the amount of smooth-muscle cells in the vessel wall, the pericyte density, and, most notably, on the length and diameter of the vessels.⁸ In this regard, the most prominent cerebral autoregulation-induced blood volume changes can be expected to occur in subcortical and pial vessels.⁸

This study explored whether QSM allows depicting and mapping of magnetic susceptibility changes in the brain as a consequence of autoregulatory changes in cerebral blood volume following a drop in blood pressure by lying down.^{9,10}

MATERIALS AND METHODS

MR Imaging

Eight healthy volunteers (6 men, 2 women) with a mean age of 32 years (age range, 28–49 years) participated in this explorative study, which was approved by the local ethics committee of the Medical University of Graz, Austria (EK 29-623 ex 16/17). MR imaging was performed on a 3T MR imaging system (Magnetom Prisma; Siemens, Erlangen, Germany) using a 64-channel head coil. For QSM, we used a 3D gradient-echo echo-planar imaging (greEPI) sequence¹¹ with TR = 50 ms, TE = 30 ms, flip angle = 15°, FOV = 250 mm, in-plane resolution = 0.65 × 0.65 mm, slice thickness = 1.5 mm, EPI factor = 15, scan time = 57 seconds. This sequence was started immediately after the volunteers had taken their supine position in the MR imaging scanner. To monitor changes in QSM, we repetitively performed this sequence 8 times, resulting in a total acquisition time of 7 minutes and 44 seconds. Thereafter, a T1-weighted true inversion recovery sequence was performed with TR = 6000 ms, TE = 11 ms, TI = 500

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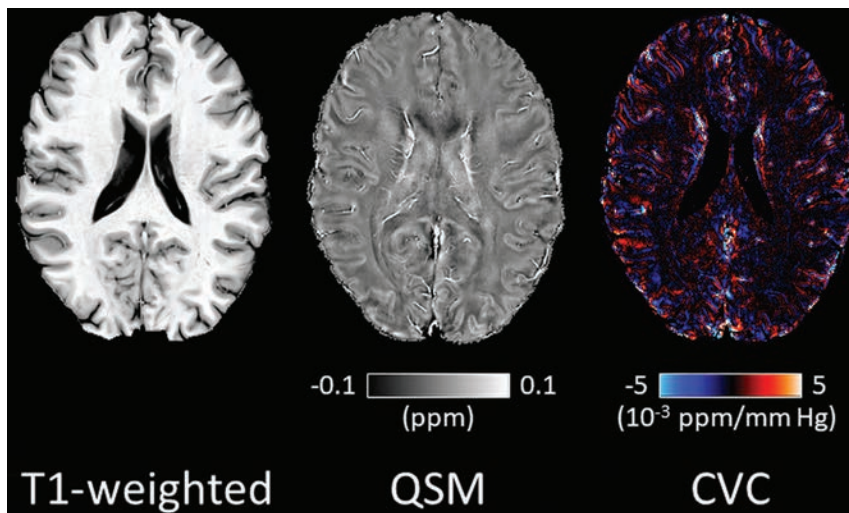


FIG 1. Representative T1-weighted image, quantitative susceptibility map, and the corresponding CVC map of an axial section from a single subject (from left to right). Additional axial sections of the same subject are shown in On-line Fig 4.

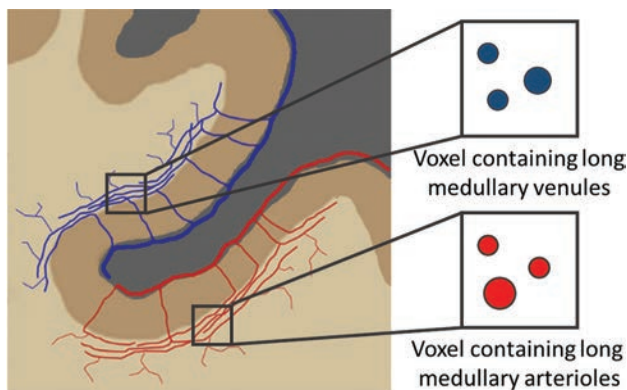


FIG 2. Schematic drawing of pial and subcortical blood vessels. The longest vessels with a high capability to modulate the diameter are the medullary arterioles and venules.¹⁶ According to Duvernoy type 5, these vessels follow the course of the subcortical interface over long distances before they branch into white matter.¹⁷

ms, flip angle = 150°, in-plane resolution = 0.65 × 0.65 mm, slice thickness = 1.5 mm, acquisition time = 4 minutes and 44 seconds.

At each start of the greEPI sequence, the systolic (SYS) and diastolic (DIA) blood pressure was measured using a blood pressure cuff at the left upper arm. Furthermore, the blood oxygenation level (peripheral capillary oxygen saturation [SpO₂]) was measured at the index finger of the right hand using a MR imaging-compatible patient monitor (Precise; Invivo, Orlando, Florida). The MAP was calculated according to $MAP = DIA + 1/3 (SYS - DIA)$.¹²

Image Processing

QSM images of each greEPI measurement were reconstructed using the total generalized variation method.¹³ To correct for head displacements during the series of greEPI scans, we registered all subsequent scans to the first greEPI scan, using FLIRT (FMRIB Linear Image Registration Tool; <https://www.fmrib.ox.ac.uk/fsl/fslwiki/FLIRT>).¹⁴ Additionally, QSM was referenced to the magnetic susceptibility of the CSF to correct for possible phase drifts.¹⁵

Assessing Vascular Compliance

In brain tissue, the magnetic susceptibility of a voxel can be considered as the relative contributions of blood and tissue components. If one assumes normal cerebral autoregulation, a change in blood pressure (ΔP) introduces a susceptibility shift for a given voxel ($\Delta\chi_{\text{voxel}}$) according to

$$\Delta\chi_{\text{voxel}}(\Delta P) = \Delta V_{\text{blood}}(\Delta P) \times (\chi_{\text{blood}} - \chi_{\text{tissue}})$$

where ΔV_{blood} is the relative change in blood volume and ΔP the relative change in MAP. A blood pressure decrease results in vasodilation and thus increases the intravascular blood volume (On-line Fig 1). Therefore, voxels containing mainly venous vessels should increase their magnetic susceptibility,

whereas voxels containing mainly arterial vessels are expected to show a susceptibility decrease (On-line Fig 2).³ This theory is because compared with tissue water, hemoglobin exhibits a negative (diamagnetic) susceptibility when fully oxygenated and a positive (paramagnetic) susceptibility when deoxygenized.³ To search for structures exhibiting CVC after the subject lies down, we correlated the magnetic susceptibility of each greEPI measurement with the MAP pixel by pixel using a linear regression model, and we mapped the slope of the linear regression, $\Delta\chi_{\text{voxel}} / \Delta P$, as an indirect measure of CVC.

For quantitative analysis, ROIs were manually defined on the CVC maps in the frontal subcortical white matter of each subject. This region was selected because of the presumed presence of vessels with large CVC according to anatomic studies.^{16,17} The mean slope of all ROIs was taken as indicative of the global CVC of each subject. The sign of the slope was used to distinguish between arterial and venous vessels.

RESULTS

In every subject, a gradual MAP drop was observed from lying down on the MR imaging table until close to the end of the greEPI scans. The strongest decrease in MAP occurred within the first 4 minutes. The maximal decrease of MAP ranged between 7 and 14 mm Hg (mean of the maximum blood pressure change during MRI = 10 ± 2 mm Hg) across all subjects (On-line Fig 3A). The SpO₂ ranged between 96% and 100% and was not affected by lying down (On-line Fig 3B).

Figure 1 shows a representative T1-weighted image and corresponding QSM and CVC maps of a single subject. Structures with blood pressure-dependent QSM changes are color-coded depending on the sign of the slope of the pixel-wise regression analysis. These structures are identified primarily on the surface and beneath the cortex. Most likely, they reflect voxels containing predominantly long arterioles (positive slope displayed in red) and venules (negative slope displayed in blue) in the subcortical white

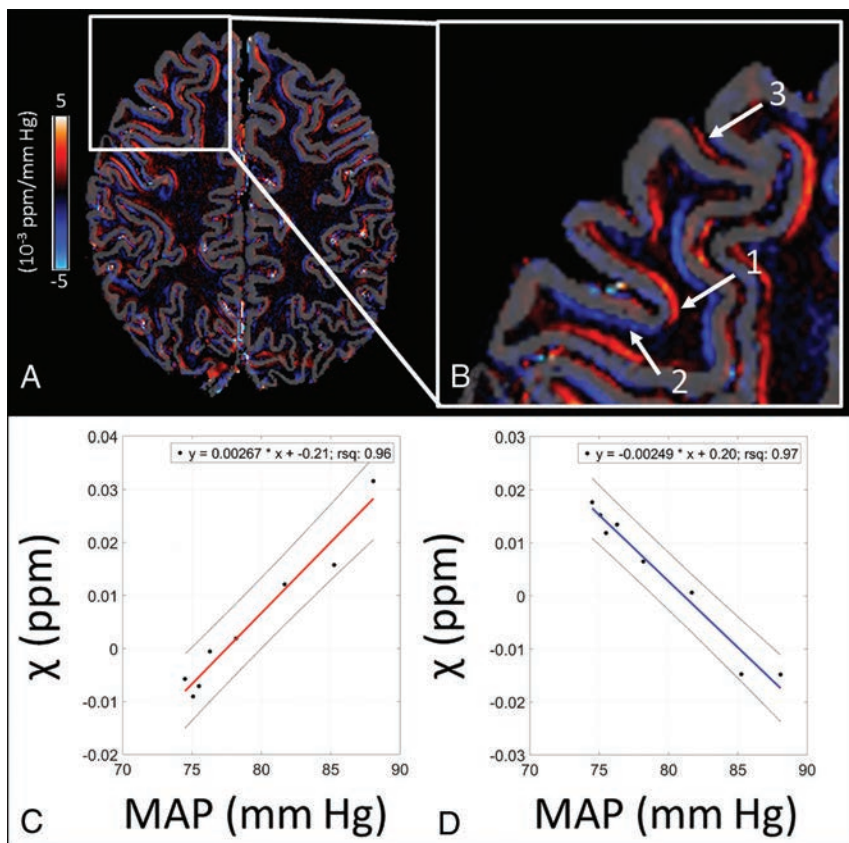


FIG 3. CVC map with a semicortical mask (A) and a zoomed-in view (B) showing regions with mainly arterial (arrow 1), venous (arrow 2), and pial arterial (arrow 3) contributions. In regions with predominantly arterial vessels (arrow 1), the susceptibility increases with increasing MAP (C), while it decreases in regions with predominantly venous vessels (arrow 2) with increasing MAP (D). The slope of the regression lines in C and D represents the CVC. rsq indicates the square of the correlation coefficient.

matter and arterial and venous blood vessels on the brain surface (Duvernoy type 5)^{16,17} as illustrated in Fig 2.

To illustrate this further, Fig 3 shows a representative compliance map with a semitransparent cortical mask in correspondence with the schematic drawing in Fig 2. The zoomed-in view highlights a subcortical region with mainly arterial contributions (arrow 1), a subcortical region with mainly venous contributions (arrow 2), and a region with pial arterial contributions (arrow 3). The relationship between MAP and susceptibility illustrates that the sign of the regression slope is different for regions with dominating arterial (Fig 3C) and venous (Fig 3D) blood volume changes.

If one assumed a differentiation of arterial and venous blood vessels by the inverse change of susceptibility with decreasing blood pressure, regional evaluation of QSM changes indicated a mean arterial compliance of $2.09 \pm 0.56 \times 10^{-3}$ ppm/mm Hg and a mean venous compliance of $-1.97 \pm 0.56 \times 10^{-3}$ ppm/mm Hg across all subjects (On-line Table).

DISCUSSION

In this exploratory study, we demonstrate that a small decrease in blood pressure such as that elicited by lying down induces magnetic susceptibility shifts in cortical and subcortical brain structures most likely reflecting contributions from vessels. The direction and extent of susceptibility changes are consistent with cerebral autoregulation,

whereby a decrease in blood pressure causes vasodilation and consequently an increase in CBV to keep CBF constant. The slope and direction of the relationship between susceptibility and MAP changes are indicative of the extent of cerebral vascular compliance in respective arterial and venous vessels.

Theoretically, QSM changes could also be caused by a change in the blood oxygenation level.¹⁸ However, this is unlikely because no physical or mental activity was required during the MR imaging examination. Considering that QSM can also pick up oxygenation-related changes in resting-state fMRI studies,¹⁹ such changes would be expected to occur predominantly in the cortex and not in such a widespread manner as we have observed. A further argument against an oxygenation-induced origin of our susceptibility changes is the constant SpO₂ during the entire MR imaging measurement.

Overall, the proposed approach promises a completely different view of cerebral blood vessels compared with angiographic techniques. Dynamic QSM imaging during changes in blood pressure may serve to assess the functional and not the morphologic component of the cerebral vasculature. Thus, only regions containing vessels with the ability to change their diameter as a consequence of cerebral autoregulation

contribute to the calculated CVC maps.²⁰ This property appears especially prominent in the long arterioles and venules of the subcortical WM and on the cortical surface. Furthermore, a differentiation between arterial and venous vascular signals is possible on the basis of the different direction of the susceptibility shift of oxygenated and deoxygenated blood.³

However, arterial and venous vessels that occupy an imaging voxel in an equal proportion cannot be depicted because their opposite susceptibility shifts will cancel out. The signal from larger vessels with high-flow velocity can also not be captured due to outflow and saturation effects.

The CVC maps represent a relative compliance measure rather than an absolute measure. This feature also explains why the CVC of the venous system seems to be almost as high as the CVC for the arterial system though fewer pericytes are present in the venous system. Apparently, the difference in susceptibility between venous blood and tissue water is much larger (~ 1.57 ppm) than the difference between arterial blood and tissue water (~ 0.26 ppm), enhancing the effect of blood volume changes in venous vessels.³

CONCLUSIONS

QSM allows a fast and noninvasive mapping of blood pressure-induced susceptibility changes, which could serve as a measure for CVC.

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REFERENCES

- De Rochefort L, Liu T, Kressler B, et al. **Quantitative susceptibility map reconstruction from MR phase data using Bayesian regularization: validation and application to brain imaging.** *Magn Reson Med* 2010;63:194–206 [CrossRef Medline](#)
- Schenck J. **The role of magnetic susceptibility in magnetic resonance imaging: MRI magnetic compatibility of the first and second kinds.** *Med Phys* 1996;23:815–50 [CrossRef Medline](#)
- Weisskoff RM, Kihne S. **MRI susceptometry: image-based measurement of absolute susceptibility of MR contrast agents and human blood.** *Magn Reson Med* 1992;24:375–83 [CrossRef Medline](#)
- Bayliss WM. **On the local reactions of the arterial wall to changes of internal pressure.** *J Physiol* 1902;28:220–31 [CrossRef Medline](#)
- Lassen NA. **Cerebral blood flow and oxygen consumption in man.** *Physiol Rev* 1959;39:183–238 [CrossRef Medline](#)
- Ursino M, Lodi CA. **A simple mathematical model of the interaction between intracranial pressure and cerebral hemodynamics.** *J Appl Physiol* 1997;82:1256–69 [CrossRef Medline](#)
- Aaslid R, Newell DW, Stooss R, et al. **Assessment of cerebral autoregulation dynamics from simultaneous arterial and venous transcranial Doppler recordings in humans.** *Stroke* 1991;22:1148–54 [CrossRef Medline](#)
- Kontos H, Wei EP, Navari RM, et al. **Responses of cerebral arteries and arterioles to acute hypotension and hypertension.** *Am J Physiol* 1978;234:H371–83 [CrossRef Medline](#)
- Panerai R. **Assessment of cerebral pressure autoregulation in humans: a review of measurement methods.** *Physiol Meas* 1998;19:305–38 [CrossRef Medline](#)
- Olufsen MS. **Blood pressure and blood flow variation during postural change from sitting to standing: model development and validation.** *J Appl Physiol* 2005;99:1523–37 [CrossRef Medline](#)
- Sati P, George IC, Shea CD, et al. **FLAIR*: a combined MR contrast technique for visualizing white matter lesions and parenchymal veins.** *Radiology* 2012;265:926–32 [CrossRef Medline](#)
- Schmidt RF, Thews G, Lang F, et al, eds. *Physiologie Des Menschen*. Berlin: Springer-Verlag; 2000 [CrossRef](#)
- Langkammer C, Bredies K, Poser BA, et al. **Fast quantitative susceptibility mapping using 3D EPI and total generalized variation.** *Neuroimage* 2015;111:622–30 [CrossRef Medline](#)
- Jenkinson M, Smith S. **A global optimisation method for robust affine registration of brain images.** *Med Image Anal* 2001;5:143–56 [CrossRef Medline](#)
- Liu Z, Spincemaille P, Yao Y, et al. **MEDI+0: morphology enabled dipole inversion with automatic uniform cerebrospinal fluid zero reference for quantitative susceptibility mapping.** *Magn Reson Med* 2018;79:2795–803 [CrossRef Medline](#)
- Moody DM, Bell MA, Challa VR. **Features of the cerebral vascular pattern that predict vulnerability to perfusion or oxygenation deficiency: an anatomic study.** *AJNR Am J Neuroradiol* 1990;11:431–39 [Medline](#)
- Duvernoy HM, Delon S, Vannson JL. **Cortical blood vessels of the human brain.** *Brain Res Bull* 1981;7:519–79 [CrossRef Medline](#)
- Fan AP, Bilgic B, Gagnon L, et al. **Quantitative oxygenation venography from MRI phase.** *Magn Reson Med* 2014;72:149–59 [CrossRef Medline](#)
- Sun H, Seres P, Wilman AH. **Structural and functional quantitative susceptibility mapping from standard fMRI studies.** *NMR Biomed* 2017;30 [CrossRef Medline](#)
- Paulson OB, Strandgaard S, Edvinsson L. **Cerebral autoregulation.** *Cerebrovasc Brain Metab Rev* 1990;2:161–92 [CrossRef Medline](#)

Acute and Evolving MRI of High-Altitude Cerebral Edema: Microbleeds, Edema, and Pathophysiology

P.H. Hackett, P.R. Yarnell, D.A. Weiland, and K.B. Reynard



ABSTRACT

SUMMARY: MR imaging of high-altitude cerebral edema shows reversible WM edema, especially in the corpus callosum and subcortical WM. Recent studies have revealed hemosiderin deposition in WM long after high-altitude cerebral edema has resolved, providing a high-altitude cerebral edema “footprint.” We wished to determine whether these microbleeds are present acutely and also describe the evolution of all MR imaging findings. In 8 patients with severe high-altitude cerebral edema, we obtained 26 studies: 18 with 3T and 8 with 1.5T scanners, during the acute stage, recovery, and follow-up in 7 patients and acutely in 1 patient. Imaging confirmed reversible cytotoxic and vasogenic WM edema that unexpectedly worsened the first week during clinical improvement before resolving. The 3T SWI, but not 1.5T imaging, showed extensive microbleeds extending beyond areas of edema seen acutely, which persisted and with time coalesced. These findings support cytotoxic and vasogenic edema leading to capillary failure/leakage in the pathophysiology of high-altitude cerebral edema and provide imaging correlation to the clinical course.

ABBREVIATIONS: HACE = high-altitude cerebral edema; HAPE = high-altitude pulmonary edema; MB = microbleed

The original MR imaging studies of acute high-altitude cerebral edema (HACE) with 1.5T magnets found FLAIR and T2 abnormalities in the corpus callosum, particularly the splenium.^{1,2} These findings were transient, attributed to vasogenic edema, and were subsequently confirmed, though descriptions of the time course and resolution of edema were incomplete.^{3,4} More recent reports using 3T SWI found microbleeds (MBs) in the corpus callosum in patients with a history of HACE 1–35 months previously, but none were studied acutely.^{5,6} When microbleeds appear in HACE, whether they change with time, how they correlate with edema, and whether their distribution in this illness is specific for HACE are all unknown.

In this study, we describe the evolution of both edema and microbleeds in 8 patients with severe HACE. These MR imaging data contribute to our understanding of HACE pathophysiology and provide clinical imaging correlations that may aid in diagnosis and management.

MATERIALS AND METHODS

We performed a retrospective study of all patients admitted to our hospital with HACE from 2011 through 2017. We examined MRIs obtained during acute illness and after discharge in all but 1 patient. In addition, we obtained a 10-year follow-up in 1 patient with HACE from 2006. Repeat MRIs were performed at the discretion of clinicians and hence at irregular intervals. Of the 26 MR imaging studies, magnet strength depended on availability: Eighteen were 3T and 8 were 1.5T.

RESULTS

Patients

All patients were evacuated from Colorado mountain communities between 2500 and 3000 m (8200–9840 feet) to the Denver area. Table 1 shows the demographics and clinical course. Seven of 8 had traveled to high altitude within 1 day from a sea level residence; 1 resided at high altitude (patient 5) and returned home after 1 week at low altitude. All patients had typical clinical and imaging findings of high-altitude pulmonary edema (HAPE, Fig 1), and all met the criteria for HACE diagnosis: altered mental status and/or ataxia in a person recently arriving at a high altitude and with acute mountain sickness or HAPE. Other diagnoses were excluded by clinical, laboratory, and imaging evaluations. All patients were treated for HAPE at mountain clinics with supplemental oxygen. Four were intubated, and 6 patients received dexamethasone. Pulmonary edema cleared in all patients during 1–3 days. Bedside callosal (disconnection syndrome) testing findings

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Indicates article with supplemental on-line table.



Indicates article with supplemental on-line photos.

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Table 1: Patient demographics and clinical course

Pt ID	Age (yr), Sex	Altitude of Onset	Days to Care ^a	SpO ₂	HACE Symptoms, Findings	Days in Hospital
1	35, M	2800 m	4	24%	Headache, anorexia, dyspraxia, coma	13
2	41, M	2970 m	5	41%	Headache, fatigue, confusion, ataxia	3
3	32, M	2740 m	4	50%	Headache, confusion, ataxia	12
4	23, F	2930 m	4	48%	Confusion, agitation	9
5	48, F	2530 m	4	74%	Crawling, incontinent, confused	5
6	47, M	2970 m	6	60%	Confusion, dysarthria, ataxia	12
7	29, M	2930 m	4	55%	Progressive confusion	12
8	34, M	2750 m	6	39%	Somnolence, confusion, ataxia	4

Note:—Pt ID indicates patient identification; SpO₂, peripheral oxygen saturation.

^aDays from onset of symptoms to presentation to clinic and immediate transfer to hospital.



FIG 1. Supine portable chest radiograph of patient 3 on admission to the hospital showing marked pulmonary edema.

were normal in the 3 patients who were tested. At hospital discharge, patients were recovering well and returned to their demanding professions.

MR Imaging Studies

The On-line Table summarizes the timing of MR imaging studies and findings.

FLAIR and T2

All 8 patients on their first scan showed increased FLAIR and T2 signal: 5 patients in the corpus callosum and subcortical WM (Fig 2, On-line Figures 1–8), 2 in subcortical WM only (patients 6 and 8, On-line Figures 9–11), and 1 (patient 5) in the periventricular WM (On-line Figure 12). In the 5 patients with repeat MR imaging within 10 days of the first, WM edema increased before completely resolving (Fig 3, On-line Figures 1–2, 4–7, 10), except for patient 5.

DWI

All 8 patients showed restricted diffusion indicating cytotoxic edema, 7 in the splenium and subcortical WM, mostly corresponding to FLAIR abnormalities (On-line Table and Fig 2, On-line Figures 1–4, 6–8, 11, 13). Patient 6 had small foci of restricted

diffusion only in left cerebellar WM and medial right frontoparietal cortex (On-line Figures 9, 10). In 6 patients, restricted diffusion was present on the initial scan, but in 2 patients, it developed or became worse between the initial and second scans. Restricted diffusion resolved in all with follow-up imaging, more quickly than FLAIR and T2 abnormalities. Patient 2 had small lacunar infarcts in the globus pallidi that persisted at follow-up (On-line Figure 3), while patient 4 had a tiny lacunar infarct in left frontal subcortical WM (On-line Figure 7).

Hemosiderin/Microbleeds

All 6 patients imaged with 3T SWI demonstrated extensive microbleeds on the first MR imaging, with a “black pepper-like” appearance, which persisted in those with follow-up imaging (Figs 4 and 5, On-line Figures 14–18). Microbleeds were present throughout the WM, including the deep tracts and middle cerebellar peduncles, but were more numerous in the corpus callosum and subcortical WM, where edema predominated. The number and extent of microbleeds (by visual inspection) did not increase during the first week, in contrast to WM edema. No microbleeds were detected in 2 patients initially scanned at 1.5T using gradient-echo T2* imaging (Fig 6), but they were identified in both patients on follow-up with 3T SWI (Fig 5, On-line Figure 14). The morphology of microbleeds changed with time, coalescing on follow-up images between 2.5 months and 10 years (Fig 6, On-line Figures 16, 18). Two patients had normal DTI tractography findings (On-line Figure 19).

DISCUSSION

This series of cases demonstrated important new findings regarding MR imaging of HACE. First, we found that extensive WM microbleeds were already present on the initial MR imaging of acutely ill patients. Second, we noted that WM vasogenic edema and, to a lesser extent, restricted diffusion both increased in the first week, even though patients were clinically improving. Both were reversible, consistent with complete recovery. In contrast, microbleeds did not worsen in the first week of hospitalization but did remain detectable for years, though they were missed with T2* gradient-echo sequences obtained at 1.5T. Across time, the microbleeds coalesced. These findings indicate that both cytotoxic and vasogenic edema are present in severe HACE and that capillary leakage is sufficient to produce microbleeds. Furthermore, this work provides a description of the evolution of MR images in HACE that may aid in diagnosis and management.

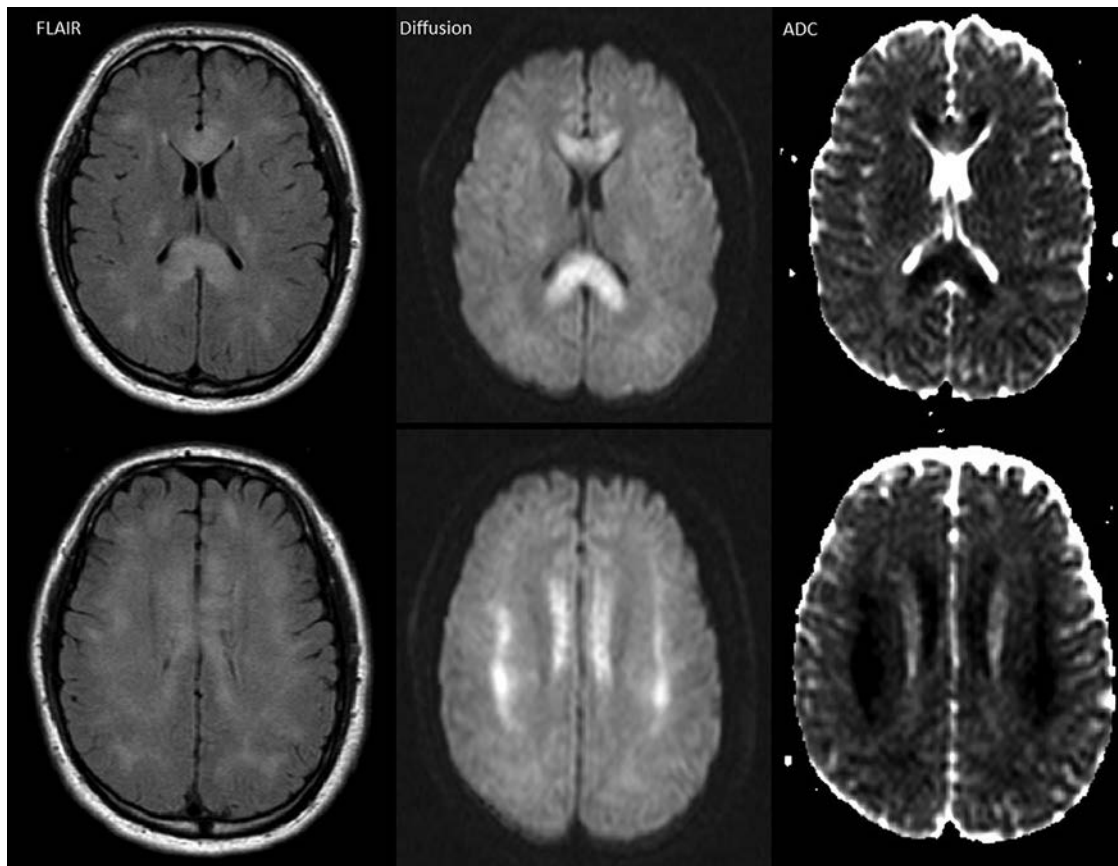


FIG 2. Patient 7, day 5, 1.5T. Axial FLAIR, diffusion, and ADC map images demonstrate hyperintensity and restricted diffusion in the entire corpus callosum and patchy areas of bilateral subcortical WM.

Microbleeds

All 6 patients on the first MR imaging with SWI showed microbleeds; we thus do not know at what stage of illness these developed. Microbleeds did not appear to correlate with the degree of edema or restricted diffusion on the initial scan or with clinical severity, though all patients were severely ill. Whether these MBs in non-fatal HACE relate to microhemorrhages reported in postmortem examinations⁷ is unknown, though similar-sized microhemorrhages in other conditions were clearly seen on gross pathology.⁸ As expected, MBs were more easily detected with higher magnetic strength and SWI.⁹

The distribution and extent of microbleeds we describe may be distinct for severe HACE. Microbleeds reported in other conditions are usually far fewer in number, in different distributions, and lack the fine black pepper appearance.⁹ Previous studies using SWI in subjects after high altitude exposure support this view. Eleven of 13 climbers with a history of HACE demonstrated residual MBs, with only severe cases or those with HAPE showing the extensive distribution similar to that in our patients.^{5,6} Schommer et al⁶ demonstrated that HAPE, acute mountain sickness, and extreme high altitude exposure by themselves do not cause MBs; Eight climbers with a history of HAPE but without HACE had no MBs, only a few microbleeds were present in 1 of 11 climbers with a history of severe acute mountain sickness, and none were found in the 8 climbers who went to 7000 m without oxygen without altitude illness.⁶ Kottke et al¹⁰ compared microbleeds before and after a Himalayan expedition and found new

ones in 3 of 15 climbers who went to >7000 m and did not have HACE or HAPE. These microbleeds were in the splenium but only 1 in 1 climber, and a few in the other 2, in marked contrast to our patients with HACE. Taken together, these studies suggest that WM microbleeds due to high altitude exposure occur infrequently, only becoming extensive as HACE develops, especially with concomitant HAPE.

Vasogenic and Cytotoxic Edema

We confirmed our previous findings of WM vasogenic edema on FLAIR and T2 MR imaging in severe HACE.¹ Most interesting, all 5 patients with repeat MR imaging within 10 days of the first one showed greater edema, though they were clinically improving. The imaging findings thus not only lag behind clinical improvement but could be misleading. A possible explanation is delayed vasogenic edema mediated by hemoglobin degradation products, a process known to take several days for maximal accumulation of edema-triggering moieties.¹¹ The decrease in cerebral blood volume and CBF with restoration of normoxia may well have allowed an increase in edema without increasing intracranial pressure.

Seven patients showed reversible restricted diffusion in the corpus callosum with a predilection for the splenium. Such cytotoxic lesions have been reported with various CNS insults, including trauma, infection, drug toxicity, and metabolic abnormalities; they are often confused with ischemia.¹² The common pathway for deranged ion transport in these entities may be cytokines, which increase extracellular glutamate, resulting in intracellular

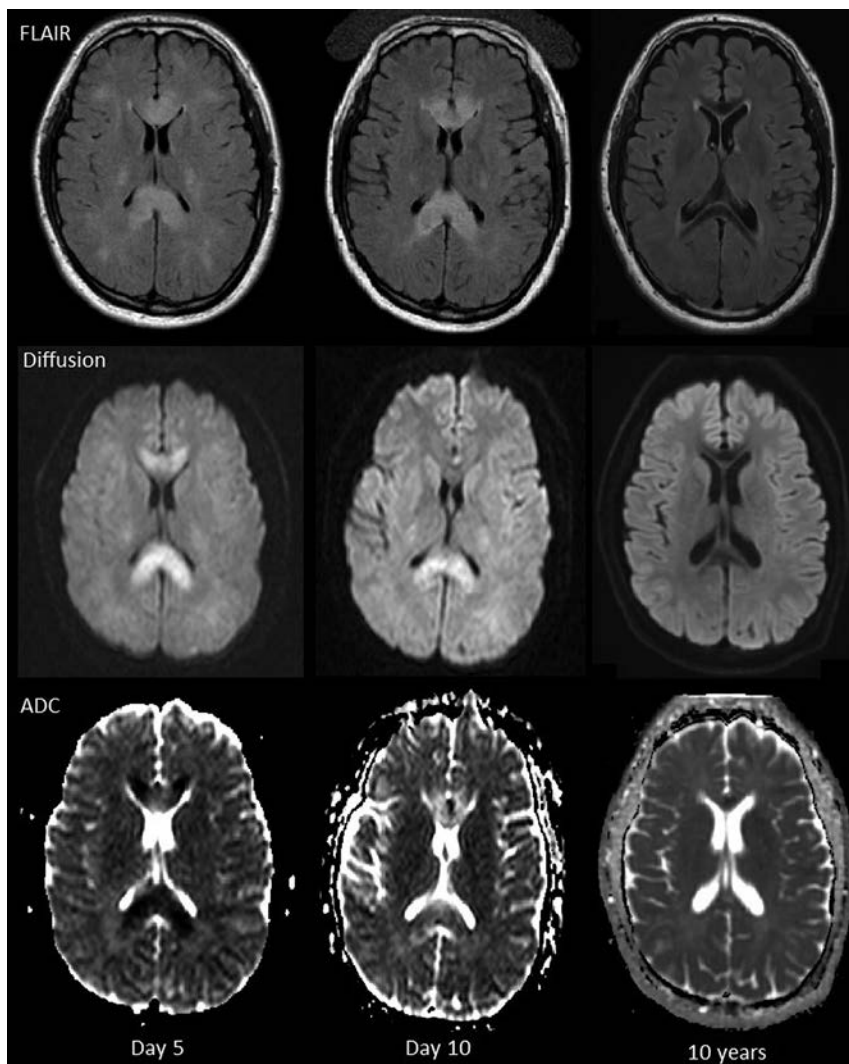


FIG 3. Patient 7, 1.5T on days 5 and 10, 3T at 10 years. Axial FLAIR, diffusion, and ADC images. FLAIR hyperintensity in the corpus callosum slightly increases at day 10 and then resolves at 10 years. Restricted diffusion in the corpus callosum decreases at day 10 and resolves at 10 years. Low signal in the genu and splenium of corpus callosum on the FLAIR images at 10 years is due to hemosiderin.

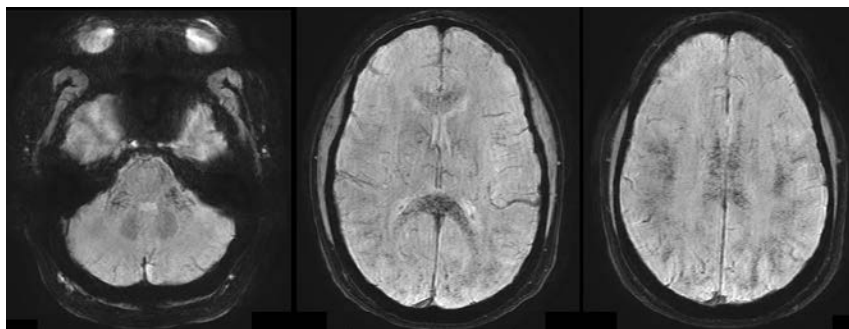


FIG 4. Patient 2. SWI. Diffuse microbleeds with a predilection for WM tracts, including the corpus callosum and middle cerebellar peduncles and subcortical WM.

swelling and restricted water diffusivity. The corpus callosum, particularly the splenium, may be more susceptible because of more glutamate and cytokine receptors.¹² Most interesting, restricted diffusion was delayed in 2 patients, consistent with a mechanism requiring time for accumulation of agents such as inflammatory mediators.

While cytotoxic edema is due to maladaptive ion transport, WM vasogenic edema is driven primarily by hydrostatic forces.¹¹ Both seem to be in play in HACE. Mild vasogenic edema (plasma ultrafiltrate) occurs in most individuals ascending to a moderate altitude (>3–4000 m), regardless of the presence of acute mountain sickness, and is related to increased cerebral perfusion.¹³ However, as HACE develops, vasogenic edema undergoes “hemorrhagic conversion,”¹¹ with extravasation of red cells and increased edema leading to increased ICP. Exactly what triggers this conversion and what precipitates the restricted diffusion are unclear. Investigators have proposed both mechanical factors, such as impaired autoregulation and excessive capillary hypertension, and permeability factors, such as vascular endothelial growth factor, reactive oxygen species, and other hypoxia-induced factors.^{13,14} The end result is loss of WM microvascular integrity.

There are analogous findings in HAPE, a frequent precipitant of HACE, which was present in our patients. In fact, HAPE with its severe gas-exchange derangements may be necessary at the modest altitudes in Colorado to trigger HACE, which is more commonly reported above 4000 m. HAPE is a hydrostatic edema due to capillary hypertension, capillary failure, and leakage of red cells, triggered by uneven hypoxic pulmonary vasoconstriction.¹⁵ Retinal hemorrhages are common in HACE, present in up to 60% of patients, but are also present in asymptomatic individuals at high altitude.¹⁶ The single pathologic study from an individual who died of HACE,¹⁷ found retinal capillary leakage. We consider that vascular leak triggered by overperfusion, capillary hypertension, and other factors influencing microvascular integrity may be similar in retinal, cerebral, and pulmonary circulations subjected to extreme hypoxemia.

Some of our findings may be incidental or questionably related to HACE. Patient 5 demonstrated mild T2/FLAIR hyperintensity in periventricular WM in an atypical distribution, which persisted at follow-up imaging, suggesting an alternative cause such as small-vessel ischemic disease. One patient lacked restricted diffusion in the corpus callosum or subcortical WM but did have small reversible foci in the left cerebellar WM and medial

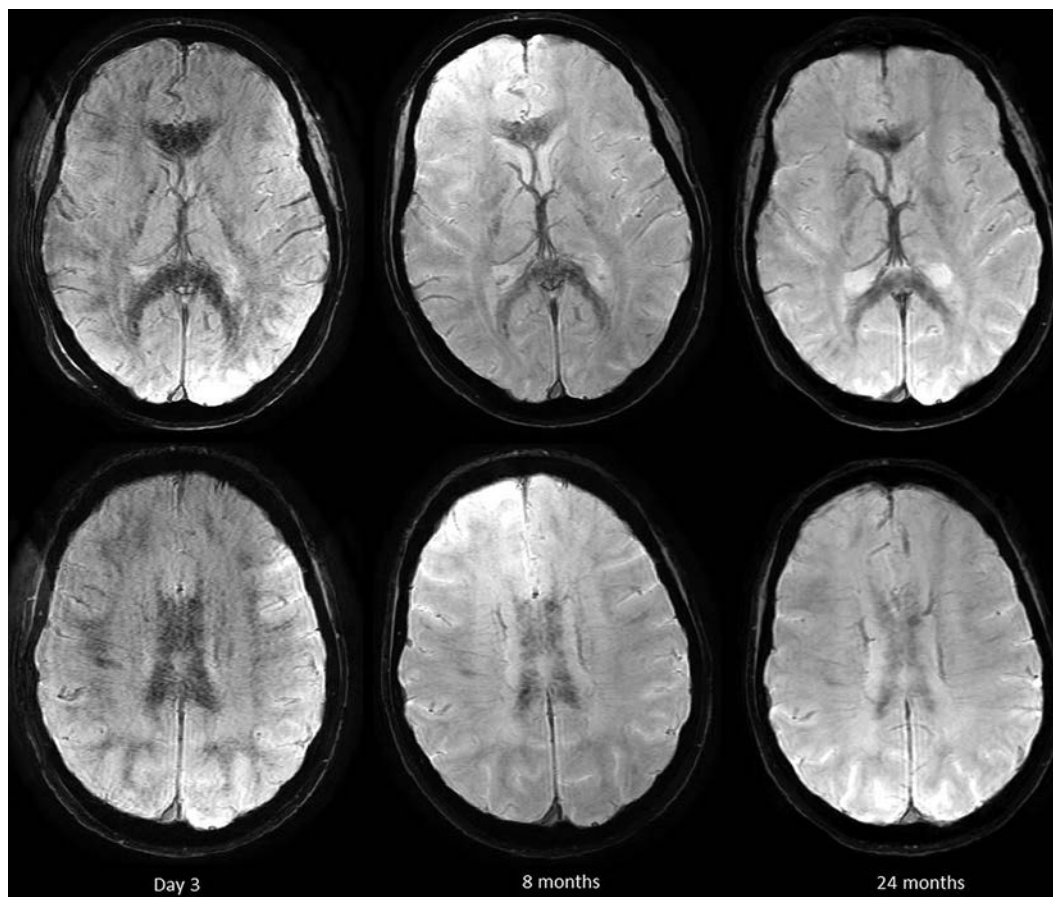


FIG 5. Patient 5, 3T. Hemosiderin-sensitive sequences at 3 days, 8 months, and 2 years. Note uniformly distributed petechial hemorrhages that persist and become more confluent with time.

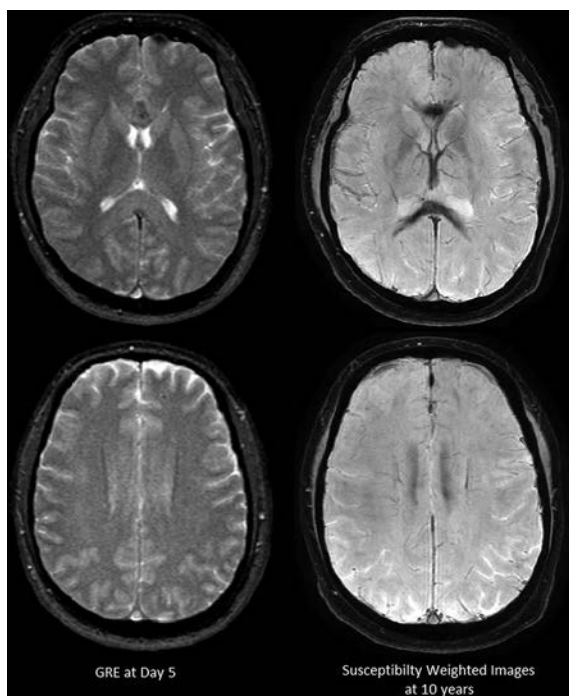


FIG 6. Patient 7. Hemosiderin-sensitive gradient echo with 1.5T on day 5 and SWI on 3T at 10 years. Microbleeds are not apparent on 1.5T. Confluent hemosiderin staining is seen in the corpus callosum at 10-year follow-up.

right frontoparietal cortex. While possibly due to the same mechanism as in the more typical lesions, ischemia could not be ruled out. Two patients had small lacunar infarcts in the basal ganglia and subcortical WM that persisted at follow-up. Similar lesions have been reported previously, consequent to altitude illness, but how these are related to HACE is unclear.¹⁸ One subject, patient 7, had clear corpus callosum atrophy on the MR imaging examination at 10 years (Online Figure 20) but had no symptoms and normal neurologic examination.

In conclusion, HACE is a potentially fatal neurologic condition, characterized with MR imaging in severe nonfatal cases by extensive fine black pepper microbleeds that leave a permanent imprint. HACE pathophysiology appears to involve reversible vasogenic and cytotoxic edema that progresses to microvascular disruption and thus microbleeds. MR imaging, notably 3T with SWI, detects both edema and microbleeds and may provide an aid in diagnosis, staging, and management of this serious condition.

REFERENCES

1. Hackett PH, Yarnell PR, Hill R, et al. **High-altitude cerebral edema evaluated with magnetic resonance imaging: clinical correlation and pathophysiology.** *JAMA* 1998;280:1920–25 [CrossRef Medline](#)
2. Yarnell PR, Heit J, Hackett PH. **High-altitude cerebral edema (HACE): the Denver/Front Range experience.** *Semin Neurol* 2000; 20:209–17 [CrossRef Medline](#)

3. Wong SH, Turner N, Birchall D, et al. **Reversible abnormalities of DWI in high-altitude cerebral edema.** *Neurology* 2004;62:335–36 [CrossRef Medline](#)
4. Venkata Nagesh I, Manoj G, Gurdarshdeep M. **High-altitude cerebral edema-serial MRI findings.** *Wilderness Environ Med* 2015;26:278–80 [CrossRef Medline](#)
5. Kallenberg K, Dehnert C, Dörfler A, et al. **Microhemorrhages in non-fatal high-altitude cerebral edema.** *J Cereb Blood Flow Metab* 2008;28:1635–42 [CrossRef Medline](#)
6. Schommer K, Kallenberg K, Lutz K, et al. **Hemosiderin deposition in the brain as footprint of high-altitude cerebral edema.** *Neurology* 2013;81:1776–79 [CrossRef Medline](#)
7. Dickinson J. **High altitude cerebral edema: cerebral acute mountain sickness.** *Seminars in Respiratory and Critical Care Medicine* 1983;5:151–58 [CrossRef](#)
8. Gibbs WN, Opatowsky MJ, Burton EC. **AIRP best cases in radiologic-pathologic correlation: cerebral fat embolism syndrome in sickle cell β -thalassemia.** *Radiographics* 2012;32:1301–06 [CrossRef Medline](#)
9. Haller S, Vernooij MW, Kuijter JPA, et al. **Cerebral microbleeds: imaging and clinical significance.** *Radiology* 2018;287:11–28 [CrossRef Medline](#)
10. Kottke R, Pichler Hefti J, Rummel C, et al. **Morphological brain changes after climbing to extreme altitudes: a prospective cohort study.** *PLoS One* 2015;10:e0141097 [CrossRef Medline](#)
11. Stokum JA, Gerzanich V, Simard JM. **Molecular pathophysiology of cerebral edema.** *J Cereb Blood Flow Metab* 2016;36:513–15 [CrossRef Medline](#)
12. Starkey J, Kobayashi N, Numaguchi Y, et al. **Cytotoxic lesions of the corpus callosum that show restricted diffusion: mechanisms, causes, and manifestations.** *Radiographics* 2017;37:562–76 [CrossRef Medline](#)
13. Wilson MH, Newman S, Imray CH. **The cerebral effects of ascent to high altitudes.** *Lancet Neurol* 2009;8:175–91 [CrossRef Medline](#)
14. Hackett P, Roach R. **High altitude cerebral edema.** *High Alt Med Biol* 2004;5:136–46 [CrossRef Medline](#)
15. Maggiorini M, Melot M, Pierre S, et al. **High-altitude pulmonary edema is initially caused by an increase in capillary pressure.** *Circulation* 2001;103:2078–83 [CrossRef Medline](#)
16. Arora R, Jha KN, Sathian B. **Retinal changes in various altitude illnesses.** *Singapore Med J* 2011;52:685–88 [Medline](#)
17. Lubin JR, Rennie D, Hackett P, et al. **High altitude retinal hemorrhage: a clinical and pathological case report.** *Ann Ophthalmol* 1982;11:1071–76 [Medline](#)
18. Usui C, Inoue Y, Kimura M, et al. **Irreversible subcortical dementia following high altitude illness.** *High Alt Med Biol* 2004;5:77–81 [CrossRef Medline](#)

Alterations in Blood-Brain Barrier Permeability in Patients with Systemic Lupus Erythematosus

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ABSTRACT

BACKGROUND AND PURPOSE: Neuropsychiatric systemic lupus erythematosus refers to central and peripheral nervous system involvement, which may occur secondary to antineuronal antibodies crossing the blood-brain barrier that preferentially target cells in the hippocampus leading to abnormal hypermetabolism and atrophy. Thus, we hypothesized that alterations in BBB permeability, detected on dynamic contrast-enhanced MR imaging, occur in the hippocampus in patients with systemic lupus erythematosus before development of neuropsychiatric systemic lupus erythematosus.

MATERIALS AND METHODS: Six patients with systemic lupus erythematosus without neuropsychiatric systemic lupus erythematosus and 5 healthy controls underwent dynamic contrast-enhanced MR imaging with postprocessing into BBB permeability parameters (K^{trans} and V_e) and CBF. Standardized methods selected ROI sampling of the abnormal brain regions detected on FDG-PET. The mean and SD of K^{trans} , V_e , and CBF were calculated. Linear regression and nonparametric Spearman rank correlation analyses of K^{trans} and V_e with CBF were performed. Dynamic contrast-enhanced curves and the area under the curve were generated for each brain region. Student *t* test comparisons were performed.

RESULTS: Quantitative data revealed that patients with systemic lupus erythematosus have statistically increased K^{trans} ($P < .001$) and V_e ($P < .001$) compared with controls. In patients with systemic lupus erythematosus, statistically significant positive correlations were seen between K^{trans} ($P < .001$) and V_e ($P < .001$) with CBF. Furthermore, the mean area under the curve revealed statistically increased BBB permeability in the hippocampus ($P = .02$) compared with other brain regions in patients with systemic lupus erythematosus compared with controls.

CONCLUSIONS: These initial findings are proof-of-concept to support the hypothesis that patients with systemic lupus erythematosus have increased BBB permeability, specifically in the hippocampus, compared with other brain regions. These findings may advance our understanding of the underlying pathophysiology affecting the brain in autoimmune diseases.

ABBREVIATIONS: ANAM = Automated Neuropsychological Assessment Metric; BBBP = BBB permeability; DCE = dynamic contrast-enhanced; DNRAb = N-methyl-D-aspartate receptor antibodies; K^{trans} = volume transfer constant; NMDAR = N-methyl-D-aspartate receptor; NPSLE = neuropsychiatric systemic lupus erythematosus; SLE = systemic lupus erythematosus; V_e = volume in the extravascular extracellular space per unit of tissue volume

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disorder characterized by a loss of immune tolerance and autoantibody production. The diverse spectrum of

symptoms reflects involvement of multiple organ systems, including musculoskeletal, renal, dermatologic, immunologic, and neurologic systems. Neuropsychiatric SLE (NPSLE) refers to central and peripheral nervous system involvement. Of the 19 clinical syndromes¹ that compose NPSLE, cognitive and mood disturbances are reported most frequently, with a prevalence as high as 80% and 75%, respectively,² and, most important, have detri-

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mental effects on quality of life.³ Although autoantibodies are universal in patients with SLE, and circulating immune complexes have been implicated in the pathogenesis of non-NPSLE symptoms, to date, only 2 autoantibodies, anti-ribosomal P and cross-reactive, anti-double stranded DNA/N-methyl D-aspartate receptor antibodies (DNRAb), have been shown to directly affect neuronal function.^{4,5} Both anti-ribosomal P antibodies and DNRAb have neurotoxic effects that have been carefully studied in murine models and electrophysiologic studies; they are mediated through different mechanisms involving N-methyl-D-aspartate receptor (NMDAR) activation, leading to enhanced intracellular Ca⁺⁺ influx and neuronal dysfunction or death.^{6,7}

DNRAbs, in particular, have been shown to preferentially target place cells in the CA1 region of the hippocampus and are associated with selective spatial memory deficits in the murine model.⁸ These results are supported by human studies in patients with SLE in which serum DNRAb titers have correlated with deficits in spatial memory testing,⁸ abnormal hippocampal hypermetabolism,⁹ and hippocampal atrophy.¹⁰ Furthermore, there have been multiple studies reported in the literature examining the CSF of patients with NPSLE, which revealed high serum antibodies within the CSF.¹¹⁻¹⁶ In particular, anti-NMDAR antibodies¹³ and anti-NR2 subunits of NMDAR¹⁴⁻¹⁶ were found in the CSF.

Despite compelling evidence for autoantibody-mediated CNS dysfunction, the caveat remains that the disruption of the BBB allows antibody access to brain tissue with subsequent neuronal alterations and cognitive loss.¹⁷ The mouse model of DNRAb-mediated cognitive dysfunction uses a nonautoimmune mouse (BALB/c strain) immunized to produce the anti-NMDAR antibodies/DNRAbs. In this model, mice with circulating DNRAbs are phenotypically intact unless lipopolysaccharide is injected intraperitoneally to mimic infection and damage the BBB.¹⁸ Following injection with lipopolysaccharide, there is evidence of DNRAb penetration in the brain with antibodies specifically binding to neurons in the hippocampus.^{18,19} However, little is known about BBB function in patients with SLE. On the basis of the mouse model, we hypothesized that patients with SLE may experience repeat BBB insults with time, mediated by episodes of infection, stress, hypertension, or smoking and that episodic damage to the BBB allows circulating autoantibodies, including DNRAbs, to access the brain, resulting in neuropsychiatric symptoms.

There has been increasing interest in quantitatively evaluating BBB permeability (BBBP) using dynamic contrast-enhanced (DCE) MR imaging. DCE-MR imaging is a technique in which multiple T1WI images are obtained before, during, and after contrast administration to provide signal enhancement as a function of time.^{20,21} DCE-MR imaging uses a 2-compartment model, specifically the intravascular space and the extravascular extracellular space, to evaluate blood flow and permeability.²² Several BBBP parameters are derived from DCE-MR imaging model-based quantitative analyses, such as volume transfer constant (K^{trans}) and volume in the extravascular extracellular space per unit of tissue volume (Ve).²⁰⁻²² K^{trans} is a flow parameter that measures the volume transfer constant from the blood plasma in the intravascular space to the extravascular extracellular space.²³ A quantitative increase in the K^{trans} and Ve values indicates leakage of fluid across the BBB into the brain tissue. The purpose of this

study was to compare the BBBP parameters (K^{trans} and Ve), as demonstrated on DCE-MR imaging, in patients with SLE and healthy controls with specific focus on the hippocampal region.

MATERIALS AND METHODS

Patient Cohort

We performed a prospective study of patients with SLE and healthy controls undergoing DCE-MR imaging and clinical and neuropsychological evaluations under our current ongoing National Institutes of Health/National Institute of Allergy and Infectious Diseases protocol (No. 1PO1A1073693). Six patients with SLE were recruited randomly from the Rheumatology Clinics at Northwell Health; all were 18 years of age or older and fulfilled the American College of Rheumatology revised criteria for SLE.²⁴ To avoid confounding influences on neuroimaging and neuropsychological end points, key exclusion criteria included the presence of active or prior NPSLE or another CNS event; current use of antidepressant, antipsychotic, or anxiolytic drugs; or a history of excessive alcohol or illicit drug use. Additionally, subjects with SLE were required to have stable disease activity and medication doses for 4 weeks before the assessments. Disease activity and accrued damage were assessed with the Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI; <https://www.gsksource.com/pharma/content/micro-sites/BenSELENA-SLEDAI/index.html>)²⁵ and the Systemic Lupus International Collaborating Clinics Damage Index (SLICC DI <https://sliccgroup.org/research/slicc-damage/>)²⁶ within 2 weeks of imaging and cognitive assessments. Cognition was assessed using the Automated Neuropsychological Assessment Metric (ANAM),²⁷ a set of computerized measures of sustained attention, visual search, computational skills, concentration, spatial and cognitive processing, and working memory. Throughput scores, representing a combination of reaction time and accuracy, were the primary measure of cognitive efficiency used in the analyses. Subjects were additionally rated for depression and anxiety with the Beck Depression Inventory and State Trait Anxiety Inventory.²⁸ Six age- and sex-matched healthy controls with no comorbid illness and no medications were recruited for comparison. Institutional review board approval and subject consent were obtained.

Data Acquisition and Postprocessing

All patients and controls underwent DCE-MR imaging on a 3T magnet (Siemens Prisma, Erlangen, Germany) dedicated to research at the main hospital site. MR imaging sequences included sagittal T1WI, axial T1WI, T2WI, FLAIR, and susceptibility- and diffusion-weighted imaging acquired according to standard departmental protocols. Whole-brain permeability imaging was performed using a dynamic contrast technique with axial 3D fast-spoiled gradient-recalled T1WI sequences and 80 cine phases using TR = 7.0 ms, TE = 3.08 ms, FOV = 24 cm, slice thickness = 5.0 mm, and matrix size = 128 × 256.

The gadolinium contrast-injection protocol was standardized for all patients with SLE and healthy controls. Gadavist gadolinium contrast (gadobutrol; Bayer Schering Pharma, Berlin, Germany) was intravenously administered according to patient body weight (0.1 mmol/kg) per manufacturer's recommendations at 3

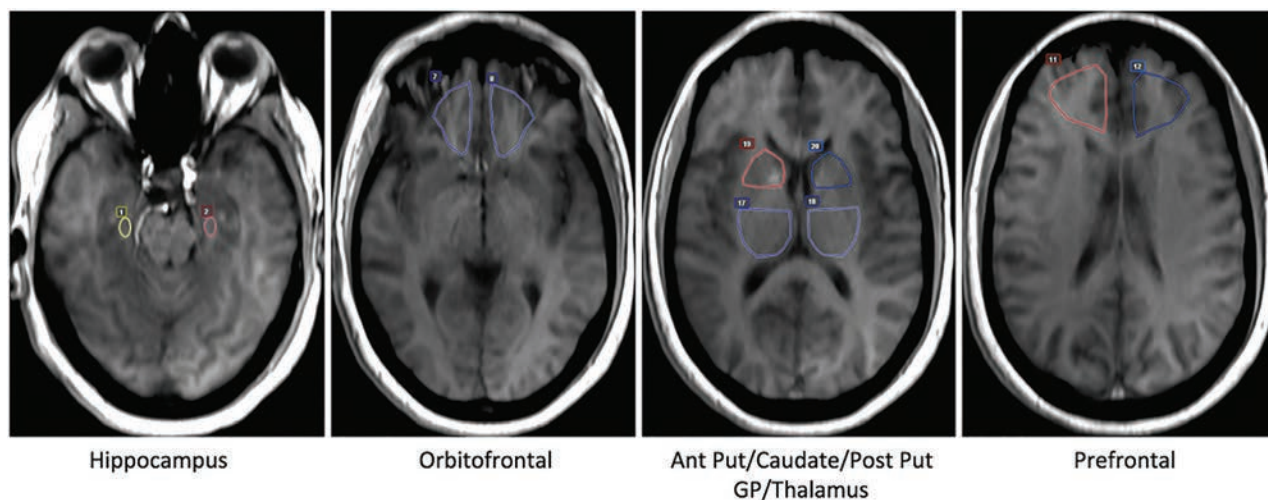


FIG 1. DCE-MR imaging data acquisition methods. Mirror ROIs were placed for sampling the abnormal regions described on FDG-PET: hippocampus, orbitofrontal, anterior putamen/caudate, posterior putamen/globus pallidus/thalamus, and prefrontal regions. Ant Put indicates anterior putamen; Post Put, posterior putamen; GP, globus pallidus.

mL/s with a 45-second delay, acquiring 5 volumes, after the DCE sequence was initiated. Immediately following contrast administration, a saline chasing bolus of 20-mL volume was intravenously administered at 3 mL/s. No prebolus contrast injection was performed in this study protocol.

Postprocessing of the acquired images into BBBP parameters of K^{trans} (milliliters/100 g/min), V_e (milliliters/100 g), and CBF (milliliters/100 g/min) was performed using Olea Sphere 2.2 and 2.3 (Olea Medical, La Ciotat, France) with the Tofts extended permeability model by trained research personnel. The postprocessing technique was standardized with the arterial input function placed at the center of the cavernous segment of the internal carotid artery in a similar fashion for all patients with SLE and healthy controls. A standardized method was used with selective ROI placement, sampling the following abnormal regions of metabolism described on FDG-PET²⁹: 1) hippocampus, 2) orbitofrontal cortex, 3) prefrontal cortex, 4) posterior putamen/globus pallidus/thalamus, and 5) anterior putamen/caudate. Mirror ROIs were placed in the cerebral hemispheres for identical sampling bilaterally at the same brain levels (Fig 1). Dynamic contrast-enhancement curves for each brain region were generated to compare the permeability phases among patients with SLE and healthy controls.

Statistical Analysis

The demographic characteristics and ANAM subtest throughput scores in patients with SLE and healthy controls were analyzed using Student *t* tests, nonparametric Mann-Whitney *U* tests, Pearson correlations, or Fisher exact tests as appropriate. Analyses were performed using SPSS 24 (IBM, Armonk, New York). All tests were 2-sided, and the significance level was set at $P < .05$.

The mean and SD for each BBBP parameter (K^{trans} and V_e) and CBF were calculated for the patients with SLE and healthy controls. The overall mean K^{trans} , V_e , and CBF for all regions were compared between the patients with SLE and healthy controls using the 2-sample Student *t* test with significance at $P < .05$.

Linear regression analyses of each BBBP factor (K^{trans} and V_e) with CBF were performed separately to evaluate the correlation coefficient (*r*), correlation of determination (R^2), and the statisti-

cal significance in patients with SLE and healthy controls. Because a large variability among the data points of patients with SLE was observed in the scatterplots, to confirm the results of the regression analyses, we additionally analyzed the data with the nonparametric Spearman rank correlation, which is robust against non-normally distributed data.

The mean dynamic contrast-enhancement curve for each brain region was generated in the patients with SLE and healthy controls. The area under the curve was computed for each brain region in reference to the baseline before contrast arrival. The mean area under the curve was compared in each brain region for the patients with SLE and healthy controls using the 2-sample Student *t* test with significance at $P < .05$.

RESULTS

All 6 patients with SLE and 5 healthy controls were included in the statistical analysis. One healthy control subject was excluded due to inadequate postprocessing of the DCE-MR imaging data from excess motion. There were no significant differences between patients with SLE and healthy controls in terms of age, race, smoking, and assessments for depression and anxiety (Table 1). However, the patients with SLE demonstrated significantly lower scores on the cognitive testing than the healthy controls. Overall, the patients with SLE had low levels of disease activity, were on very little prednisone, and were all serologically negative for anti-cardiolipin antibodies and lupus anticoagulant, and 3 of them had hypertension controlled with medication but no other comorbid illnesses. Half of the subjects with SLE and 1 healthy control had elevated serum DNRAb titers. A comparison of mean scores for the Beck Depression Inventory, State Trait Anxiety Inventory, and ANAM tests between those with high serum DNRAb titers (DNRAb+) and those with low serum DNRAb titers demonstrated trends of higher depression and anxiety scores and lower throughput scores on the ANAM tests for the DNRAb+ group, though none reached statistical significance (data not shown).

The model-based quantitative data revealed that patients with SLE have statistically significant increases in K^{trans} ($P < .001$) and

Ve ($P < .001$) compared with healthy controls (Table 2) using all brain regions. These findings indicate that patients with SLE have increased flow across the BBB (K^{trans}) coupled with accumulation of fluid in the extravascular extracellular space (Ve) in the brain.

Linear regression analyses of K^{trans} and Ve with CBF, separately, demonstrated statistically significant moderate positive correlations between K^{trans} ($r = 0.47$, $R^2 = 0.22$, $P < .001$) and Ve

($r = 0.47$, $R^2 = 0.23$, $P < .001$) with CBF in patients with SLE (Fig 2). In addition, the nonparametric Spearman rank correlation of K^{trans} with CBF ($r = 0.435$, $P = .0005$) and Ve with CBF ($r = 0.44$, $P = .0004$) also revealed statistically significant moderate positive correlations. These findings are in contrast to the healthy controls, which demonstrate under normal conditions, as the CBF increases, K^{trans} and Ve do not significantly change ($r = 0.22$ and $r = 0.25$ respectively) and do not correlate with CBF ($P > .05$). In addition, this data demonstrates much higher variance in the quantitative data for the patients with SLE. On the other hand, the K^{trans} and Ve data in the healthy controls show much lower variance, with strong consistency in the data clustered in the same quantitative range.

When we qualitatively compared the generated mean dynamic contrast-enhancement curves in the different brain regions, patients with SLE demonstrated increased BBBP, specifically in the hippocampal region compared with healthy controls (Fig 3). Comparison of the mean area under the curve for patients with SLE and healthy controls revealed a statistically significant increased BBB permeability only in the hippocampal region ($P = .02$). All other brain regions demonstrated no statistically significant difference in the patients with SLE and healthy controls in the orbitofrontal ($P = .72$), prefrontal ($P = .55$), posterior putamen/globus pallidus/thalamus ($P = .83$), and anterior putamen/caudate ($P = .60$). Furthermore, model-based quantitative data revealed that patients with SLE have statistically significant increased K^{trans} ($P = .04$), Ve ($P = .04$), and CBF ($P = .01$) in the hippocampal region compared with healthy controls (Table 3). All other brain regions did not demonstrate a statistically significant increase in both K^{trans} and Ve with increased CBF ($P > .05$).

DISCUSSION

Neuropsychiatric symptoms, mainly cognitive dysfunction and mood disturbances, frequently occur in patients with SLE, significantly impacting their quality of life. Since neurotoxic autoantibodies, DNRAb and anti-ribosomal P antibodies in particular, have been shown to mediate cognitive and behavioral disturbances in murine models^{6,7} and are associated with cognitive and behavioral dysfunctions in human SLE,⁸ there is increasing focus

Table 1: Clinical characteristics and neuropsychological testing

	SLE (n = 6)	Healthy Controls (n = 5)	P Value
Age (mean) (yr)	38.0 ± 13.2	34.2 ± 10.5	.619
Race			.292
Caucasian	2 (33%)	0	
Hispanic	0	2 (40%)	
African American	3 (50%)	2 (40%)	
Asian	1 (17%)	1 (20%)	
Smoking	1	1	.361
High serum DNRAb titer	3 (50%)	1 (20%)	.545
ANAM testing ^a			
Matching grids	25.8 ± 9.2	40.4 ± 10.8	.042
Match to sample	16.4 ± 5.9	35.7 ± 15.1	.043
Continuous processing	65.6 ± 5.5	88.7 ± 14.0	.018
Beck Depression Inventory	4 ± 4.3	1.8 ± 3.0	.362
State Trait Anxiety Inventory	27.4 ± 5.9	25 ± 6.9	.573
SLEDAI (mean)	2.3 ± 1.5		
SLICC DI (mean)	0.5 ± 0.8		
Disease duration (mean) (range, 1–33) (yr)	13.3 ± 11.1		
Medications			
Prednisone	1 (17%) (5 mg QD)		
Immunosuppression ^b	2 (33%)		
Hydroxychloroquine	5 (83%)		

Note:—QD indicates once daily.

^a Automated Neuropsychological Assessment Metric: throughput scores that represent efficiency as a function of accuracy and time.

^b Both subjects were on mycophenolate mofetil; 1000 mg QD and 500 mg QD, respectively.

Table 2: Comparison of the mean values (SDs) for the BBBP parameters (K^{trans} and Ve) using all brain regions in patients with SLE and healthy controls

BBBP Parameters	Patients with SLE	Healthy Controls	P Value
K^{trans} (mL/100 g/min)	0.0345 (±0.0715)	0.0008 (±0.0034)	.0004
Ve (100 g/min)	0.0920 (±0.1817)	0.0006 (±0.0031)	.0002

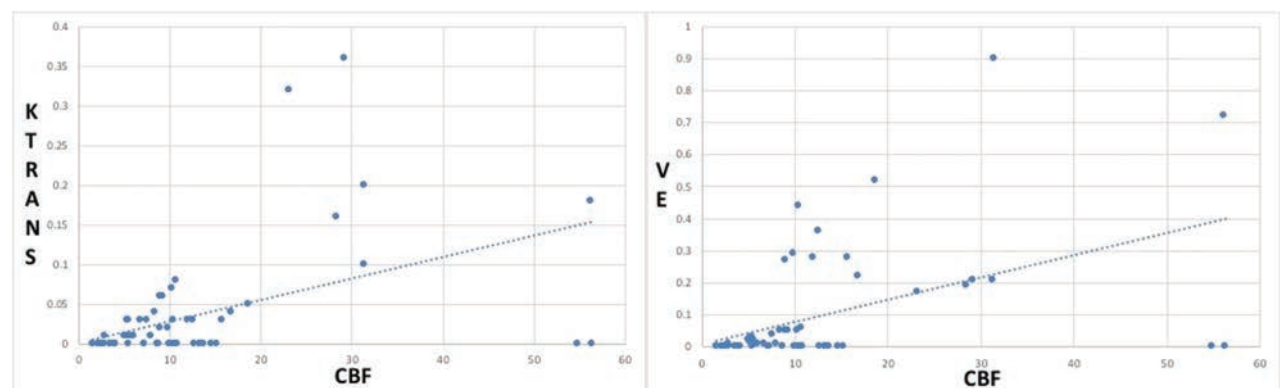


FIG 2. Linear regression analyses of the correlation of the BBBP factors (K^{trans} and Ve) with CBF using all brain regions for patients with SLE. Patients with SLE have a statistically significant moderate positive correlation between K^{trans} and Ve with CBF separately. Higher variance seen in patients with SLE compared with controls may be attributed to disease- and/or treatment-related variability. Healthy controls demonstrate strong consistency in the quantitative data for both K^{trans} and Ve (not shown).

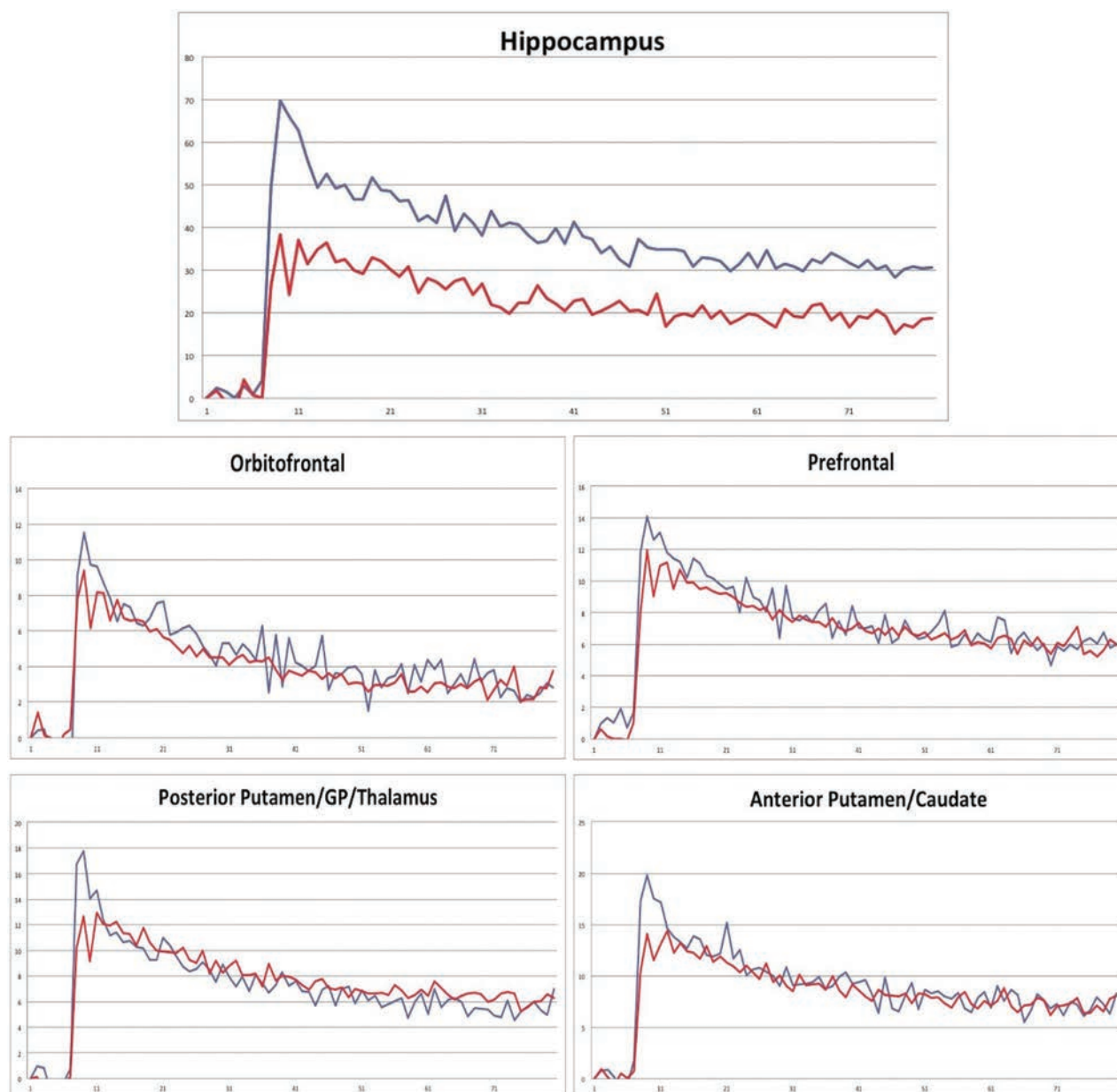


FIG 3. Dynamic contrast-enhancement curves for patients with SLE (blue) and healthy controls (red) according to the brain regions sampled. Signal intensity is represented on the y-axis, and the cine phase is represented on the x-axis. The hippocampus is the only brain region that demonstrates statistically significant increased BBB permeability ($P = .02$) in the patients with SLE compared with the healthy controls. GP indicates globus pallidus.

Table 3: Comparison of the mean values (SD) for the BBBP parameters (K^{trans} and V_e) and CBF in the hippocampal region in patients with SLE and healthy controls

BBBP Parameters	Patients with SLE	Healthy Controls	P Value
K^{trans} (mL/100 g/min)	0.1100 (± 0.1331)	0.019 (± 0.0499)	.0405
V_e (100 g/min)	0.2000 (± 0.3018)	0.0080 (± 0.0162)	.0397
CBF (mL/100 g/min)	28.84 (± 18.82)	13.14 (± 5.89)	.0128

on studying the BBB to understand how autoantibodies access the brain as well as to develop a potential target for treatment.

Overall, this study supports the hypothesis that patients with SLE have increased BBB permeability compared with healthy controls. The model-based quantitative data revealed that patients with SLE have statistically significant increased K^{trans} and V_e

compared with healthy controls. These findings represent a permeable BBB profile with increased flow across the BBB (as measured by K^{trans}) coupled with the accumulation of fluid in the interstitial space in the brain (as measured by V_e). Furthermore, the linear regression and nonparametric Spearman rank analyses demonstrated that patients with SLE have statistically significant positive correlations between each BBBP parameter (K^{trans} and V_e) and CBF, indicating that leakage of fluid across the BBB is affected by CBF as would be expected with a permeable BBB. Thus, daily changes in CBF, as may occur with fluctuations in systemic blood pressure, will increase flow across a permeable BBB in patients with SLE.

Additionally, this study supports the hypothesis that the hippocampal region specifically has increased BBB permeability in

patients with SLE compared with healthy controls. The dynamic contrast-enhancement curves in the hippocampal region demonstrated statistically significant increased BBBP in patients with SLE. All other sampled brain regions (orbitofrontal, prefrontal, anterior putamen/caudate, and posterior putamen/globus pallidus/thalamus) did not demonstrate significant differences between patients with SLE and healthy controls. These findings were confirmed with the model-based quantitative data that revealed a statistically significant increase in both BBBP parameters in the hippocampal region in patients with SLE, representing a permeable BBB profile with increased flow across the BBB (K^{trans}) coupled with accumulation of fluid in the interstitial space (V_e) in the brain.

Several other prior studies support our findings that BBB permeability plays an important role in NPSLE. Hirohata et al³⁰ evaluated anti-NMDAR antibody and albumin levels in CSF samples from 81 patients with SLE with active neuropsychiatric manifestations and concluded that transudation of autoantibodies through a damaged BBB plays a crucial role in NPSLE. Gulati et al¹⁷ studied 11 juvenile patients with SLE and 11 healthy controls with DCE-MR imaging and found altered BBB function in the parahippocampal gyrus, which supports our finding that the hippocampus is the area of concern in patients with SLE.¹¹ In another study by Lauvsnes et al,¹⁰ the presence of anti-NMDAR antibodies in the CSF of patients with SLE and primary Sjögren syndrome correlated significantly with reduced hippocampal volumes on MR imaging.

This study and several others demonstrate BBB dysfunction in patients with SLE. However, there has been no established imaging technique to reliably evaluate BBB permeability. Standard CT or MR imaging can be used to infer BBB dysfunction by evaluating the presence of contrast in the brain tissue; however, evaluation of subtle leaks across the BBB is limited secondary to lack of spatial resolution.³¹ CSF analysis can provide a quantitative assessment; however, a lumbar puncture is an invasive procedure with associated risks. FDG-PET imaging can be used to evaluate brain perfusion; however, this examination exposes patients to a high radiation dose. Dynamic-susceptibility contrast MR imaging can also be used to evaluate brain perfusion; however, many studies have reported conflicting results, demonstrating either increased CBF and CBV in patients with SLE compared with healthy controls,^{32,33} decreased CBV in patients with SLE,³⁴ or no significant difference between patients with SLE and healthy controls.³⁵ In particular, Wang et al³² evaluated 24 patients with NPSLE, 21 patients with SLE, and 21 healthy controls with DSC-MR imaging and found that patients with SLE have increased CBV and CBF in the right posterior thalamus, right hypothalamus, left parahippocampal gyrus, posterior cingulate gyrus, and left hypothalamus compared with healthy controls. In addition, Gasparovic et al³³ studied DSC-MR imaging in 42 patients with SLE with 19 age- and sex-matched healthy controls and also found elevated CBF and CBV in patients with SLE in all gray and white matter of the frontal, temporal, occipital, and parietal lobes. In contrast, Zimny et al³⁴ evaluated 22 patients with NPSLE and 13 patients with SLE and 20 age-matched healthy controls using perfusion-weighted MR imaging, which showed decreased CBV in the bilateral temporal, occipital, frontal, and parietal cortices in patients with SLE

and NPSLE compared with healthy controls. Furthermore, Emmer et al³⁵ evaluated 15 patients with active NPSLE, 26 patients with inactive NPSLE, and 11 controls with DSC-MR imaging and found that there were no differences in CBF, CBV, and MTT between patients with active or inactive NPSLE or healthy controls in the bilateral cerebral gray and white matter and thalami.

In contrast, our study used advanced imaging with dynamic contrast-enhanced MR imaging, which relies on the micron scale displacement of water molecules and can evaluate subtle changes in the capillary bed that no other imaging technique can provide with a minimal associated risk profile.²³ To avoid confounding influences on BBB assessments, we also focused on subjects with SLE who had stable/low disease activity, were on low doses of corticosteroids, and had no history of acute NPSLE or other CNS events. We therefore infer that the increased BBBP identified in our study is not attributable to acute events at the time of imaging. Our study suggests that DCE-MR imaging may be an additional technique to quantitate blood-brain barrier permeability in relation to perfusion, potentially gaining further understanding of the underlying pathophysiologic mechanisms affecting the brain in patients with SLE.

Most important, this study demonstrates increased BBB permeability in patients with SLE with no history of CNS compromise but who demonstrate impaired function on tests of working memory, sustained attention, and spatial processing. Half of the subjects with SLE had elevated serum DNRAb titers as did 1 healthy control; and even in this small group, there was a trend toward lower mean test scores and higher scores for anxiety and depression as has been shown previously.⁵ Although patients with SLE with a known history of acute or chronic neuropsychiatric disease, particularly NPSLE, were excluded from this study, the subjects with SLE still performed worse than the healthy controls on cognitive testing. This finding highlights the prevalence of impaired cognition even in patients with SLE with no known history of neuropsychiatric disease. Increased BBB permeability that we demonstrate in this study supports the hypothesis that circulating neurotoxic autoantibodies may gain access to the CNS. The recent interest in BBB permeability as a mechanism for drug delivery to the CNS has led to an appreciation of the numerous instances in which the BBB may be compromised as a result of normal aging, microvascular disease, infection, stress, uncontrolled hypertension, toxic exposures, and neuroinflammatory states in which inflammatory molecules produced by activated microglial cells damage the BBB.^{36,37}

While we have controlled for many of these conditions in our small study, we were not able to control for medication effects on the BBB. At the time of imaging, only 2 patients with SLE were on immunosuppressive medications (mycophenolate mofetil at doses of 1000 and 500 mg) and only 1 patient was on prednisone, 5 mg daily. Although high doses of corticosteroids have been associated with psychosis and altered cognition, there is much controversy over possible side effects of moderate corticosteroid use. A low dose of 5 mg daily of prednisone should not have significant cognition-altering side effects. Two of the 6 patients were on disease-modifying drugs at low doses of 1000 and 500 mg daily of mycophenolate mofetil, which is not known to have any cognition-altering effects. Five of 6 patients with SLE were on hydroxy-

chloroquine, which is not immunosuppressive and also is not associated with cognition-altering effects. However, future DCE-MR imaging studies on newly diagnosed patients with SLE would provide critical information regarding medication effects on the BBB.

This initial study has several limitations, most important, the small sample size. Thus, we cannot completely exclude the possibility of false-positives on the primary analyses performed between patients with SLE and healthy controls. Nonetheless, the proof-of-concept findings of this study provide the first evidence supporting the hypothesis that patients with SLE have increased BBBP in the hippocampus relative to other brain regions. The quantitative data from patients with SLE demonstrated higher variances compared with healthy controls, which may be due to disease-related variability such as differences in disease severity or duration, treatment regimen, and response to treatment. Given our small sample size, further subanalyses could not be performed. A larger prospective study is necessary to confirm our findings and further investigate other subanalyses.

CONCLUSIONS

DCE-MR imaging quantitative BBBP parameters may be used as a noninvasive method to indicate a permeable BBB profile, demonstrating increased flow across the BBB (as measured by K^{trans}) coupled with accumulation of fluid in the interstitial tissue (as measured by V_e) in the brain. These initial data are proof-of-concept to support our hypothesis that the BBB is selectively compromised, particularly in the hippocampal region, in subjects with SLE with little to no disease activity and no history of CNS insult who demonstrate impaired performance on cognitive testing. The significance of these findings may advance our understanding of the underlying pathophysiologic mechanisms affecting the brain in autoimmune diseases. Most important, larger studies are necessary to validate these results and confirm the value of DCE-MR imaging methodology as a potential biomarker for BBB permeability imaging.

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REFERENCES

- Gulinello M, Wen J, Putterman C. Neuropsychiatric symptoms in lupus. *Psychiatr Ann* 2012;42:322–28 CrossRef Medline
- Rayes HA, Tani C, Kwan A, et al. What is the prevalence of cognitive impairment in lupus and which instruments are used to measure it?

- A systematic review and meta-analysis. *Semin Arthritis Rheum* 2018; 48:240–55 CrossRef Medline
- Calderón J, Flores P, Aguirre JM, et al. Impact of cognitive impairment, depression, disease activity, and disease damage on quality of life in women with systemic lupus erythematosus. *Scand J Rheumatol* 2017;46:273–80 CrossRef Medline
- González A, Massardo L. Antibodies and the brain: antiribosomal P protein antibody and the clinical effects in patients with systemic lupus erythematosus. *Curr Opin Neurol* 2018;31:300–05 10.1097/WCO.0000000000000549 Medline
- Mader S, Brimberg L, Diamond B. The role of brain-reactive autoantibodies in brain pathology and cognitive impairment. *Front Immunol* 2017;8:1101 CrossRef Medline
- Bravo-Zehnder M, Toledo EM, Segovia-Miranda F, et al. Anti-ribosomal P protein autoantibodies from patients with neuropsychiatric lupus impair memory in mice. *Arthritis Rheumatol* 2015;67:204–14 CrossRef Medline
- Segovia-Miranda F, Serrano F, Dyrda A, et al. Pathogenicity of lupus anti-ribosomal P antibodies: role of cross-reacting neuronal surface P antigen in glutamatergic transmission and plasticity in a mouse model. *Arthritis Rheumatol* 2015;67:1598–610 CrossRef Medline
- Chang EH, Volpe BT, Mackay M, et al. Selective impairment of spatial cognition caused by autoantibodies to the N-methyl-D-aspartate receptor. *EBioMedicine* 2015;2:755–64 CrossRef Medline
- Mackay M. Lupus brain fog: a biologic perspective on cognitive impairment, depression, and fatigue in systemic lupus erythematosus. *Immunol Res* 2015;63:26–37 CrossRef Medline
- Lauvsnes MB, Beyer MK, Kvaloy JT, et al. Association of hippocampal atrophy with cerebrospinal fluid antibodies against the NR2 subtype of the N-methyl-D-aspartate receptor in patients with systemic lupus erythematosus and patients with primary Sjögren's syndrome. *Arthritis Rheumatol* 2014;66:3387–94 CrossRef Medline
- Diamond B, Volpe BT. Antibodies and brain disease: a convergence of immunology and physiology. *PLoS Med* 2006;3:e498 CrossRef Medline
- Sharp CD, Hines I, Houghton J, et al. Glutamate causes a loss in human cerebral endothelial barrier integrity through activation of NMDA receptor. *Am J Physiol Heart Circ Physiol* 2003;285:H2592–98 CrossRef Medline
- Fragoso-Loyo H, Cabiedes J, Orozco-Narváez A, et al. Serum and cerebrospinal fluid autoantibodies in patients with neuropsychiatric lupus erythematosus: implications for diagnosis and pathogenesis. *PLoS One* 2008;3:e3347 CrossRef Medline
- Arinuma Y, Yanagida T, Hirohata S. Association of cerebrospinal fluid anti-NR2 glutamate receptor antibodies with diffuse neuropsychiatric systemic lupus erythematosus. *Arthritis Rheum* 2008;58:1130–35 CrossRef Medline
- Gono T, Kawaguchi Y, Kaneko H, et al. Anti-NR2A antibody as a predictor for neuropsychiatric systemic lupus erythematosus. *Rheumatology (Oxford)* 2011;50:1578–85 CrossRef Medline
- Yoshio T, Onda K, Nara H, et al. Association of IgG anti-NR2 glutamate receptor antibodies in cerebrospinal fluid with neuropsychiatric systemic lupus erythematosus. *Arthritis Rheum* 2006;54:675–78 CrossRef Medline
- Gulati G, Jones JT, Lee G, et al. Altered blood-brain barrier permeability in patients with systemic lupus erythematosus: a novel imaging approach. *Arthritis Care Res (Hoboken)* 2017;69:299–305 CrossRef Medline
- Diamond B, Volpe BT. A model for lupus brain disease. *Immuno Rev* 2012;248:56–67 CrossRef Medline
- Kowal C, Degiorgio LA, Lee JY, et al. Human lupus autoantibodies against NMDA receptors mediate cognitive impairment. *Proc Natl Acad Sci U S A* 2006;103:19854–59 CrossRef Medline
- Latchaw R, Yonas H, Hunter G, et al; Council on Cardiovascular Radiology of the American Heart Association. Guidelines and recommendations for perfusion imaging in cerebral ischemia: a scientific statement for healthcare professionals by the writing group on

- perfusion imaging, from the Council on Cardiovascular Radiology of the American Heart Association. *Stroke* 2003;34:1084–104 CrossRef Medline
21. Essig M, Shiroishi M, Nguyen T, et al. **Perfusion MRI: the five most frequently asked technical questions.** *AJR Am J Roentgenol* 2013;200:24–34 CrossRef Medline
22. Heye AK, Culling RD, Valdés Hernández Mdel C, et al. **Assessment of blood-brain barrier disruption using dynamic contrast-enhanced MRI: a systematic review.** *Neuroimage Clin* 2014;6:262–74 CrossRef Medline
23. Ivanidze J, Kallas ON, Gupta A, et al. **Application of blood-brain barrier permeability imaging in global cerebral edema.** *AJNR Am J Neuroradiol* 2016;37:1599–603 CrossRef Medline
24. Hartman EA, van Royen-Kerkhof A, Jacobs JW, et al. **Performance of the 2012 Systemic Lupus International Collaborating Clinics classification criteria versus the 1997 American College of Rheumatology classification criteria in adult and juvenile systemic lupus erythematosus: a systematic review and meta-analysis.** *Autoimmun Rev* 2018;17:316–22 CrossRef Medline
25. Petri M, Kim MY, Kalunian KC, et al. **Combined oral contraceptives in women with systemic lupus erythematosus.** *N Engl J Med* 2005;353:2550–58 CrossRef Medline
26. Gladman DD, Urowitz MB, Goldsmith CH, et al. **The reliability of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index in patients with systemic lupus erythematosus.** *Arthritis Rheum* 1997;40:809–13 CrossRef Medline
27. Roebuck-Spencer TM, Yarboro C, Nowak M, et al. **Use of computerized assessment to predict neuropsychological functioning and emotional distress in patients with systemic lupus erythematosus.** *Arthritis Rheum* 2006;55:434–41 CrossRef Medline
28. Julian LJ, Tonner C, Yelin E, et al. **Cardiovascular and disease-related predictors of depression in systemic lupus erythematosus.** *Arthritis Care Res (Hoboken)* 2011;63:542–49 CrossRef Medline
29. Mackay M, Tang CC, Volpe BT, et al. **Brain metabolism and autoantibody titres predict functional impairment in systemic lupus erythematosus.** *Lupus Sci Med* 2015;2:e000074 CrossRef Medline
30. Hirohata S, Arinuma Y, Yanagida T, et al. **Blood-brain barrier damages and intrathecal synthesis of anti-N-methyl-D-aspartate receptor NR2 antibodies in diffuse psychiatric/neuropsychological syndromes in systemic lupus erythematosus.** *Arthritis Res Ther* 2014;16:R77 CrossRef Medline
31. Tomkins O, Kaufer D, Korn A, et al. **Frequent blood-brain barrier disruption in the human cerebral cortex.** *Cell Mol Neurobiol* 2001;21:675–91 CrossRef Medline
32. Wang P, Cagnoli P, McCune W, et al. **Perfusion-weighted MR imaging in cerebral lupus erythematosus.** *Acad Radiol* 2012;19:965–70 CrossRef Medline
33. Gasparovic C, Roldan C, Sibbitt WL, et al. **Elevated cerebral blood flow and volume in systemic lupus measured by dynamic susceptibility contrast magnetic resonance imaging.** *J Rheumatol* 2010;37:1834–43 CrossRef Medline
34. Zimny A, Szmyrka-Kaczmarek M, Szewczyk P, et al. **In vivo evaluation of brain damage in the course of systemic lupus erythematosus using magnetic resonance spectroscopy, perfusion-weighted and diffusion-tensor imaging.** *Lupus* 2014;23:10–19 CrossRef Medline
35. Emmer B, van Osch M, Wu O, et al. **Perfusion MRI in neuro-psychiatric systemic lupus erythematosus.** *J Magn Reson Imaging* 2010;32:283–88 CrossRef Medline
36. Danielski LG, Giustina AD, Badawy M, et al. **Brain barrier breakdown as a cause and consequence of neuroinflammation in sepsis.** *Mol Neurobiol* 2018;55:1045–53 CrossRef Medline
37. Reinhold AK, Rittner HL. **Barrier function in the peripheral and central nervous system—a review.** *Pflugers Arch* 2017;469:123–34 CrossRef Medline

Longitudinal White Matter Changes following Carbon Monoxide Poisoning: A 9-Month Follow-Up Voxelwise Diffusional Kurtosis Imaging Study

M.-C. Chou, J.-Y. Li, and P.-H. Lai



ABSTRACT

BACKGROUND AND PURPOSE: Patients with carbon monoxide (CO) intoxication exhibit progressive WM changes that are not well-understood. The purpose of this study was to detect longitudinal WM changes using voxelwise diffusional kurtosis imaging in patients with CO intoxication from the acute-to-chronic stage after CO intoxication.

MATERIALS AND METHODS: Twenty-four patients with CO intoxication and 21 age- and sex-matched healthy controls were enrolled in this study. Diffusional kurtosis imaging was performed on all subjects and was conducted repeatedly in patients at 1 week and 1, 3, and 9 months after CO intoxication. Voxelwise diffusional kurtosis imaging analysis was performed to detect global WM changes in the patients with and without WM lesions. Receiver operating characteristic analysis was performed to compare the performance of diffusional indices in differentiating patients with delayed neuropsychiatric sequelae from patients without them.

RESULTS: In voxelwise analysis, progressive WM changes were detected in patients with WM lesions. In the acute phase, WM injuries were found mainly in the dopaminergic pathways at 1 week, whereas in the chronic stage, WM injuries extended toward subcortical areas from 1 to 9 months. However, no significant WM change was noted in patients without WM lesions during the 9 months after CO intoxication. Moreover, receiver operating characteristic analysis demonstrated that axial kurtosis and mean kurtosis values had better performance than other diffusional indices in differentiating patients with delayed neuropsychiatric sequelae from patients without them at 1 week after CO intoxication.

CONCLUSIONS: Voxelwise diffusional kurtosis imaging analysis was helpful to longitudinally investigate WM changes and predict the prognosis of patients after CO intoxication.

ABBREVIATIONS: AD = axial diffusivity; AK = axial kurtosis; CO = carbon monoxide; CP = cerebral peduncle; DKI = diffusional kurtosis imaging; DNS = delayed neuropsychiatric sequelae; FA = fractional anisotropy; FWM = frontal white matter; GP = globus pallidus; IC = internal capsule; MD = mean diffusivity; MK = mean kurtosis; RD = radial diffusivity; RK = radial kurtosis; WML = white matter lesion

Carbon monoxide (CO) intoxication is an aggravating health issue that can cause coma or death following accidental inhalation or attempted suicide. Survivors of carbon monoxide intoxication may exhibit acute or chronic neurologic or psychological problems that can dramatically impact their daily activities.^{1,2} Hyperbaric oxygen therapy is usually performed at the acute stage

to reduce carboxyhemoglobin concentration in the blood and to mitigate neurologic and psychological symptoms.¹⁻⁴ However, delayed neuropsychiatric sequelae (DNS) were observed even after a series of hyperbaric oxygen therapy treatments in patients with CO intoxication.^{3,5}

Because patients with CO intoxication with neuropsychiatric symptoms commonly exhibit WM abnormalities, many studies performed DTI analysis to demonstrate relationships between WM injuries following CO intoxication and delayed encephalopathy,^{6,7} cognitive functions,⁸⁻¹¹ neuropsychologi-

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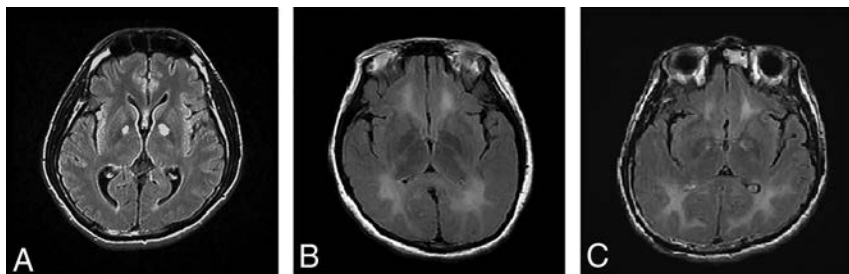


FIG 1. The FLAIR images of 3 patients acquired at 1 month after CO intoxication. A, A male patient (32 years of age) who had only GP lesions did not develop DNS. B, A female patient (37 years of age) who had only diffuse WMLs developed DNS. C, A male patient (49 years of age) who had both diffuse WMLs and GP lesions developed DNS.

cal scores,^{8,9} and myelin basic protein levels.^{12,13} However, DTI assumes a Gaussian distribution for water diffusion and cannot accurately estimate diffusion heterogeneity (non-Gaussian diffusion) of biologic tissues.¹⁴ In contrast, diffusional kurtosis imaging (DKI), which quantifies the non-Gaussianity of water diffusion, was demonstrated to reflect the microstructural complexity of biologic tissues^{15,16} and to be a potential early biomarker of the neurodegenerative process.¹⁷ Recent studies further used DKI to detect early WM injuries in patients with CO intoxication.^{18,19}

However, these patients may exhibit delayed encephalopathy and neuropsychiatric symptoms after a lucid period²⁰; therefore, it is important to understand the longitudinal WM changes that predict the prognosis of patients with CO intoxication. A previous study performed longitudinal DTI analysis and demonstrated progressive WM changes 3–10 months after CO exposure.⁹ Another study performed longitudinal DKI analysis and showed that DKI better characterized brain damage in 1 patient from 6 days to 20 weeks after CO intoxication,²¹ but it remains unclear how WM change progresses from acute-to-chronic stages and whether more accurate DKI indices can help in the early prediction of prognosis. Therefore, the purposes of this study were to investigate the longitudinal WM changes in patients with CO intoxication using voxelwise DKI analysis and predict their prognoses from early WM injuries detected 1 week after CO intoxication using receiver operating characteristic analysis.

MATERIALS AND METHODS

This prospective study was approved by the local institutional review board of Kaohsiung Veterans General Hospital. This study included 24 patients with CO intoxication (M/F ratio = 11:13; mean age = 39.1 ± 13.2 years) and 21 age- and sex-matched healthy controls (M/F ratio = 10:11; mean age = 41.0 ± 11.9 years). The exclusion criteria included a history of major neurologic or psychiatric disorders, pregnancy, a metal implant, and claustrophobia. Because delayed sequelae are commonly associated with WM changes, the patients with CO intoxication were divided into 2 subgroups based on the presence or absence of WM lesions (WMLs) observed within 9 months of follow-up. The WMLs were defined as diffusive, symmetric, or asymmetric hyperintense areas in the deep WM tissues of both cerebral hemispheres on FLAIR images as demonstrated in Fig 1. The patients who exhibited WMLs at any stage of the follow-up were categorized as the WML group and

others as the non-WML group. In addition, all patients with CO intoxication were evaluated by an experienced neurologist regularly at 1 week and 1, 3, and 9 months. This study watched for newly developed neurologic symptoms and signs, including motor deficits, cognitive impairment, dysphagia, dysarthria, gait disturbance, Parkinsonism, seizures, psychosis, and mood disorders. DNS was defined as the appearance of neurologic sequelae after a lucid period of variable duration (usually 2–4 weeks after CO intoxication).²⁰

MR Imaging Acquisition

MR imaging was performed on a 1.5T MR imaging scanner (Signa HDxt, GE Healthcare, Milwaukee, Wisconsin) with an 8-channel head coil. After T1WI, T2WI, and FLAIR imaging were acquired, whole-brain DKI data were acquired using a twice-refocused spin-echo diffusion-weighted pulse sequence with TR/TE = 10,000/91 ms, b-values = 1000 and 2000 s/mm², number of b₀ images = 4, acceleration factor = 2, number of diffusion directions = 30, matrix size = 80 × 80, FOV = 240 × 240 mm, slice thickness = 3 mm (isotropic resolution), and number of excitations = 1. The scan time for DKI was about 10 minutes.

Voxel-Based DKI Analysis

All imaging data were postprocessed using FSL (<http://www.fmrib.ox.ac.uk/fsl>), Diffusion Kurtosis Estimator (Neuro-Imaging Tools and Resources Collaboratory; <https://www.nitrc.org/projects/dke/>), and SPM12 software (<http://www.fil.ion.ucl.ac.uk/spm/software/spm12>). First, DKI data were corrected for motion and eddy current distortions using rigid-body and affine registrations, respectively. Second, the FSL Brain Extraction Tool (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/BET>) was used to remove nonbrain signals. Third, the Diffusion Kurtosis Estimator tool was used to calculate axial diffusivity (AD), radial diffusivity (RD), mean diffusivity (MD), fractional anisotropy (FA), axial kurtosis (AK), radial kurtosis (RK), and mean kurtosis (MK). In DTI-related indices, AD and RD are the diffusivities parallel and perpendicular to axons, respectively, whereas MD is the averaged diffusivity of a diffusion tensor. FA is the diffusion anisotropy that reflects tissue integrity. In DKI-related indices, AK and RK are the diffusional kurtosis values (non-Gaussianity) parallel and perpendicular to axons, respectively, whereas MK is the averaged kurtosis of a diffusion kurtosis tensor. Finally, whole-brain FA maps were spatially normalized to an International Consortium for Brain Mapping FA template,²² which was constructed by normalizing the FA maps of 81 healthy subjects into an International Consortium for Brain Mapping 152-T1 template, using both linear affine and nonlinear demon registrations to minimize global and local differences between individual and template images, respectively. The displacement maps generated from the previous steps were applied to spatially transform the corresponding diffusion maps.

Table 1: Demographic characteristics of enrolled subjects

	Patients with CO Intoxication		Controls
	WML	Non-WML	
Sex (M/F)	6:5	5:8	10:11
Age (mean) (yr)	44.5 ± 15.3	35.7 ± 9.3	41.0 ± 11.9
Duration of coma (mean) (hr)	44.7 ± 48.8 ^a	11.7 ± 17.6 ^a	NA
Carboxyhemoglobin (mean) (%)	22.3 ± 20.9	31.37 ± 15.1	NA
Sessions of HBOT (mean)	11.2 ± 10.1	8.9 ± 2.5	NA
DNS (No.) (M/F)	5 (3:2)	0	NA
GP involvement (No.) (M/F)	8 (5:3)	4 (2:2)	NA

Note:—HBOT indicates hyperbaric oxygen therapy; NA, not applicable.

^a $P < .05$.

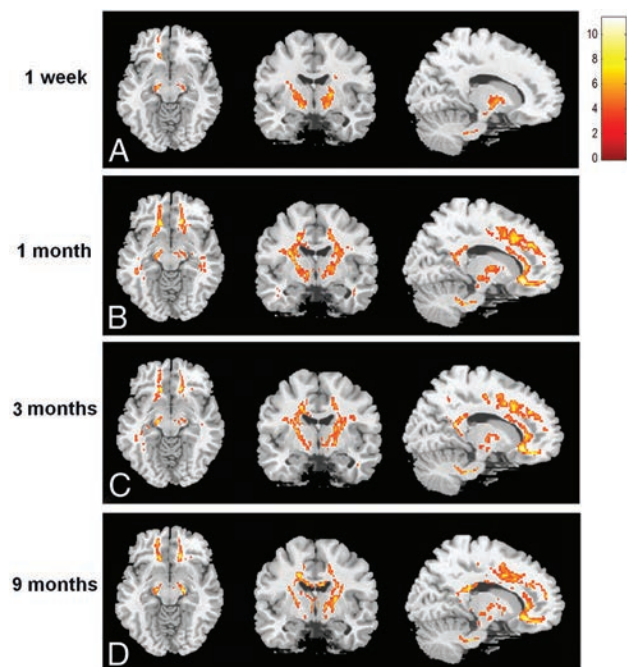


FIG 2. The voxelwise comparison of FA values between patients with WMLs and healthy controls. The yellow-to-red areas indicate regions with values that were significantly decreased in the patients, and the color bar on the right-hand side indicates T values.

Statistical Analysis

For clinical data, a nonparametric Mann-Whitney U test was performed to examine the difference between WML and non-WML groups, and the results were considered significant with $P < .05$. For DKI data, the voxelwise comparisons between patients and healthy subjects were performed using a 2-sample t test with age and sex as covariates to null the aging and sex effects. The difference was considered significant with cluster-level-corrected $P < .05$ (uncorrected $P < .001$ and cluster > 100 voxels). Moreover, receiver operating characteristic analysis was performed for all patients with CO intoxication to compare the performance of diffusion indices in differentiating patients with and without DNS at 1 week after CO intoxication.

RESULTS

Demographic Characteristics

The demographic characteristics of the patients with CO intoxication and control subjects are listed in Table 1. There were no significant differences in age, sex, hyperbaric oxygen therapy ses-

sions, or carboxyhemoglobin levels between the WML and non-WML groups. However, the WML group underwent a significantly longer duration of coma than the non-WML group. Of the 24 patients with CO intoxication, 11 developed visible WMLs within 9 months of follow-up. Most patients with WMLs developed them at 1 month, but 3 patients developed them at only 1 week after CO intoxication. None of the non-WML group had DNS, but 5 of the 11 patients with WMLs had DNS after a lu-

cid period of 3–6 weeks (mean, 30.2 ± 7.33 days). Moreover, 12 patients had lesions of the globus pallidus (GP); only 3 had DNS, and 8 developed visible WMLs. However, 5 patients with WMLs and 1 without them did not undergo MR imaging at 1 week due to severe coma; 1 patient with WMLs and 1 without them did not undergo MR imaging at 3 months due to loss of contact; and 4 patients with WMLs and 3 without them did not undergo MR imaging at 9 months due to loss of contact or drop-out.

Longitudinal Changes of DTI and DKI Indices

In patients with WMLs, the DTI indices were significantly altered in the pons, bilateral cerebral peduncle (CP) anterior to the substantia nigra, bilateral internal capsule (IC) next to the thalamus and striatum, bilateral forceps minor, left superior corona radiata, and genu of corpus callosum at 1 week after CO intoxication, as shown in Figs 2 and On-line Figs 1–3. At 1 month after CO intoxication, the regions with significantly altered DTI and DKI indices had extended to the splenium of the corpus callosum, bilateral anterior and posterior limbs of the IC, bilateral anterior corona radiata, superior corona radiata, posterior corona radiata, and bilateral inferior longitudinal fasciculus. At 3 months after CO intoxication, the regions with significantly altered DTI and DKI indices had extended farther toward the subcortical areas and involved the bilateral forceps major; however, the RD, RK, and MK in the bilateral IC were partially normalized. At 9 months after CO intoxication, the regions with significantly altered DTI and DKI indices further involved the body of the corpus callosum and had extended farther into the subcortical areas; however, the FA, RK, and MK of the bilateral IC had normalized further, as shown in Figs 2 and 3 and On-line Figs 1–5. In patients without WMLs, the voxelwise comparison did not reveal significant change of DTI and DKI indices within 9 months after CO intoxication.

Receiver Operating Characteristic Analysis

The receiver operating characteristic analysis for all patients at 1 week after CO intoxication showed that areas under the curve of > 0.7 were observed for FA in the left CP; AD and AK in the bilateral IC; AD and AK in the right frontal WM (FWM); and RD, MD, and MK in the left FWM. Notably, the area under the curve for MK in the left FWM was > 0.8 , and the areas under the curve for AK in the right IC and right FWM were > 0.9 (Table 2). In addition, the longitudinal comparisons of DTI and DKI indices in these regions between patients with and without DNS are shown in On-line Figs 6–12.

DISCUSSION

To the best of our knowledge, this is the first study in which voxelwise DKI analysis was applied to a longitudinal investigation of WM injuries in patients from 1 week to 9 months after CO intoxication. Unlike in previous studies, we divided the patients into 2 subgroups according to WML development after CO intoxication. The results demonstrated different progressions of WM injuries in the 2 subgroups, and all patients without WMLs did not have DNS, whereas 5 of the 11 (45%) patients with WMLs developed DNS after CO intoxication. This finding suggests that DNS may be associated with WMLs. In addition, a previous study reported that dysfunctions of the GP and dopamine transporter may be associated with poor cognitive function and the presence of Parkinsonian features.⁸ In another study, a patient with GP involvement did not have Parkinsonism, though a patient with only WMLs did.²³ In the present study, only 3 of the 12 patients (25%) with GP lesions were found to have

DNS, indicating a stronger relationship between DNS and WMLs alone than between DNS and a GP lesion alone.

In patients with WMLs, significant WM injuries were initially detected (at 1 week after CO intoxication) in the pons, bilateral CP (anterior to the substantia nigra), bilateral IC, genu of the corpus callosum, and bilateral anterior prefrontal WMs. Consistent with a previous study,¹⁹ the WM injuries broadly reflected the alterations of dopaminergic pathways that may be responsible for Parkinsonian symptoms in patients with WMLs. In addition, the WM injuries gradually progressed to the subcortical and periventricular WM areas at 1 month and consistently deteriorated from 3 to 9 months. These results further suggest that the WM injuries in the subcortical brain regions may be associated with neuropsychiatric symptoms observed in patients with WMLs at the chronic stage. Similar to a previous study,⁹ the present study found that the changes in the DKI indices of the bilateral IC had normalized somewhat between 3 and 9 months after CO intoxication. The slight normalization of DKI indices suggests that the WM integrity of the bilateral IC was partially recovered between 3 and 9 months after CO intoxication.

In general, early WM injuries detected in this study were consistent with those reported in previous studies,^{18,19} though the discrepancy may likely result from the grouping strategy used in this study, in which patients were separated into WML and non-WML subgroups. This study further revealed that diffusional kurtosis-related indices outperformed diffusion tensor-related indices in differentiating patients with DNS from those without them and that the patients with DNS had significantly higher diffusional kurtosis values than those without them at 1 week after CO exposure. These findings suggest that early WM changes in the dopaminergic pathways were different between patients with and without DNS and that patients with DNS had a greater restriction of water diffusion in the WM tissues than the patients without DNS, likely due to more cytotoxic edema (hypoxia) at the early stage of CO intoxication.

Moreover, the results of this study may reflect the pathophysiologic mechanism of CO-induced WM injuries. First, inhalation of CO is known to cause hypoxia or oxidative stress in tissues that may

lead to cytotoxic edema as a result of influx of calcium ions into the cells.¹ As mentioned above, this study significantly demonstrated higher kurtosis values of WM tissues in patients with DNS than in those without DNS at 1 week, suggesting that patients with DNS may have undergone worse hypoxia than those without them. Second, free CO in plasma would gradually lead to subsequent inflammation in the tissues.^{24,25} This study shows that patients with WMLs exhibit significantly increased RD and unchanged AD in many WM regions between 1 week and 3 months, suggestive of WM demyelination due to the production of reactive oxygen species and lipid peroxidation at the subacute stage.²⁶ Third, ongoing inflammation and hypoxia would eventually lead to apoptosis and necrosis of tissues.^{24,25} This study demonstrates a significant increase

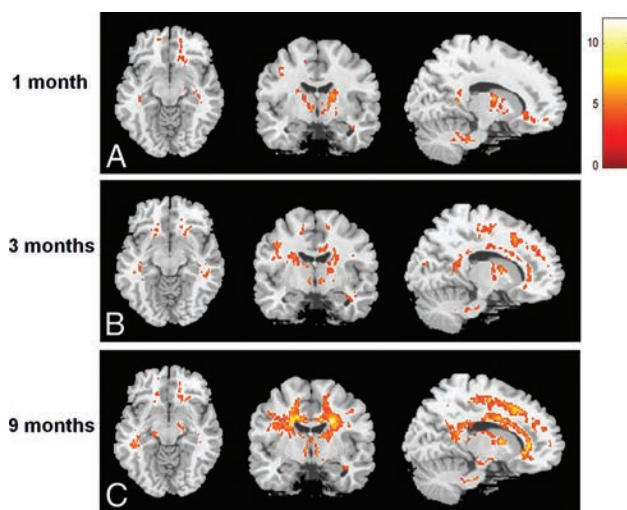


FIG 3. The voxelwise comparison of MK values between patients with WMLs and healthy controls. The yellow-to-red areas indicate regions with values that were significantly decreased in the patients, and the color bar on the right-hand side indicates *T* values.

Table 2: The ROC analysis of diffusional indices for CP, IC, and FWM in differentiating patients with DNS from those without DNS at 1 week after CO intoxication^a

Brain Regions (MNI Coordinates) (mm)	DNS	Non-DNS	Controls	AUC (DNS vs non-DNS)
Lt. CP (−14, −14, −12)				
FA (mean)	0.52 ± 0.03	0.56 ± 0.06	0.60 ± 0.05	.7394
Rt. IC (17, −10, 0)				
AD (mean)	1.38 ± 0.08	1.49 ± 0.14	1.49 ± 0.08	.7394
AK (mean)	0.87 ± 0.05	0.74 ± 0.08	0.80 ± 0.03	.9156 ^b
Lt. IC (−17, −10, 0)				
AD (mean)	1.38 ± 0.06	1.49 ± 0.13	1.48 ± 0.11	.7762
AK (mean)	0.89 ± 0.06	0.80 ± 0.08	0.81 ± 0.08	.7113
Rt. FWM (14, 31, −12)				
AD (mean)	1.30 ± 0.03	1.18 ± 0.14	1.19 ± 0.14	.7436
AK (mean)	1.03 ± 0.04	0.86 ± 0.12	0.83 ± 0.09	.9057 ^b
Lt. FWM (−14, 31, −12)				
RD (mean)	0.78 ± 0.04	0.74 ± 0.07	0.62 ± 0.07	.7436
MD (mean)	0.94 ± 0.03	0.94 ± 0.05	0.90 ± 0.06	.7299
MK (mean)	0.98 ± 0.06	0.86 ± 0.07	0.89 ± 0.12	.8627 ^b

Note:—AUC indicates area under the curve; ROC, receiver operating characteristic; Lt., left; Rt., right; MNI, Montreal Neurological Institute.

^a The unit for AD, RD, and MD is 10^{−3} mm²/s.

^b *P* < .05.

in diffusivity and significant decreases in diffusion anisotropy and kurtosis in widespread WM tissues at 9 months after CO intoxication. These findings suggest that the ongoing inflammation eventually leads to axonal loss and increased microstructural complexity in WM tissues at the chronic stage. Nevertheless, in patients without WMLs, no significant change of diffusion indices was noted during the 9 months following CO intoxication, though some of these patients had GP lesions. We speculate that the WM may remain intact with relatively slight CO intoxication and that DNS was more closely related to WM changes than to GP lesions in patients with CO intoxication.

We acknowledge that this study has some limitations. First, the small sample size may have introduced statistical errors in the results. Second, the DKI data were acquired with only 2 high b-values; therefore, the results may have been affected by the choice of b-values.²⁷ Third, some patients did not undergo all DKI acquisitions because of severe coma, loss of contact, or drop-out, and the incomplete datasets may have affected the statistical results. Finally, the control group underwent only 1 MR imaging without follow-up; therefore, the WM injuries found within 9 months of CO intoxication may have been affected by aging.

CONCLUSIONS

Voxelwise DKI analysis revealed longitudinal WM changes in patients after CO intoxication. DNS developed in 45% of patients with WMLs but in none of the patients without WMLs. The voxelwise comparisons also showed that patients without WMLs did not exhibit progressive WM changes after CO intoxication, whereas patients with WMLs had early WM injuries to the dopaminergic pathways at 1 week after CO intoxication, with WM injuries progressing toward the subcortical and periventricular regions from 1 to 9 months. The values of AK and MK in the IC and FWM performed better than other diffusion indices in differentiating patients with DNS from those without them. We conclude that voxelwise DKI analysis was helpful for assessing longitudinal WM injuries and in predicting the prognosis of patients after CO intoxication.

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REFERENCES

- Weaver LK. Clinical practice: carbon monoxide poisoning. *N Engl J Med* 2009;360:1217–25 CrossRef Medline
- Ng PC, Long B, Koyfman A. Clinical chameleons: an emergency medicine focused review of carbon monoxide poisoning. *Intern Emerg Med* 2018;13:223–29 CrossRef Medline
- Weaver LK, Hopkins RO, Chan KJ, et al. Hyperbaric oxygen for acute carbon monoxide poisoning. *N Engl J Med* 2002;347:1057–67 CrossRef Medline
- Weaver LK. Hyperbaric oxygen therapy for carbon monoxide poisoning. *Undersea Hyperbaric M* 2014;41:339–54 Medline
- Weaver LK, Valentine KJ, Hopkins RO. Carbon monoxide poisoning: risk factors for cognitive sequelae and the role of hyperbaric oxygen. *Am J Resp Crit Care* 2007;176:491–97 CrossRef Medline
- Hou XM, Ma LL, Wu LH, et al. Diffusion tensor imaging for predicting the clinical outcome of delayed encephalopathy of acute carbon monoxide poisoning. *Eur Neurol* 2013;69:275–80 CrossRef Medline
- Lo CP, Chen SY, Chou MC, et al. Diffusion-tensor MR imaging for evaluation of the efficacy of hyperbaric oxygen therapy in patients with delayed neuropsychiatric syndrome caused by carbon monoxide inhalation. *Eur J Neurol* 2007;14:777–82 CrossRef Medline
- Chang CC, Chang WN, Lui CC, et al. Clinical significance of the pallidoreticular pathway in patients with carbon monoxide intoxication. *Brain* 2011;134(Pt 12):3632–46 CrossRef Medline
- Chang CC, Chang WN, Lui CC, et al. Longitudinal study of carbon monoxide intoxication by diffusion tensor imaging with neuropsychiatric correlation. *J Psychiatr Neurosci* 2010;35:115–25 CrossRef Medline
- Lin WC, Lu CH, Lee YC, et al. White matter damage in carbon monoxide intoxication assessed in vivo using diffusion tensor MR imaging. *AJNR Am J Neuroradiol* 2009;30:1248–55 CrossRef Medline
- Chen PC, Chen MH, Chen HL, et al. Callosal damage and cognitive deficits in chronic carbon monoxide intoxication: a diffusion tensor imaging study. *J Neurol Sci* 2015;355:101–07 CrossRef Medline
- Beppu T, Fujiwara S, Nishimoto H, et al. Fractional anisotropy in the centrum semiovale as a quantitative indicator of cerebral white matter damage in the subacute phase in patients with carbon monoxide poisoning: correlation with the concentration of myelin basic protein in cerebrospinal fluid. *J Neurol* 2012;259:1698–705 CrossRef Medline
- Fujiwara S, Beppu T, Nishimoto H, et al. Detecting damaged regions of cerebral white matter in the subacute phase after carbon monoxide poisoning using voxel-based analysis with diffusion tensor imaging. *Neuroradiology* 2012;54:681–89 CrossRef Medline
- Basser PJ, Mattiello J, Lebiha D. MR diffusion tensor spectroscopy and imaging. *Biophys J* 1994;66:259–67 CrossRef Medline
- Jensen JH, Helper JA, Ramani A, et al. Diffusional kurtosis imaging: the quantification of non-Gaussian water diffusion by means of magnetic resonance imaging. *Magn Reson Med* 2005;53:1432–40 CrossRef Medline
- Veraart J, Poot DH, Van Hecke W, et al. More accurate estimation of diffusion tensor parameters using diffusion kurtosis imaging. *Magn Reson Med* 2011;65:138–45 CrossRef Medline
- Arab A, Wojna-Pelczar A, Khairnar A, et al. Principles of diffusion kurtosis imaging and its role in early diagnosis of neurodegenerative disorders. *Brain Res Bull* 2018;139:91–98 CrossRef Medline
- Tsai PH, Chou MC, Chiang SW, et al. Early white matter injuries in patients with acute carbon monoxide intoxication: a tract-specific diffusion kurtosis imaging study and STROBE compliant article. *Medicine (Baltimore)* 2017;96:e5982 CrossRef Medline
- Chou MC, Lai PH, Li JY. Early white matter injuries associated with dopamine transporter dysfunction in patients with acute CO intoxication: a diffusion kurtosis imaging and Tc-99m TRODAT-1 SPECT study. *Eur Radiol* 2018 Aug 24. [Epub ahead of print] CrossRef Medline
- Choi IS. Delayed neurologic sequelae in carbon-monoxide intoxication. *Arch Neurol* 1983;40:433–35 CrossRef Medline
- Fan W, Zheng W, Chen X. A Better Characterization of brain damage in carbon monoxide intoxication assessed in vivo using diffusion kurtosis imaging. In: *Proceedings of the Annual Meeting of the International Conference on Biological Sciences and Technology*, Guangzhou, China. January 8–10, 2016:263–68
- Mori S, Oishi K, Jiang HY, et al. Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. *Neuroimage* 2008;40:570–82 CrossRef Medline
- Sohn YH, Jeong Y, Kim HS, et al. The brain lesion responsible for parkinsonism after carbon monoxide poisoning. *Arch Neurol* 2000;57:1214–18 CrossRef Medline
- Piantadosi CA, Zhang J, Levin ED, et al. Apoptosis and delayed neuronal damage after carbon monoxide poisoning in the rat. *Exp Neurol* 1997;147:103–14 CrossRef Medline
- Cronje FJ, Carraway MS, Freiberger JJ, et al. Carbon monoxide acts as O-2-limited heme degradation in the rat brain. *Free Radic Biol Med* 2004;37:1802–12 CrossRef Medline
- Thom SR, Bhopale VM, Han ST, et al. Intravascular neutrophil activation due to carbon monoxide poisoning. *Am J Resp Crit Care* 2006;174:1239–48 CrossRef Medline
- Chou MC, Ko CW, Chiu YH, et al. Effects of b value on quantification of rapid diffusion kurtosis imaging in normal and acute ischemic brain tissues. *J Comput Assist Tomogr* 2017;41:868–76 CrossRef Medline

Focal Hypoperfusion in Acute Ischemic Stroke Perfusion CT: Clinical and Radiologic Predictors and Accuracy for Infarct Prediction

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ABSTRACT

BACKGROUND AND PURPOSE: Perfusion CT may improve the diagnostic performance of noncontrast CT in acute ischemic stroke. We assessed predictors of focal hypoperfusion in acute ischemic stroke and perfusion CT performance in predicting infarction on follow-up imaging.

MATERIALS AND METHODS: Patients from the Acute STroke Registry and Analysis of Lausanne data base with acute ischemic stroke and perfusion CT were included. Clinical and radiologic data were collected. We identified predictors of focal hypoperfusion using multivariate analyses.

RESULTS: From the 2216 patients with perfusion CT, 38.2% had an acute ischemic lesion on NCCT and 73.3% had focal hypoperfusion on perfusion CT. After we analyzed 104 covariates, high-admission NIHSS, visual field defect, aphasia, hemineglect, sensory deficits, and impaired consciousness were positively associated with focal hypoperfusion. Negative associations were pure posterior circulation, lacunar strokes, and anticoagulation. After integrating radiologic variables into the multivariate analyses, we found that visual field defect, sensory deficits, hemineglect, early ischemic changes on NCCT, anterior circulation, cardioembolic etiology, and arterial occlusion were positively associated with focal hypoperfusion, whereas increasing onset-to-CT delay, chronic vascular lesions, and lacunar etiology showed negative association. Sensitivity, specificity, and positive and negative predictive values of focal hypoperfusion on perfusion CT for infarct detection on follow-up MR imaging were 66.5%, 79.4%, 96.2%, and 22.8%, respectively, with an overall accuracy of 76.8%.

CONCLUSIONS: Compared with NCCT, perfusion CT doubles the sensitivity in detecting acute ischemic stroke. Focal hypoperfusion is independently predicted by stroke severity, cortical clinical deficits, nonlacunar supratentorial strokes, and shorter onset-to-imaging delays. A high proportion of patients with focal hypoperfusion developed infarction on subsequent imaging, as did some patients without focal hypoperfusion, indicating the complementarity of perfusion CT and MR imaging in acute ischemic stroke.

ABBREVIATIONS: AIS = acute ischemic stroke; ASTRAL = Acute STroke Registry and Analysis of Lausanne; FHP = focal hypoperfusion; MVA = multivariate analysis; PCT = perfusion CT

Neuroimaging plays a major role in the evaluation of patients with acute ischemic stroke (AIS). CT-based imaging is currently the most frequently used acute technique, differentiating

ischemic from hemorrhagic stroke and identifying some stroke mimics.^{1,2} It is also the most commonly used method for selecting patients for endovascular recanalization treatment³ and has shown promise in predicting treatment response⁴ and improving clinical outcome.⁵ However, its limited sensitivity for detecting early ischemia is a major drawback, even if scores of systematic analysis of CT may improve patient selection.^{6,7} Thresholds in perfusion imaging are still subject to debate,⁸ despite progress in the field,⁹ however.

Knowledge of the performance of perfusion CT (PCT) in predicting focal hypoperfusion (FHP) in AIS may help to improve stroke recognition¹⁰⁻¹⁴ and thereby decrease the proportion of stroke mimics. Better diagnosis of stroke mimics and “chameleons”¹⁵ will lead to better patient disposition and lower thrombolysis rates of mimics.¹⁶

The aims of this study were to determine the clinical and

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Indicates article with supplemental on-line tables.



Indicates article with supplemental on-line photo.

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Table 1: Selected patient characteristics from the overall patient population and in patients with and without FHP^a

Variable	Population (n = 2216)	FHP (n = 1624)	No FHP (n = 592)	Odds Ratio	95% CI
Demographics					
Age (yr)	71.4 (20)	72 (19.5)	69.7 (21)	1.01 ^b	1.00–1.01
Female sex	958 (43.3)	723 (44.6)	235 (39.8)	1.22 ^b	1.01–1.48
Preexisting mRS score	0 (1)	0 (1)	0 (1)	0.96	0.87–1.05
Anticoagulation at onset	211 (9.6)	158 (9.8)	53 (9)	1.10	0.80–1.54
Clinical presentation					
Admission NIHSS (points)	8 (11)	10 (12)	4 (4)	1.21 ^b	1.18–1.24
Aphasia	831 (38)	743 (46.4)	88 (15)	4.91 ^b	3.85–6.32
Hemineglect	583 (26)	555 (35)	28 (4.8)	10.70 ^b	7.36–16.2
Decreased level of consciousness	252 (11.6)	226 (14.3)	26 (4.5)	3.58 ^b	2.40–5.55
Sensory deficit	1237 (56.9)	1021 (64.1)	216 (37.1)	3.03 ^b	2.49–3.69
Visual field defect	882 (40.6)	836 (52.6)	46 (7.9)	13.00 ^b	9.58–18.07
Stroke localization					
Pure posterior circulation	394 (18)	182 (11.3)	212 (36.9)	0.22 ^b	0.17–0.27
Pure anterior circulation	1657 (75.4)	1393 (86.6)	254 (44.3)	8.12 ^b	6.54–10.12
Stroke mechanism					
Atherosclerotic	301 (14.1)	249 (15.8)	52 (9.2)	1.87 ^b	1.37–2.58
Cardioembolic	729 (34)	633 (40.2)	96 (16.9)	3.31 ^b	2.61–4.23
Lacunar	238 (11.1)	42 (2.7)	196 (34.5)	0.05 ^b	0.04–0.07
Risk factors					
Atrial fibrillation	619 (28)	536 (33.1)	83 (14)	3.03 ^b	2.36–3.92
Hypercholesterolemia	1606 (73.1)	1147 (71.2)	459 (78)	0.70 ^b	0.56–0.87
Acute CT imaging					
Onset-to-CT time (hr)	4.3 (10.4)	3.5 (8.6)	8.1 (12.9)	0.96 ^b	0.95–0.97
Early ischemic changes on NCCT	831 (38.2)	771 (48.5)	60 (10.3)	8.20 ^b	6.21–10.99
Arterial pathology in ischemic territory	242 (16.2)	237 (20.7)	5 (1.4)	18.01 ^b	8.19–50.89

^a Data are summarized as medians (with interquartile range) for continuous variables and as absolute numbers (with percentage) for categorical ones.

^b Statistically significant.

radiologic predictors of FHP on PCT in AIS and to assess the diagnostic performance of FHP for infarction on follow-up imaging.

MATERIALS AND METHODS

Study Population

All consecutive patients admitted to the stroke unit and/or intensive care unit of the Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland, with a main diagnosis of AIS were included in the Acute STroke Registry and Analysis of Lausanne (ASTRAL), from January 1, 2003¹⁷ to June 30, 2015. AIS was diagnosed according to the World Health Organization definition.¹⁸ Only patients arriving in our emergency department within 24 hours of AIS onset or at last proof of good health were included. Patients with transient ischemic attack, intracerebral hemorrhage, subarachnoid hemorrhage, and cerebral sinus venous thrombosis were collected in another register.

The indication for PCT imaging in our institution is suspected AIS with the patient arriving within 24 hours of onset; for pure clinical posterior fossa syndrome, the decision to perform PCT is left to the treating physician.¹⁷ Patients with known iodinated contrast allergy, known renal clearance of <30 mL/minute, and severe agitation do not undergo PCT.

For the present analysis, we selected all patients in the ASTRAL with a good-quality PCT performed within 24 hours of onset. PCT was considered of good quality if the arterial input curve re-descended to baseline before the end of image acquisition and if the rise of the venous transit curve occurred later than the arterial one and if there were no major movement artifacts and at least 2 good-quality slices available for analysis. Patients with NCCT

only or MR imaging in the acute phase were excluded. A total of 104 variables regarding demographics, vascular risk factors, clinical information, acute laboratory findings, stroke localization, acute neuroimaging findings, and acute treatment were used for analysis and are listed in Table 1 and On-line Tables 1 and 2.

Cerebral CT Imaging Protocol

Cerebral CT was performed on a 16–detector row multidetector CT scanner (LightSpeed; GE Healthcare, Milwaukee, Wisconsin) until November 2005 and on a 64–detector row multidetector CT scanner (LightSpeed VCT; GE Healthcare) thereafter. NCCT, PCT, CT angiography, and postcontrast series were acquired.

NCCT and postcontrast series were acquired in the axial mode from the skull base to the vertex (16-cm z-axis coverage) using the following imaging parameters: 120-kV(peak) tube voltage, 320-mA tube current, slice thickness = 5 mm, 32-cm scan FOV, 512 × 512 matrix.

All PCT series were acquired in the axial scan mode with 80-kVp tube voltage, 120-mA tube current, 32-cm scan FOV, and 512 × 512 matrix, as described in Wintermark et al.¹⁹ PCT was positioned at the level of the basal ganglia and the third ventricle above the orbits to protect the lens. Eighteen groups of 4 slices of 10 mm (40-mm z-axis coverage) were used until November 2005; then, 18 groups of 16 slices of 5 mm (80-mm z-axis coverage) were used from November 2005 to June 2015. Hence, the PCT series did not include the posterior fossa in the first 3 years of the study; thereafter, the PCT series usually included the upper half of the posterior fossa due to the increased z-axis coverage of the 64–detector row multidetector CT scanner. PCT images were acquired during 50 seconds in a cine mode with a delay of 5–7 seconds after injection of 50 mL of iodinated contrast (Accupaque

300, iohexol 300 mg/mL; GE Healthcare) at a flow rate of 5 mL per second, followed by 50 mL of 0.9% saline solution at the same flow rate into an antecubital vein using a power injector.

PCT data were re-analyzed off-line specifically for research purposes using the most recent Brilliance Workspace Portal (Philips Healthcare, Best, the Netherlands) and on the basis of the central volume principle using deconvolution to create parametric maps of mean transit time. Cerebral blood volume was calculated from the area under the time-enhancement curves, and cerebral blood flow was derived from the formula $CBF = CBV / MTT$. Regarding deconvolution, we always used an appropriate threshold for MTT, TTP, CBV, and CBF, as described by Man et al.²⁰

CT angiography was acquired in the helical scan mode (parameters: 120-kVp tube voltage, 150- to 260-mA tube current, 0.984 pitch, 0.625-mm slice thickness, 50-cm scan FOV, 512 × 512 matrix) from the aortic arch to the top of the frontal sinuses after injection of 50 mL of iodinated contrast (Accupaque 300, 300 mg/mL) at a flow rate of 5 mL per second (same parameters as for perfusion data) followed by 50 mL of 0.9% saline solution at the same flow rate.

Cerebral CT Imaging Analysis

An experienced vascular neurologist (P.M.) and 2 senior neuro-radiologists, all with 15-years' experience reading multimodal CT, independently reviewed NCCT, PCT, MR imaging, and CTA images. In cases of discordance, a consensus was found in multidisciplinary meetings, with awareness of the type and side of the clinical deficits. On NCCT, early ischemic changes, ASPECTS, the hyperdense middle cerebral artery sign, chronic or subacute infarct, and leukoaraiosis were recorded. On PCT, FHP was defined as clearly prolonged MTT visible on >1 slice, corresponding to an arterial territory that was not attributable to an underlying chronic tissue lesion and consistent with the clinical syndrome. Hence, we used any discernable visual change in the MTT parameter maps as a sign of FHP rather than a numeric threshold.

We chose MTT because it is a more sensitive marker of focal hypoperfusion than CBF²¹⁻²³ (with a small risk of overdiagnosing ischemia however) and it has high interrater agreement in our institution ($\kappa = 0.79$ in 100 patients with acute supratentorial stroke symptoms) and in the literature.^{24,25}

The raw axial and maximal-intensity-projection CTA images were also reviewed for significant ($\geq 50\%$ stenosis or occlusion) extra- and intracranial arterial pathology leading to the ischemic territory.

Follow-up imaging (either CT or MR imaging) performed any time after 24 hours of onset was reviewed for new ischemic lesions corresponding to the clinical picture.

Statistical Analysis

All analyses were conducted using R-3.2.3 (<http://www.r-project.org/>). Continuous variables are shown as median (interquartile range). First, a univariate comparison of patients with and without FHP was performed for all acute-phase variables (Table 1 and On-line Tables 1 and 2). Then, a multivariate analysis (MVA) was performed using all variables available before neuroimaging (ie, demographic and clinical data and AIS characteristics such as lo-

calization, stroke mechanism) to assess the association of these variables with FHP before neuroimaging. Finally, a second MVA was conducted in which all pertinent radiologic data (early ischemic changes, leukoaraiosis, chronic infarcts, significant arterial pathology) were added to the first MVA, to include all available information pertinent for hyperacute-treatment decision-making. In all multivariate analyses, imputation of missing data was performed using the chained equations methodology. Five imputed datasets were generated for each MVA. We performed a separate analysis on each imputed dataset, determining the important covariates associated with the response using backward elimination methods. The finalized outputs of the imputed analyses were appropriately combined to produce the results of this study.

Bivariate associations between each predictor and the outcomes were assessed using a logistic regression model. The odds ratio, 95% confidence intervals, and associated *P* values quantified the strength of the association between the predictors and the response in both univariate and multivariate logistic analyses. Significance was set at the .05 (5%) level.

RESULTS

A total of 3322 AISs were registered in ASTRAL during the 12-year observation period. Of these, 1031 (31.0%) patients were excluded because they did not undergo PCT on admission. Reasons for PCT exclusions are shown in On-line Figure: acute MR imaging performed instead of CT ($n = 45$), known/suspected iodine contrast allergy ($n = 46$), not attempted because the patient was agitated or moving ($n = 9$), PCT performed later than 24 hours after AIS onset ($n = 70$), renal insufficiency ($n = 204$), AIS considered as vertebrobasilar ($n = 317$), and physician's choice ($n = 340$). After we excluded 75 others (2%) for technical reasons, (<2 PCT slices available for analysis [$n = 4$], injection failure [$n = 32$], or movement artifacts [$n = 39$]), 2216 patients remained in the analysis, of which 467 (21%) were admitted between November 2003 and 2005, and 1749 (79%), between December 2005 and June 2015.

Excluded patients had similar age and sex, higher preadmission mRS scores, less severe admission NIHSS scores, and more frequent cardioembolic and lacunar stroke etiology in the univariate comparison (On-line Tables 1 and 2).

The demographics, risk factors, and clinical data of the included population are listed in Table 1 and On-line Tables 1 and 2. Overall, 831 (38.2%) had early ischemic changes on NCCT, and 1624 (73.3%) had FHP on PCT. In 532 (24%), findings of both NCCT and PCT were considered normal. For the 1404 patients admitted within 6 hours of AIS onset, 506 (36%) had early ischemic changes on NCCT and 1027 (73.2%) had FHP on PCT.

Among the 1657 patients with pure anterior circulation AIS, NCCT showed early ischemic changes in 710 (43.1%) and FHP was seen on PCT in 1393 patients (86.6%). For the 394 with pure posterior circulation AIS, the numbers were 75 (19%) and 182 (11.3%), respectively.

Considering preimaging data in the MVA, acute NIHSS, the presence of cortical signs (hemineglect, aphasia, and visual field defects), sensory deficits, and impaired consciousness all showed significant association with FHP. Pretreatment with anticoagu-

lants, pure posterior circulation localization, and lacunar etiology were less associated with FHP (Table 2).

In the second MVA with added acute neuroimaging findings, FHP was independently associated with hemineglect, visual field

defects, sensory deficits, early ischemic changes on NCCT, anterior circulation localization, significant arterial pathology in the ischemic territory, and cardiac stroke mechanism. Increasing onset-to-CT delay, chronic vascular lesions, and lacunar mechanism were negatively associated with FHP (Table 2).

This study also investigated the performance of NCCT and acute PCT findings regarding predicting a definitive infarct lesion on follow-up imaging in the subacute or chronic phase. From the 2216 patients, 873 patients had at least 1 follow-up MR imaging, 980 had a subsequent CT, and 363 patients had no follow-up imaging.

On the basis of these patient data, we calculated the sensitivity and specificity of admission NCCT to predict a follow-up lesion on any type of imaging as 43.3% and 96.6%, respectively (Table 3).

In the same population, the sensitivity of FHP to detect a lesion on any follow-up imaging was 80.1%, and 66.5% if only MR imaging follow-up images were considered, indicating that a substantial number of FHPs do not necessarily turn into visible infarction.

The specificity of FHP on acute PCT (for the absence of a lesion on any follow-up imaging) was 57.9%, and 79.4% if only MR imaging follow-up images were considered. This finding indicates that about 20% of PCTs show that patients have FHP, without a visible lesion on later MR imaging (Fig. 1).

The positive predictive value of FHP toward an infarct was 91.2% (96.2% considering only MR imaging lesions), indicating that PCT has very few false-positives (Table 3).

Table 2: Multivariate analysis of clinical and combined clinical and radiologic variables associated with FHP

Variables	OR	95% CI
Clinical predictors of FHP in MVA		
Admission NIHSS score	1.12	1.08–1.16
Visual field defects on admission	7.79	4.51–13.45
Aphasia at admission	2.03	1.37–3.00
Hemineglect at admission	4.50	2.46–8.22
Sensory deficit at admission	1.39	1.00–1.93
Decreased level of consciousness	6.32	2.49–16
Posterior circulation stroke	0.32	0.22–0.47
Lacunar stroke mechanism	0.14	0.08–0.24
Anticoagulation before stroke onset	0.45	0.28–0.72
Clinical and radiologic predictors of FHP in MVA		
Symptom onset-to-CT delay	0.97	0.95–0.99
Visual field defect at admission	6.09	3.43–10.81
Hemineglect at admission	4.13	2.06–8.27
Sensory deficit at admission	1.53	1.07–2.17
Cardioembolic stroke mechanism	1.87	1.11–3.13
Lacunar stroke mechanism	0.45	0.24–0.85
Early ischemic changes on CT	4.68	2.73–8.04
Chronic CT lesions (old strokes or leukoariosis)	0.54	0.33–0.87
Anterior circulation stroke	3.13	2.13–4.55
Arterial stenosis or occlusion in ischemic territory	2.29	1.32–3.99

Table 3: Accuracy of PCT as a diagnostic test for infarct identification on follow-up CT and MRI

	n Test +	n Test -	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	95% CI
Acute NCCT description (test) for any lesion at follow-up (condition)	673	880	43.3	96.6	98	23	51.2	(48.8–53.5)
PCT description (test) toward any lesion at follow-up (condition)	1260	313	80.1	57.9	91.2	33.9	67.9	(64.7–71.0)
PCT description (test) toward any lesion at MRI follow-up (condition)	516	260	66.5	79.4	96.2	22.8	76.8	(74.8–78.7)

Note:—PPV indicates positive predictive value; NPV, negative predictive value; +, positive; -, negative; n, number of patients.

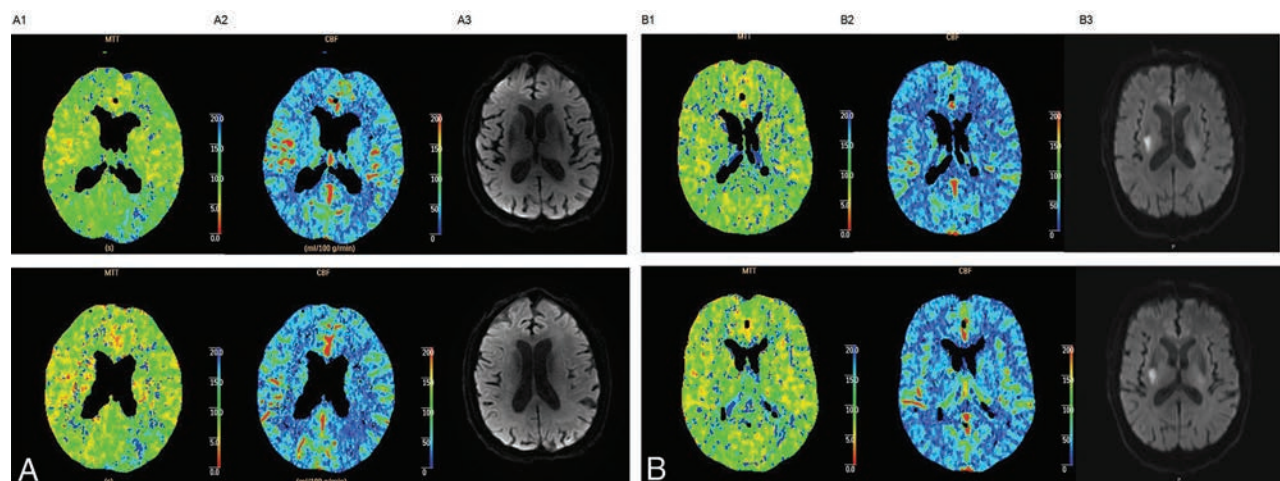


FIG 1. A, Patient with left MCA stroke, NIHSS 4, and acute PCT showing an FHP corresponding to the clinical deficit (A1, MTT and A2, CBF). Subacute MR imaging at 3 days shows no DWI lesion (A3). B, A patient with right MCA stroke, NIHSS 6, and normal findings on acute PCT (B1, MTT and B2, CBF), but an acute DWI lesion at 1 day after admission (B3) corresponding to the clinical deficit. These examples convey the complementarity of acute PCT and MR imaging.

The diagnostic accuracy for infarct detection on follow-up imaging was 76.8% for PCT and 51.2% for NCCT.

DISCUSSION

In this comprehensive analysis of a large number of consecutive AISs, we show that FHP is associated with cortical semiology, anterior circulation ischemia, nonlacunar strokes, earlier imaging, and the presence of arterial pathology and FHP has a moderate sensitivity, high specificity, and very high positive predictive value for radiologically visualized lesion development on MR imaging. Overall, PCT doubles the sensitivity of AIS detection compared with NCCT.

Clinical and Radiologic Predictors of FHP on PCT

Among the 8 clinical variables independently predicting FHP (Table 2), NIHSS, hemineglect, aphasia, and visual field defects on admission were expected because they are frequently associated with hemispheric lesions of large volume; furthermore, the ischemic lesions associated with these variables tend to be covered by PCT protocols.²⁶ The posterior fossa, however, is covered incompletely by most current PCT acquisitions, and sensitivity in this region might be further lowered by the smaller lesion volumes and radiation absorption by bone and bone artifacts.^{11,27} The association between FHP and decreased level of consciousness is likely explained by the large hemispheric lesions that have a high detection rate on PCT. AIS of lacunar origin showed FHP in only 2.7% of cases, probably because of the limited resolution of PCT.²⁸ The finding that anticoagulation was negatively associated with FHP in the MVA may be explained by the tendency of anticoagulation to protect against large emboli.^{29,30} Following the clinical associations, we found a patient presenting with a rather severe hemispheric syndrome and normal PCT findings should be suspected of having an AIS mimic. Similarly, a clinician who wants to confirm AIS in a patient with minor symptoms of lacunar origin or with a posterior fossa syndrome should directly perform MR imaging as the initial study.

When we added imaging data to the MVA (Table 2), the finding that a shorter delay from symptom onset to CT was a predictor of FHP is likely explained by patients with more severe strokes arriving more rapidly to the hospital and therefore imaging,³¹ as well as the increasing probability of spontaneous recanalization with time.^{32–34} Not surprising, abnormal arterial findings (stenosis of >50% or occlusion) were also associated with FHP on PCT, which may help the radiologist identify stenosis or occlusion in distal arteries. In contrast to other studies,^{26,35} we did not find an association between the volume of brain covered by PCT (number of slices) and FHP.

Diagnostic Performance of FHP for Infarction on Follow-Up Imaging

The performance of PCT for the prediction of a subsequent infarct on any type of follow-up imaging was 80.1% sensitive, and 66.5% if only MR imaging was used for follow-up, compared with 43.3% sensitivity for NCCT. The low rate of early ischemic changes on NCCT could be explained by the rapid onset-to-hospital timings (median, 3 hours). The almost doubled detection rate of AIS by PCT compared with NCCT is very welcome, particularly if diagnosis of AIS is uncertain and when DWI-based MR

imaging is not available.⁷ We would therefore recommend adding PCT, especially in patients with cortical symptoms.

The specificity of PCT using MR imaging as a reference standard was high (79.4%), indicating that in 20% of patients with findings negative for infarct on MR imaging, FHP was visible by acute PCT. Nevertheless, acute DWI remains more sensitive than multimodal CT-based imaging, as described in previous studies.⁷ However, our findings speak for the complementarity of both techniques to diagnose AIS.

Strengths and Limitations

Strengths of this analysis include the large number of consecutive PCTs during a long period and the use of prespecified data using up-to-date scales, definitions, and neurovascular imaging methods. The large database allowed us to test multiple clinical and radiologic variables, increasing the chances of obtaining significant results in multivariate analyses. Limitations of our work include being a single center and the retrospective, observational, noncontrolled, and nonrandomized nature of the study, without previous power calculation. In addition, we excluded patients without PCT imaging or with data of insufficient quality. However, the excluded patients were quite similar to the studied population except for the lower NIHSS scores and more cardioembolic strokes. Our study design did not allow testing the accuracy of PCT to diagnose AIS, and indeed, limitations of PCT include only showing selected brain areas, with the risk of some ischemic areas not being covered. In addition, our PCT methodology evolved during the observation period: The number of slices increased and slice thickness decreased. Brain coverage with PCT was less complete before November 2005, particularly for the vertex and posterior fossa. Most interesting, in our study, the number of slices available for analysis did not influence the FHP detection rate, and modification of the reconstruction algorithm did not seem to influence PCT parameters at a regular radiation dose.³⁶

We used visually clear prolonged MTT in a focal vascular area to detect FHP rather than a numeric threshold that is more objective. Thresholds for ischemia in perfusion imaging remain a matter of debate,⁸ however, and may not add to the clinical question of ischemia detection, which is why we looked at FHP in the context of a clinical syndrome. Another drawback of using MTT could be overdiagnosis of ischemia in cases of benign oligemia²⁵ distal to an arterial stenosis. An alternative method to PCT for detection of hypoperfusion is polyphasic CTA, which adequately selected patients in a large randomized clinical trial³⁷ and with less radiation exposure and shorter processing time. Finally, the follow-up imaging included all imaging performed in the subacute or chronic phase, which could lead to heterogeneous results but is consistent with common practice.

CONCLUSIONS

The present work identifies independent predictors of FHP on PCT in AIS, potentially allowing detection of more stroke mimics (from normal PCT findings) and more chameleons (from unexpected FHP in an acute neurologic deficit). It also indicates that acute PCT may add to the AIS diagnostic value in conjunction with NCCT and delayed MR imaging. Taken together, these could potentially improve AIS management.

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REFERENCES

1. de Lucas EM, Sánchez E, Gutiérrez A, et al. **CT protocol for acute stroke: tips and tricks for general radiologists.** *Radiographics* 2008; 28:1673–87 CrossRef Medline
2. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. **Tissue plasminogen activator for acute ischemic stroke.** *N Engl J Med* 1995;333:1581–87 CrossRef Medline
3. Goyal M, Menon BK, van Zwam WH, et al; HERMES collaborators. **Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials.** *Lancet* 2016;387:1723–31 CrossRef Medline
4. Zhu G, Michel P, Aghaebrahim A, et al. **Prediction of recanalization trumps prediction of tissue fate: the penumbra: a dual-edged sword.** *Stroke* 2013;44:1014–19 CrossRef Medline
5. Bill O, Faouzi M, Meuli R, et al. **Added value of multimodal computed tomography imaging: analysis of 1994 acute ischaemic strokes.** *Eur J Neurol* 2017;24:167–74 CrossRef Medline
6. Barber PA, Demchuk AM, Zhang J, et al. **Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy: ASPECTS Study Group—Alberta Stroke Programme Early CT Score.** *Lancet* 2000; 355:1670–74 CrossRef Medline
7. Chalela JA, Kidwell CS, Nentwich LM, et al. **Magnetic resonance imaging and computed tomography in emergency assessment of patients with suspected acute stroke: a prospective comparison.** *Lancet* 2007;369:293–98 CrossRef Medline
8. Dani KA, Thomas RG, Chappell FM, et al; Translational Medicine Research Collaboration Multicentre Acute Stroke Imaging Study. **Computed tomography and magnetic resonance perfusion imaging in ischemic stroke: definitions and thresholds.** *Ann Neurol* 2011; 70:384–401 CrossRef Medline
9. Kidwell CS, Jahan R, Gornbein J, et al. **Analysis of MR RESCUE dataset employing DEFUSE 2 target mismatch criteria for defining penumbra.** *Stroke* 2014;45. <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L71465318>. Accessed February 5, 2019
10. Lev MH, Segal AZ, Farkas J, et al. **Utility of perfusion-weighted CT imaging in acute middle cerebral artery stroke treated with intra-arterial thrombolysis: prediction of final infarct volume and clinical outcome.** *Stroke* 2001;32:2021–28 Medline
11. Eastwood JD, Lev MH, Azhari T, et al. **CT perfusion scanning with deconvolution analysis: pilot study in patients with acute middle cerebral artery stroke.** *Radiology* 2002;222:227–36 CrossRef Medline
12. Wintermark M, Reichhart M, Thiran JP, et al. **Prognostic accuracy of cerebral blood flow measurement by perfusion computed tomography, at the time of emergency room admission, in acute stroke patients.** *Ann Neurol* 2002;51:417–32 CrossRef Medline
13. Koenig M, Klotz E, Luka B, et al. **Perfusion CT of the brain: diagnostic approach for early detection of ischemic stroke.** *Radiology* 1998; 209:85–93 CrossRef Medline
14. Mayer TE, Hamann GF, Baranczyk J, et al. **Dynamic CT perfusion imaging of acute stroke.** *AJNR Am J Neuroradiol* 2000;21:1441–49 Medline
15. Richoz B, Hugli O, Dami F, et al. **Acute stroke chameleons in a university hospital: risk factors, circumstances, and outcomes.** *Neurology* 2015;85:505–11 CrossRef Medline
16. Zinkstok SM, Engelter ST, Gensicke H, et al. **Safety of thrombolysis in stroke mimics: results from a multicenter cohort study.** *Stroke* 2013;44:1080–84 CrossRef Medline
17. Michel P, Odier C, Rutgers M, et al. **The Acute STroke Registry and Analysis of Lausanne (ASTRAL): design and baseline analysis of an ischemic stroke registry including acute multimodal imaging.** *Stroke* 2010;41:2491–98 CrossRef Medline
18. World Health Organization. **Global atlas on cardiovascular disease prevention and control.** *Stroke, Cerebrovascular accident.* *Health Topics*, 2014: http://www.who.int/topics/cerebrovascular_accident/en/index.html
19. Wintermark M, Smith WS, Ko NU, et al. **Dynamic perfusion CT: optimizing the temporal resolution and contrast volume for calculation of perfusion CT parameters in stroke patients.** *AJNR Am J Neuroradiol* 2004;25:720–29 Medline
20. Man F, Patrie JT, Xin W, et al. **Delay-sensitive and delay-insensitive deconvolution perfusion-CT: similar ischemic core and penumbra volumes if appropriate threshold selected for each.** *Neuroradiology* 2015;57:573–81 CrossRef Medline
21. Wintermark M, Flanders AE, Velthuis B, et al. **Perfusion-CT assessment of infarct core and penumbra: receiver operating characteristic curve analysis in 130 patients suspected of acute hemispheric stroke.** *Stroke* 2006;37:979–85 CrossRef Medline
22. Cao W, Yassi N, Sharma G, et al. **Diagnosing acute lacunar infarction using CT perfusion.** *J Clin Neurosci* 2016;29:70–72 CrossRef Medline
23. Pallesen LP, Gerber J, Dzialowski I, et al; BASICS Study Group. **Diagnostic and prognostic impact of pc-ASPECTS applied to perfusion CT in the Basilar Artery International Cooperation Study.** *J Neuroimaging* 2015;25:384–89 CrossRef Medline
24. Thierfelder KM, Sommer WH, Baumann AB, et al. **Whole-brain CT perfusion: reliability and reproducibility of volumetric perfusion deficit assessment in patients with acute ischemic stroke.** *Neuroradiology* 2013;55:827–35 CrossRef Medline
25. Kidwell CS, Alger JR, Saver JL. **Beyond mismatch: evolving paradigms in imaging the ischemic penumbra with multimodal magnetic resonance imaging.** *Stroke* 2003;34:2729–35 CrossRef Medline
26. Parsons MW. **Perfusion CT: is it clinically useful?** *Int J Stroke* 2008; 3:41–50 CrossRef Medline
27. Wintermark M, Fischbein NJ, Smith WS, et al. **Accuracy of dynamic perfusion CT with deconvolution in detecting acute hemispheric stroke.** *AJNR Am J Neuroradiol* 2005;26:104–12 Medline
28. Yong M, Kaste M. **Dynamic of hyperglycemia as a predictor of stroke outcome in the ECASS-II trial.** *Stroke* 2008;39:2749–55 CrossRef Medline
29. Xian Y, O'Brien EC, Liang L, et al. **Association of preceding anti-thrombotic treatment with acute ischemic stroke severity and in-hospital outcomes among patients with atrial fibrillation.** *JAMA* 2017;317:1057–67 CrossRef Medline
30. Hylek EM, Go AS, Chang Y, et al. **Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation.** *N Engl J Med* 2003;11:1019–26 Medline
31. Saver JL, Smith EE, Fonarow GC, et al; GWTG-Stroke Steering Committee and Investigators. **The “golden hour” and acute brain ischemia: presenting features and lytic therapy in >30,000 patients arriving within 60 minutes of stroke onset.** *Stroke* 2010;41:1431–39 CrossRef Medline
32. Zanette EM, Roberti C, Mancini G, et al. **Spontaneous middle cerebral artery reperfusion in ischemic stroke: a follow-up study with transcranial Doppler.** *Stroke* 1995;26:430–33 CrossRef Medline
33. Toni D, Fiorelli M, Zanette EM, et al. **Early spontaneous improvement and deterioration of ischemic stroke patients: a serial study with transcranial Doppler ultrasonography.** *Stroke* 1998;29:1144–48 CrossRef Medline
34. Molina CA, Montaner J, Abilleira S, et al. **Timing of spontaneous**

- recanalization and risk of hemorrhagic transformation in acute cardioembolic stroke. *Stroke* 2001;32:1079–84 [CrossRef](#) [Medline](#)
35. Mori S, Obata T, Nakajima N, et al. **Volumetric perfusion CT using prototype 256-detector row CT scanner: preliminary study with healthy porcine model.** *AJNR Am J Neuroradiol* 2005;26:2536–41 [Medline](#)
36. Murphy A, So A, Lee TY, et al. **Low dose CT perfusion in acute ischemic stroke.** *Neuroradiology* 2014;56:1055–62 [CrossRef](#) [Medline](#)
37. Goyal M, Demchuk AM, Menon BK, et al; ESCAPE Trial Investigators. **Randomized assessment of rapid endovascular treatment of ischemic stroke.** *N Engl J Med* 2015;372:1019–30 [CrossRef](#) [Medline](#)

Complementary Roles of Dynamic Contrast-Enhanced MR Imaging and Postcontrast Vessel Wall Imaging in Detecting High-Risk Intracranial Aneurysms

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ABSTRACT

BACKGROUND AND PURPOSE: Individual assessment of the absolute risk of intracranial aneurysm rupture remains challenging. Emerging imaging techniques such as dynamic contrast-enhanced MR imaging and postcontrast vessel wall MR imaging may improve risk estimation by providing new information on aneurysm wall properties. The purpose of this study was to investigate the relationship between aneurysm wall permeability on dynamic contrast-enhanced MR imaging and aneurysm wall enhancement on postcontrast vessel wall MR imaging in unruptured intracranial aneurysms.

MATERIALS AND METHODS: Patients with unruptured saccular intracranial aneurysms were imaged with vessel wall MR imaging before and after gadolinium contrast administration. Dynamic contrast-enhanced MR imaging was performed coincident with contrast injection using 3D T1-weighted spoiled gradient-echo imaging. The transfer constant (K^{trans}) was measured adjacent to intracranial aneurysm and adjacent to the normal intracranial artery.

RESULTS: Twenty-nine subjects were analyzed (mean age, 53.9 ± 13.5 years; 24% men; PHASES score: median, 8; interquartile range, 4.75–10). K^{trans} was higher in intracranial aneurysms compared with the normal intracranial artery (median, 0.0110; interquartile range, 0.0060–0.0390 versus median, 0.0032; interquartile range, 0.0018–0.0048 min^{-1} ; $P < .001$), which correlated with intracranial aneurysm size (Spearman $\rho = 0.54$, $P = .002$) and PHASES score ($\rho = 0.40$, $P = .30$). Aneurysm wall enhancement, detected in 19 (66%) aneurysms, was associated with intracranial aneurysm size and the PHASES score but not significantly with K^{trans} ($P = .30$). Aneurysms of 2 of the 9 patients undergoing conservative treatment ruptured during 1-year follow-up. Both ruptured aneurysms had increased K^{trans} , whereas only 1 had aneurysm wall enhancement at baseline.

CONCLUSIONS: Dynamic contrast-enhanced MR imaging showed increased K^{trans} adjacent to intracranial aneurysms, which was independent of aneurysm wall enhancement on postcontrast vessel wall MR imaging. Increased aneurysm wall permeability on dynamic contrast-enhanced MR imaging provides new information that may be useful in intracranial aneurysm risk assessment.

ABBREVIATIONS: AWE = aneurysm wall enhancement; DCE = dynamic contrast-enhanced; IA = intracranial aneurysm; IQR = interquartile range; K^{trans} = transfer constant; PHASES = Population, Hypertension, Age, Size, Earlier Subarachnoid Hemorrhage, and Site; WEI = wall enhancement index

Intracranial aneurysm (IA) is a common vascular malformation, affecting approximately 3.2% of the general population.^{1,2} IA rupture is the most common cause of spontaneous subarach-

noid hemorrhage, and 80% of aneurysmal SAHs result in death or permanent neurologic deficits.³ Thus, the role of prevention in the clinical management of IAs cannot be overemphasized. Although preemptive treatment with either surgical or endovascular intervention is effective in preventing IA rupture, it also subjects patients to the risk of iatrogenic complications.^{4,5} Thus, individual risk assessment is needed to justify preventive treatment in high-risk patients to

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avoid aneurysmal SAH and predict those who do not need invasive treatment to avoid iatrogenic complications. A number of patient-specific and aneurysm-specific risk factors have been proposed from large prospective cohort studies.⁴ Yet estimating the absolute risk of IA rupture remains difficult.

In most previous studies,^{4,6} IAs were characterized using luminal imaging, which provides little information on patho-

physiologic changes or the integrity of the aneurysm wall, which could be more directly associated with IA rupture than IA morphology. Histologic studies of surgically resected IAs showed evidence of aneurysm wall remodeling.^{7,8} Furthermore, during an operation, focal wall thinning of the aneurysm dome was noticeable as translucent regions, which may precede rupture.⁹ Vakil et al¹⁰ performed dynamic contrast-enhanced (DCE) MR imaging in patients with unruptured IAs and found that the contrast extravasation rate (transfer constant [K^{trans}]) was high in the adjacent region of clinically defined high-risk IAs, indicating a leaky aneurysm wall as a potential marker of high-risk unruptured IAs. On the other hand, with high-resolution vessel wall MR imaging, postcontrast aneurysm wall enhancement (AWE) has been observed, which was also shown to be a marker of high-risk IAs.^{11,12} It is unclear whether increased K^{trans} on DCE-MR imaging may result from an enhanced aneurysm wall. To better understand the nature of increased K^{trans} in unruptured IAs, this study sought to investigate the relationship between aneurysm wall permeability by DCE-MR imaging and AWE by vessel wall MR imaging.

MATERIALS AND METHODS

Study Population

This observational study was approved by the institutional ethics committee of Tsinghua University. Signed consent forms were acquired. Patients referred to the neurosurgery clinics who were diagnosed with unruptured saccular IAs by digital subtraction angiography were invited to participate. Exclusion criteria were contraindications to MR imaging or gadolinium contrast injection. Thirty-two patients (24 women; mean age, 54.2 ± 13.1 years) with a total of 41 unruptured saccular aneurysms were recruited. Clinical risk assessment was performed by

evaluating morphology characteristics on DSA, including IA size,¹³ location (anterior or posterior circulation), and blebs. The Population, Hypertension, Age, Size, Earlier Subarachnoid Hemorrhage, and Site (PHASES) score,¹⁴ which aggregates multiple clinical risk factors to provide a more accurate estimate of individual risk (Table 1), was calculated. Twenty-three patients received preemptive surgical treatment (clipping; $n = 5$; coiling; $n = 18$). The remaining 9 patients who refused or were not eligible for preemptive surgery were treated conservatively and followed for 1 year.

Imaging Protocol

Patients were scanned on a 3T whole-body scanner (Achieva TX; Philips Healthcare, Best, the Netherlands) with a 32-channel head coil. First, the target aneurysm was localized by a 3D time-of-flight MRA sequence. For patients with multiple IAs, the referring clinician indicated the target aneurysm for imaging. This was necessary because to ensure

Table 1: Components of the PHASES score¹⁴

PHASES Aneurysm Risk Score	Points
(P) Population	
North American, European (other than Finnish)	0
Japanese	3
Finnish	5
(H) Hypertension	
No	0
Yes	1
(A) Age	
Younger than 70 yr	0
70 yr or older	1
(S) Size of aneurysm	
<7.0 mm	0
7.0–9.9 mm	3
10.0–19.9 mm	6
≥20.0 mm	10
(E) Earlier SAH from another aneurysm	
No	0
Yes	1
(S) Site of aneurysm	
ICA	0
MCA	2
ACA/PcomA/posterior circulation	4

Note:—ACA indicates anterior cerebral arteries (including the anterior cerebral artery, anterior communicating artery, and pericallosal artery); ICA, internal carotid artery; MCA, middle cerebral artery; PcomA, posterior communicating artery; SAH, subarachnoid hemorrhage.

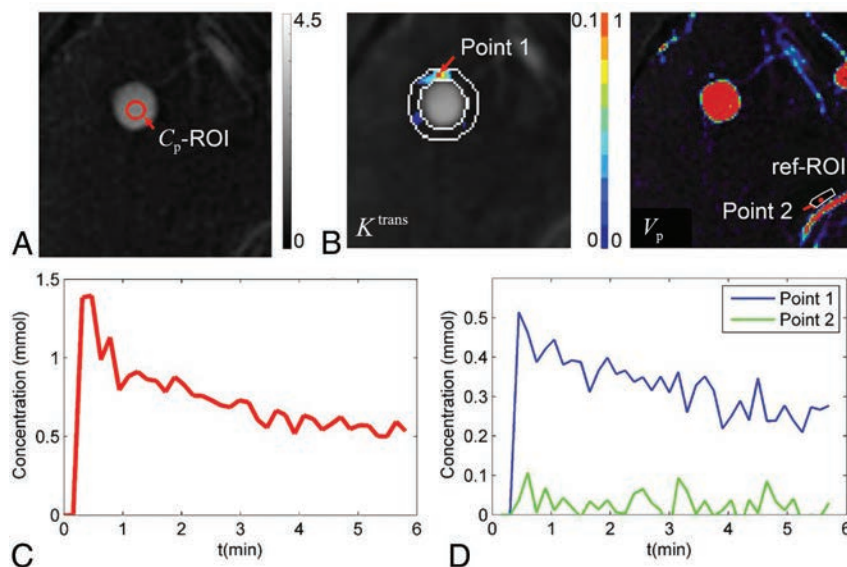


FIG 1. Measuring aneurysm wall permeability by DCE-MR imaging. Signal intensity in the lumen was measured on DCE imaging series (red contour in A) to obtain contrast concentration in plasma at different time points, which gave the arterial input function $C_p(t)$ (red curve in C). The concentration-time curve of tissue $C(t)$ was fitted voxel by voxel using the extended Kety/Tofts model, which generated parametric maps that were overlaid onto DCE images (B). ROIs were placed on the slice with highest K^{trans} to measure K^{trans} in the region adjacent to intracranial aneurysms (IA-ROI, white contour on K^{trans} map in B) and near a normal artery. The concentration-time curves of points 1 and 2 (red dots in B) are shown in D. ref-ROI indicates reference ROI.

high temporal and spatial resolution, the DCE-MR imaging used in this study had a limited longitudinal coverage, which made it difficult to simultaneously image multiple IAs that might exist.

The imaging parameters of 3D time-of-flight were the following: TR/TE = 25/3.5 ms; flip angle = 20°; FOV = 200 × 200 × 84 mm³; reconstructed voxel size = 0.35 × 0.35 × 0.7 mm³. Before DCE-MR imaging, a 3D black-blood T1-weighted volume isotropic turbo spin-echo acquisition sequence¹⁵ was performed to acquire precontrast vessel wall images with the following parameters: TR/TE = 700/30 ms; TSE factor = 49; FOV = 160 × 160 × 54 mm³; voxel size = 0.6 × 0.6 × 0.6 mm³; 90 transverse slices. DCE-MR imaging was performed with the imaging slab centered on the target aneurysm. For DCE-MR imaging, precontrast T1 mapping was performed using a 3D variable flip angle sequence with optimized flip angles: 2°, 4°, 9°, and 25°. ¹⁶ B₁ mapping was also performed to correct variations of the prescribed flip angle using the actual flip angle method.¹⁷ Then, DCE images were acquired using a 3D T1-weighted spoiled gradient-echo sequence: TR/TE = 3.9/2 ms; flip angle = 15°; FOV = 160 × 160 mm²; spatial resolution = 0.8 × 0.8 mm²; slice thickness = 2 mm; number of slices = 10; time resolution = 8.8 seconds. Coincident with the fifth dynamic scan, a bolus of 0.1 mmol/kg of Gd-DTPA (Magnevist; Bayer HealthCare Pharmaceuticals, Wayne, New Jersey) was injected intravenously at a rate of 1.5 mL/s, followed by a 20-mL saline flush at the same rate. The total scan time of DCE-MR imaging was about 6 minutes. During the DCE acquisition, a spatial saturation band was positioned proximal to the imaging plane to induce T1 weighting for flowing blood. After DCE-MR imaging, the 3D black-blood T1-weighted volume isotropic turbo spin-echo acquisition sequence was repeated for postcontrast vessel wall images with the same imaging parameters as for the precontrast acquisition.

Image Analysis

The extended Kety/Tofts model¹⁸ was used to describe the pharmacokinetics of the contrast agent in DCE-MR imaging:

$$1) \quad C(t) = K^{trans} \int_0^t e^{-K^{trans}/V_e \times (t-\tau)} C_p(\tau) d\tau + V_p C_p(t),$$

where K^{trans} (min⁻¹) is the transfer rate of contrast agent from the intravascular space to the extracellular extravascular space; V_e is the extracellular extravascular fractional volume; V_p is the fractional plasma volume; $C(t)$ is the tissue concentration of contrast agent, calculated using signal intensity values in DCE images and precontrast T1 mapping data; and $C_p(t)$ is the plasma concentration of contrast agent or arterial input function.¹⁹ The kinetic model was fitted for each pixel using the least-squares method to generate parametric maps including K^{trans} and V_p (Fig 1). To measure aneurysm wall permeability, we selected the slice showing the highest K^{trans} near the aneurysm. An ROI immediately adjacent to the aneurysm was defined by 2 concentric contours: The first was drawn to just enclose the aneurysm, and the second was drawn by expanding the first one 3 pixels away from the aneurysm. Aneurysm wall

permeability was measured as mean K^{trans} within the ROI excluding pixels with blood signal contamination ($V_p > 0.5$).¹⁰ To measure normal intracranial artery permeability, we placed a reference ROI immediately adjacent to a normal intracranial artery on the same slice.

The pre- and postcontrast 3D T1-weighted volume isotropic turbo spin-echo acquisition images were reformatted into 2-mm slices that matched the DCE-MR images. Blinded to DCE-MR imaging analysis, we evaluated the presence of aneurysm wall enhancement by comparing pre- and postcontrast vessel wall images.²⁰ Additionally, the wall-enhancement index (WEI)²¹ was measured to provide a quantitative measurement of aneurysm wall enhancement:

$$2) \quad WEI = \frac{\frac{SI_{Wall}_{postcontrast}}{SI_{Brain}_{postcontrast}} - \frac{SI_{Wall}_{precontrast}}{SI_{Brain}_{precontrast}}}{\frac{SI_{Wall}_{precontrast}}{SI_{Brain}_{precontrast}}},$$

where $SI_{Brain}_{precontrast}$ and $SI_{Brain}_{postcontrast}$ were measured in brain white matter for signal intensity normalization. All imaging measurements were repeated by a second reader to assess inter-reader reproducibility or reliability.

Data Analysis

Categoric variables were summarized as count (percentage). The PHASES score was summarized as median (interquartile range, [IQR]). The Kolmogorov-Smirnov test was used to test each continuous variable for whether a normal distribution could be assumed, after which the variable was summarized as mean ± SD or median (IQR) as appropriate. The Wilcoxon signed rank test was used to compare K^{trans} between aneurysms and normal arteries. The Mann-Whitney *U* test was used to compare K^{trans} among different aneurysm groups. The Spearman correlation coefficient was used to evaluate the correlation between K^{trans} and WEI as well as the relationships of K^{trans} and WEI to age, aneurysm size, and the PHASES score. To assess interreader reproducibility or reliability, we used the intraclass correlation coefficient (2-way model) for K^{trans} and WEI, while the Cohen κ was used for the presence of conspicuous wall enhancement. All statistical analyses were conducted as 2-tailed tests in SPSS (IBM, Armonk, New York). $P < .05$ was defined as statistical significance.

RESULTS

Patient Demographics

Three patients were excluded from DCE analysis because of signal contamination from the cavernous sinus after contrast injection. Clinical characteristics of the remaining 29 patients (mean age, 53.9 ± 13.5 years; male sex, 24%) are summarized in Table 2. Of the 29 IAs, 18 (62%) were located in the anterior circulation (internal carotid artery, $n = 13$; anterior communicating artery, $n = 4$; middle cerebral artery, $n = 1$), and 11 (38%) were located in the posterior circulation (basilar artery, $n = 10$; posterior cerebral artery, $n = 1$). Twenty-three (79%) patients had a PHASES score of ≥4.

Aneurysm Wall Permeability by DCE-MR Imaging

K^{trans} measured adjacent to an IA was higher than that measured adjacent to a normal intracranial artery (median, 0.0110; IQR, 0.0060–0.0390 versus median, 0.0032; IQR, 0.0018–0.0048 min^{-1} ; $P < .001$). Substantial variations in aneurysm wall permeability were present (Fig 2). Spearman correlation analysis showed that K^{trans} was moderately correlated with IA size ($\rho = 0.54$, $P = .002$; Fig 3) and the PHASES score ($\rho = 0.40$, $P = .030$). Other clinical and imaging characteristics were not significantly associated with K^{trans} .

Aneurysm Wall Enhancement

Conspicuous wall enhancement was detected in 19 (66%) aneurysms. IA size and the PHASES score were significantly different between aneurysms with and without AWE (IA size: median, 15.0 mm; IQR, 9.0–22.1 mm versus median, 5.1 mm; IQR, 4.3–8.5; $P < .001$;

PHASES score: median, 10; IQR, 8–10.75 versus median 3.5; IQR, 2–5; $P < .001$). As a quantitative measure of AWE, the median WEIs were 4.0 (IQR, 2.4–6.7) and 1.4 (IQR, 1.1–1.5) in aneurysms with and without conspicuous wall enhancement, respectively; $P < .001$. By contrast, K^{trans} was not significantly associated with AWE (median, 0.0157; IQR, 0.0065–0.0421 versus median, 0.0089; IQR, 0.0059–0.0338 min^{-1} ; $P = .30$; Fig 4). The scatterplot in Fig 4 shows a poor concordance between K^{trans} and the WEI in individual patients despite a statistically significant correlation coefficient in the overall sample ($\rho = 0.39$, $P = .040$).

Follow-Up Findings

During the 1-year follow-up, 2 of the 9 patients undergoing conservative treatment had aneurysmal SAH at 1 month and 5 months, respectively. Figure 5 shows the inhomogeneous K^{trans} maps and vessel wall images of the 2 aneurysms that ruptured within a year. Notably, both ruptured aneurysms had high K^{trans} in the region adjacent to the aneurysm, whereas only 1 had obvious wall enhancement on baseline MR imaging. In fact, the 2 ruptured aneurysms had the highest and second highest baseline K^{trans} among the 9 aneurysms that were followed. Baseline K^{trans} was significantly higher in the ruptured aneurysms than in the other aneurysms ($P = .040$), whereas IA size, the PHASES score, and WEI were not significantly different between the 2 groups ($P = .56$, $>.99$, and $.38$, respectively).

Repeat Measurements

All MR imaging measurements were repeated by an independent reader to evaluate interreader reproducibility or reliability. The intraclass correlation coefficients were 0.991 (95% CI, 0.981–0.996) and 0.74 (95% CI, 0.51–0.87) for K^{trans} and WEI, respectively. The Cohen κ for the presence of conspicuous wall enhancement was 0.79 (95% CI, 0.56–1.00).

DISCUSSION

DCE-MR imaging and high-resolution vessel wall MR imaging are emerging techniques that may provide information about aneurysm wall properties relevant to IA rupture.^{10,20,21} However, the nature of the imaging findings by these techniques remains elusive given the difficulties with histopathologic validation. To our knowledge, this is the first study to evaluate the relationship between increased K^{trans} on DCE-MR imaging and AWE on vessel wall MR imaging. Our observations support increased K^{trans} as a distinctive finding in high-risk IAs rather than explaining it by the coexisting AWE. Therefore, increased K^{trans} likely represents contrast leakage from the aneurysm into the adjacent region captured by time-resolved imaging. Measuring aneurysm wall permeability has the potential to allow more precise risk assessment of IA rupture.

DCE-MR imaging collects a time-se-

Table 2: The demography and aneurysm characteristics of the study sample (N = 29)^a

	No. (%), Mean, or Median (IQR)
Age (yr)	53.9 $\pm$ 13.5
Male sex	7 (24%)
Current smoking	5 (17%)
Hypertension	11 (38%)
Diabetes	2 (7%)
Location	
Anterior circulation	18 (62%)
Posterior circulation	11 (38%)
Size	
<7.0 mm	7 (24%)
7.0–9.9 mm	8 (28%)
10.0–19.9 mm	7 (24%)
≥ 20.0 mm	7 (24%)
Blebs	3 (10%)
PHASES score	8 (4.75–10)
K^{trans} (min^{-1})	0.0107 (0.0060–0.0390)
Aneurysm wall enhancement	19 (66%)

^a See Table 1 for details of the PHASES score.

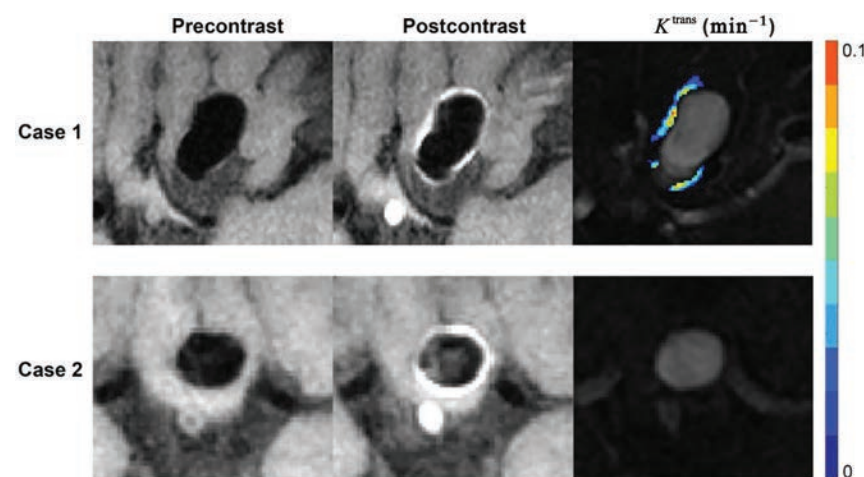


FIG 2. Enhanced aneurysm wall with and without increased permeability. Case 1: A 51-year-old woman who presented with a 19.5-mm aneurysm in the internal carotid artery. Pre- and postcontrast vessel wall images show conspicuous wall enhancement. DCE-MR imaging shows increased wall permeability ($K^{\text{trans}} = 0.0346 \text{ min}^{-1}$). Case 2: A 61-year-old woman who presented with a 9-mm aneurysm in the anterior communicating artery. Pre- and postcontrast vessel wall imaging shows conspicuous wall enhancement, but DCE-MR imaging did not show increased wall permeability ($K^{\text{trans}} = 0.0096 \text{ min}^{-1}$).

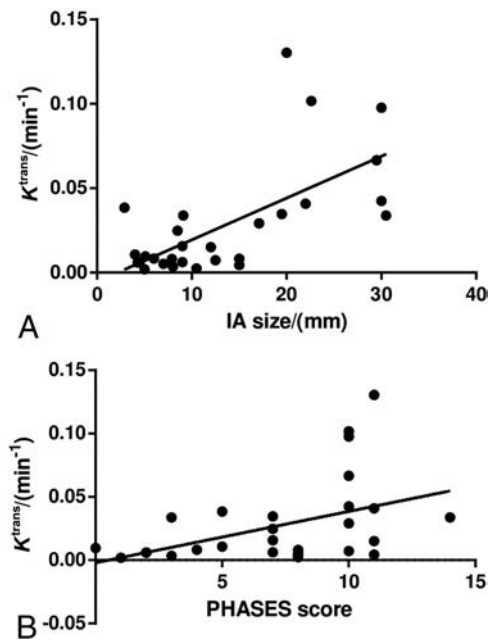


FIG 3. Associations between aneurysm wall permeability and size (A) and the PHASES score (B). Spearman correlation analysis shows that K^{trans} is positively correlated with aneurysm size ($\rho = 0.54$, $P = .002$) and the PHASES score ($\rho = 0.40$, $P = .030$).

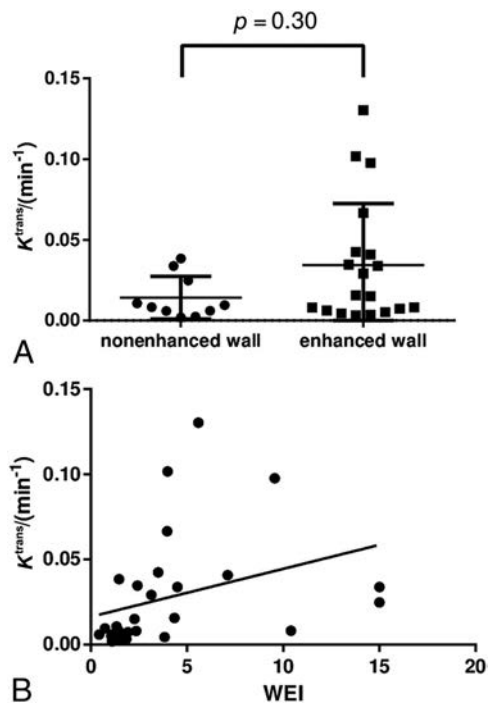


FIG 4. Association between K^{trans} and aneurysm wall enhancement. K^{trans} shows no statistically significant association with the presence of aneurysm wall enhancement (A) and a poor concordance with the wall enhancement index (B).

ries of contrast-enhanced images on intravenous injection of gadolinium contrast. Data are then subject to pharmacokinetic modeling to estimate the contrast extravasation rate (K^{trans}), which reflects vessel permeability. In a recent study, Vakil et al¹⁰ applied DCE-MR imaging to 27 unruptured IAs and noted that some aneurysms appeared to be “leaky,” supported by increased K^{trans}

in the region adjacent to aneurysm. In vivo detection of leaky aneurysm walls may allow us to capture an asymptomatic, precursor stage of IA rupture, with important implications for the prevention of aneurysmal SAH. However, the relationship between increased K^{trans} on DCE-MR imaging and AWE on vessel wall MR imaging needs to be clarified. First, high K^{trans} can result from AWE in the presence of partial volume effects and/or aneurysm wall motion. Second, assessing AWE is easier to do clinically than measuring K^{trans} . Thus, K^{trans} must provide pathologic information different from that provided by AWE to justify its clinical utility.

Consistent with Vakil et al,¹⁰ we also observed that K^{trans} measured adjacent to the IA was higher (leakier) than that measured adjacent to the normal intracranial artery. Of note, 66% of the studied aneurysms had conspicuous wall enhancement (AWE), with a median WEI of 4.0 (IQR, 2.4–6.7) compared with 1.4 (IQR, 1.1–1.5) in those without AWE. Nonetheless, further analyses indicated that high K^{trans} adjacent to an IA was unlikely due to AWE. First, about half of the aneurysms with AWE did not have increased K^{trans} , while aneurysms without AWE could have increased K^{trans} . Second, although K^{trans} had a statistically significant association with WEI, the correlation was weak ($\rho = 0.39$, $P = .040$). In fact, the correlation of K^{trans} with IA size appeared stronger ($\rho = 0.54$, $P = .002$), suggesting that K^{trans} and WEI are unlikely to represent different imaging measurements of the same pathology. Most interesting, IA rupture was seen during follow-up in the 2 aneurysms with the highest baseline K^{trans} , but only 1 had AWE. Overall, our data support increased K^{trans} , reflecting a pathophysiologic phenomenon that is different from AWE.

The exact pathophysiology of increased IA wall permeability remains speculative. Nonetheless, histopathologic findings, intraoperative observations, and patient symptoms appear to support the existence of focally present, thin, and leaky wall regions that may predispose to rupture. Kataoka et al¹⁸ compared 44 ruptured and 27 unruptured IA specimens and found that ruptured aneurysms more often had disrupted endothelial linings and hyaline-like wall structures that may result from inflammatory cell infiltration. Kadasi et al²² described translucent wall regions under an intraoperative microscope that represented focal wall thinning and correlated with the distribution of low wall shear stress. Furthermore, many patients with aneurysmal SAH recalled that they had a warning headache before SAH, which is thought to indicate a minor leak.^{23,24} Alternatively, a vasa vasorum, which has been noted in the histologic examination of aneurysm walls,²⁵ may be the source of contrast medium leakage into the surrounding CSF. In atherosclerotic plaque, a vasa vasorum has been shown to be leaky on DCE-MR imaging, particularly under inflammatory conditions.²⁶ Radiologic-pathologic correlation studies are critically needed to elucidate the underlying pathophysiologic mechanism of increased IA wall permeability on DCE-MR imaging.

K^{trans} measured in this study was lower than that reported by Vakil et al.¹⁰ This finding can be explained by the different methods that the 2 studies used to measure mean K^{trans} on parametric maps. While the previous study used a single contour to define an ROI (≥ 10 pixels) that was placed adjacent to aneurysm wall to measure the “ K^{trans} hotspot,” the present study used 2 concentric

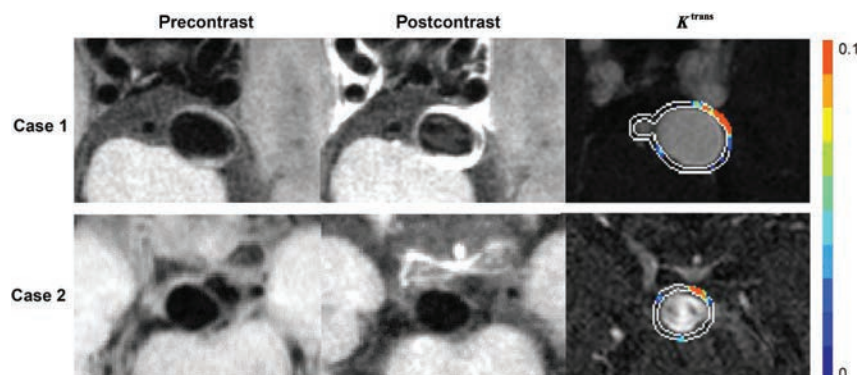


FIG 5. Baseline MR images of the 2 aneurysms that ruptured during follow-up. Case 1: A 36-year-old man has a 17.1-mm aneurysm in the basilar artery. The patient was concerned about surgical risk and received conservative treatment. Subarachnoid hemorrhage occurred 5 months after the baseline scan (no aneurysm wall enhancement; $K^{\text{trans}} = 0.0449 \text{ min}^{-1}$). Case 2: A 68-year-old man had an 8.5-mm aneurysm in the basilar artery. The patient was concerned about surgical risk and received conservative treatment. Subarachnoid hemorrhage occurred 1 month after baseline scan (no aneurysm wall enhancement; $K^{\text{trans}} = 0.0524 \text{ min}^{-1}$).

contours to define an ROI that enclosed the entire circumferential region. In the former, ROIs of different sizes may generate different K^{trans} measurements from the same K^{trans} map. The ROI in the latter method is more objectively defined, which may facilitate comparison of K^{trans} measurements among subjects. However, it is possible that the risk of IA rupture could be determined by a leaky wall segment that is focally present. Therefore, both methods may have limitations. Similar results were found (data not shown) when image review was redone using the single-contour method. Nonetheless, a standardized method to obtain segmental wall permeability (eg, fixed size ROI) of an IA may be worth exploring in the future.

The International Study of Unruptured Intracranial Aneurysms reported that the risk of IA rupture increased with increased IA size.⁴ Currently, IA size is arguably the most important factor clinically to determine the risk of IA rupture. However, given the much higher prevalence of small IAs than large ones, aneurysmal SAH most frequently results from small IAs.^{27,28} Recent efforts have attempted to aggregate multiple risk factors into clinical risk scores, such as the PHASES score.¹⁴ External data indicated that the PHASES score may only have moderate sensitivity (75%) and specificity (64%) in detecting high-risk IAs,²⁹ which would translate into 25% of high-risk IAs left untreated and 36% of treated IAs being low-risk ones. In this context, the moderate correlations of K^{trans} with IA size and the PHASES score add to the expectation that assessing aneurysm wall permeability may eventually allow clinicians to better identify individuals at risk of IA rupture than current risk markers. However, this expectation is beyond the scope of the present study and will await future large-scale investigations as more centers accrue experience with the technique.

Several important limitations of this study are worth mentioning. First, this is a proof-of-concept study with a relatively small sample size. Despite the promising results, the robustness of DCE-MR imaging in measuring IA permeability remains to be explored more extensively in future research to understand factors that may compromise the accuracy of the K^{trans} measurement, especially if K^{trans} is studied for potential use in the man-

agement of individual patients. To eliminate any influence from aneurysm wall motion, cardiac triggering using electrocardiography or a peripheral pulse unit may be used in data acquisition. However, because cardiac gating will reduce the imaging efficiency and increase the scan time, different k -space trajectories and advanced reconstruction algorithms may be required to accelerate DCE-MR imaging.³⁰ Second, the DCE-MR imaging sequence used in this study provides limited longitudinal coverage (20 mm). It is impossible to cover multiple aneurysms in 1 DCE-MR imaging scan. Thus, a priori selection of the target aneurysm is necessary in patients with multiple aneurysms. Furthermore, image analysis for certain ICA aneurysms can be difficult due to strong

enhancement of the cavernous sinus. Third, associations of imaging findings with intraoperative observations and/or histologic findings were not performed, which could have provided further insights into the nature of increased K^{trans} on DCE-MR imaging. Last, the test-retest reproducibility of K^{trans} remains to be studied. The interreader reproducibility of K^{trans} was found to be excellent; the outcome was not surprising because most steps in DCE-MR imaging analysis were automatic. However, it will be critical to evaluate its test-retest reproducibility.

CONCLUSIONS

In our series of unruptured IAs referred to the neurosurgery clinics, DCE-MR imaging showed increased K^{trans} in the adjacent region of the IA compared with the normal intracranial artery. Such increases in K^{trans} were not explained by AWE on vessel wall MR imaging, though both were associated with large IA size. Therefore, increased K^{trans} likely represents a real phenomenon of increased aneurysmal wall permeability, which provides different information from AWE. Future studies are warranted to evaluate its prognostic value independent of clinical risk assessment.

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REFERENCES

1. Thompson BG, Brown RD Jr, Amin-Hanjani S, et al; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, and Council on Epidemiology and Prevention, American Heart Association, American Stroke Association. **Guidelines for the Manage-**

- ment of Patients with Unruptured Intracranial Aneurysms: a Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association. *Stroke* 2015;46:2368–400 CrossRef Medline
2. Vlak MH, Algra A, Brandenburg R, et al. Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis. *Lancet Neurol* 2011;10:626–36 CrossRef Medline
 3. van Gijn J, Kerr RS, Rinkel GJE. Subarachnoid haemorrhage. *Lancet* 2007;369:306–18 CrossRef Medline
 4. Wiebers DO, Whisnant JP, Huston J 3rd, et al; International Study of Unruptured Intracranial Aneurysms Investigators. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. *Lancet* 2003;362:103–10 CrossRef Medline
 5. Raaymakers TW, Rinkel GJ, Limburg M, et al. Mortality and morbidity of surgery for unruptured intracranial aneurysms: a meta-analysis. *Stroke* 1998;29:1531–38 CrossRef Medline
 6. Morita A, Kirino T, Hashi K, et al; UCAS Japan Investigators. The natural course of unruptured cerebral aneurysms in a Japanese cohort. *N Engl J Med*. 2012;366:2474–82 CrossRef Medline
 7. Frösen J, Piippo A, Paetau A, et al. Remodeling of saccular cerebral artery aneurysm wall is associated with rupture: histological analysis of 24 unruptured and 42 ruptured cases. *Stroke* 2004;35:2287–93 CrossRef Medline
 8. Kataoka K, Taneda M, Asai T, et al. Structural fragility and inflammatory response of ruptured cerebral aneurysms: a comparative study between ruptured and unruptured cerebral aneurysms. *Stroke* 1999;30:1396–401 CrossRef Medline
 9. Kadasi LM, Dent WC, Malek AM. Colocalization of thin-walled dome regions with low hemodynamic wall shear stress in unruptured cerebral aneurysms. *J Neurosurg* 2013;119:172–79 CrossRef Medline
 10. Vakil P, Ansari SA, Cantrell CG, et al. Quantifying intracranial aneurysm wall permeability for risk assessment using dynamic contrast-enhanced MRI: a pilot study. *AJNR Am J Neuroradiol* 2015;36:953–59 CrossRef Medline
 11. Matouk CC, Mandell DM, Günel M, et al. Vessel wall magnetic resonance imaging identifies the site of rupture in patients with multiple intracranial aneurysms: proof of principle. *Neurosurgery* 2013;72:492–96; discussion 496 CrossRef Medline
 12. Nagahata S, Nagahata M, Obara M, et al. Wall enhancement of the intracranial aneurysms revealed by magnetic resonance vessel wall imaging using three-dimensional turbo spin-echo sequence with motion-sensitized driven-equilibrium: a sign of ruptured aneurysm? *Clin Neuroradiol* 2016;26:277–83 CrossRef Medline
 13. Backes D, Vergouwen MDI, Velthuis BK, et al. Difference in aneurysm characteristics between ruptured and unruptured aneurysms in patients with multiple intracranial aneurysms. *Stroke* 2014;45:1299–303 CrossRef Medline
 14. Greving JP, Wermer MJ, Brown RD Jr, et al. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. *Lancet Neurol* 2014;13:59–66 CrossRef Medline
 15. Qiao Y, Steinman DA, Qin Q, et al. Intracranial arterial wall imaging using three-dimensional high isotropic resolution black blood MRI at 3.0 Tesla. *J Magn Reson Imaging* 2011;34:22–30 CrossRef Medline
 16. Cheng HL, Wright GA. Rapid high-resolution T(1) mapping by variable flip angles: accurate and precise measurements in the presence of radiofrequency field inhomogeneity. *Magn Reson Med* 2006;55:566–74 CrossRef Medline
 17. Yarnykh VL. Actual flip-angle imaging in the pulsed steady state: a method for rapid three-dimensional mapping of the transmitted radiofrequency field. *Magn Reson Med* 2007;57:192–200 CrossRef Medline
 18. Tofts PS, Brix G, Buckley DL, et al. Estimating kinetic parameters from dynamic contrast-enhanced T1-weighted MRI of a diffusable tracer: standardized quantities and symbols. *J Magn Reson Imaging* 1999;10:223–32 CrossRef Medline
 19. Yang C, Karczmar GS, Medved M, et al. Reproducibility assessment of a multiple reference tissue method for quantitative dynamic contrast enhanced-MRI analysis. *Magn Reson Med* 2009;61:851–59 CrossRef Medline
 20. Liu P, Qi H, Liu A, et al. Relationship between aneurysm wall enhancement and conventional risk factors in patients with unruptured intracranial aneurysms: a black-blood MRI study. *Interv Neuroradiol* 2016;22:501–05 CrossRef Medline
 21. Omodaka S, Endo H, Niizuma K, et al. Quantitative assessment of circumferential enhancement along the wall of cerebral aneurysms using MR imaging. *AJNR Am J Neuroradiol* 2016;37:1262–66 CrossRef Medline
 22. Kadasi LM, Dent WC, Malek AM. Cerebral aneurysm wall thickness analysis using intraoperative microscopy: effect of size and gender on thin translucent regions. *J Neurointerv Surg* 2013;5:201–06 CrossRef Medline
 23. Juvela S. Minor leak before rupture of an intracranial aneurysm and subarachnoid hemorrhage of unknown etiology. *Neurosurgery* 1992;30:7–11 CrossRef Medline
 24. Oda S, Shimoda M, Hirayama A, et al. Neuroradiologic diagnosis of minor leak prior to major SAH: diagnosis by T1-FLAIR mismatch. *AJNR Am J Neuroradiol* 2015;36:1616–22 CrossRef Medline
 25. Larsen N, von der Brelie C, Trick D, et al. Vessel wall enhancement in unruptured intracranial aneurysms: an indicator for higher risk of rupture? High-resolution MR imaging and correlated histologic findings. *AJNR Am J Neuroradiol* 2018;39:1617–21 CrossRef Medline
 26. Wang J, Chen H, Sun J, et al. Dynamic contrast-enhanced MR imaging of carotid vasa vasorum in relation to coronary and cerebrovascular events. *Atherosclerosis* 2017;263:420–26 CrossRef Medline
 27. Forget TRJ, Benitez R, Veznedaroglu E, et al. A review of size and location of ruptured intracranial aneurysms. *Neurosurgery* 2001;49:1322–25; discussion 1325–26 CrossRef Medline
 28. Weir B, Disney L, Karrison T. Sizes of ruptured and unruptured aneurysms in relation to their sites and the ages of patients. *J Neurosurg* 2002;96:64–70 Medline
 29. Bijlenga P, Gondar R, Schilling S, et al. PHASES score for the management of intracranial aneurysm: a cross-sectional population-based retrospective study. *Stroke* 2017;48:2105–12 CrossRef Medline
 30. Feng L, Grimm R, Block KT, et al. Golden-angle radial sparse parallel MRI: combination of compressed sensing, parallel imaging, and golden-angle radial sampling for fast and flexible dynamic volumetric MRI. *Magn Reson Med* 2014;72:707–17 CrossRef Medline

Flow-Diversion Treatment of Unruptured Saccular Anterior Communicating Artery Aneurysms: A Systematic Review and Meta-Analysis

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ABSTRACT

BACKGROUND: Flow diversion for anterior communicating artery aneurysms required further investigation.

PURPOSE: Our aim was to analyze outcomes after treatment of anterior communicating artery aneurysms with flow-diverter stents.

DATA SOURCES: A systematic search of 3 data bases was performed for studies published from 2008 to 2018.

STUDY SELECTION: According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, we included studies reporting anterior communicating artery aneurysms treated with flow diversion.

DATA ANALYSIS: Random-effects meta-analysis was used to pool the following: aneurysm occlusion rate, complications, and factors influencing the studied outcomes.

DATA SYNTHESIS: We included 14 studies and 148 unruptured saccular anterior communicating artery aneurysms treated with flow diversion. The long-term complete/near-complete (O'Kelly-Marotta C–D) occlusion rate was 87.4% (91/105; 95% CI, 81.3%–93.6%; $I^2 = 0\%$) (mean radiologic follow-up of 11 months). The treatment-related complication rate was 8.6% (14/126; 95% CI, 4%–13.1%; $I^2 = 0\%$), with morbidity and mortality rates of 3.5% (5/126; 95% CI, 2%–7%; $I^2 = 0\%$) and 2.5% (2/148; 95% CI, 0.3%–5%; $I^2 = 0\%$), respectively. Most complications were periprocedural (12/126 = 7%; 95% CI, 3%–11%; $I^2 = 0\%$). Thromboembolic events were slightly higher compared with hemorrhagic complications (10/126 = 6%; 95% CI, 2%–10%; $I^2 = 0\%$ and 4/126 = 3%; 95% CI, 1%–6%; $I^2 = 0\%$). Branching arteries (A2 or the recurrent artery of Heubner) covered by the stent were occluded in 16% (7/34; 95% CI, 3.5%–28%; $I^2 = 25\%$) of cases. Pre- and posttreatment low-dose and high-dose of antiplatelet therapy was not associated with significantly different complication and occlusion rates.

LIMITATIONS: We reviewed small and retrospective series.

CONCLUSIONS: Flow diversion for unruptured saccular anterior communicating artery aneurysms appears to be an effective alternative treatment for lesions difficult to treat with coiling or microsurgical clipping. The treatment-related complication rate was relatively low. However, larger studies are needed to confirm these results.

ABBREVIATIONS: AcomA = anterior communicating artery; ASA = acetylsalicylic acid; AT = antiplatelet therapy; CP = clopidogrel; IQR = interquartile range; OKM = O'Kelly-Marotta; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Anterior communicating artery (AcomA) aneurysms are among the most common intracranial aneurysms. Determining the best treatment strategy for such lesions is often difficult

because AcomA aneurysms may present a therapeutic challenge for both clipping (deep location, anatomic variability, perforator arteries)¹ and endovascular treatment (wide-neck lesions incorporating branching vessels).² In addition, AcomA aneurysms may have a risk of rupture higher than those in other locations.³ On the basis of their ability to reconstruct the parent artery, the off-label uses of flow-diverter stents are constantly extended, especially for aneurysms with unfavorable anatomy.^{2,4,5} Flow-diversion treatment of complex AcomA aneurysms has been recently reported as an alternative strategy when conventional coiling or stent-assisted coiling is not a feasible option. However, data describing treatment-related outcomes of flow diversion for lesions located at the AcomA region are scanty, and the

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Indicates article with supplemental on-line photos.

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efficacy and safety of this technique remain unclear. Our meta-analysis examined occlusion rates and procedure-related complications of saccular unruptured AcomA aneurysms treated with flow-diverter stents.

MATERIALS AND METHODS

Literature Search

A comprehensive literature search of PubMed, Ovid MEDLINE, and Ovid EMBASE was conducted for studies published from January 2008 to September 2018. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines⁶ were followed. The key words and the detailed search strategy are reported in On-line Table 1, and the studies included in our review are reported in On-line Table 2. The inclusion criterion was the following: studies reporting series with patients with unruptured AcomA aneurysms treated with flow-diverter stents. Exclusion criteria were the following: 1) case reports, 2) review articles, 3) studies published in languages other than English, 4) in vitro/animal studies, and 5) series reporting aneurysms located at the A1 or distal to the AcomA region (A2, A3). In cases of overlapping patient populations, only the series with the largest number of patients or most detailed data were included. Two independent readers screened articles in their entirety to determine eligibility for inclusion. A third author solved discrepancies.

Data Collection

We extracted the following information: 1) technical success rate, 2) occlusion rate, 3) treatment-related complications, and 4) clinical outcome. Occlusion and complication rates were analyzed on the basis of the influence of the following: 1) aneurysm size (saccular aneurysms, small- and medium-sized versus large-giant); 2) patient age (younger versus older than 60 years); 3) type of flow-diverter stents; 4) first treatment versus retreatment; and 5) flow diverter alone versus flow diverter plus coiling.

Complete/near-complete aneurysm occlusion was defined on the basis of the following: O'Kelly-Marotta (OKM) grade⁷ C–D, when digital subtraction angiography follow-up was available or when “complete occlusion” and “neck remnant” were used in the study. Treatment-related complications were divided into the following: 1) periprocedural/early events (within 30 days) and delayed events (after 30 days); 2) transient (asymptomatic events or complete neurologic recovery) and permanent complications (symptomatic events with permanent deficits); and 3) ischemic and hemorrhagic complications. The angiographic outcome of covered arteries (A2 or the recurrent artery of Heubner) was evaluated as the following: 1) arterial narrowing, or 2) arterial occlusion. Finally, good outcome was defined as a modified Rankin Scale score of 0–2 or a Glasgow Outcome Score of 4–5, or it was assumed if the study used the terms “no morbidity,” “good recovery,” or “no symptoms.”

Outcomes

The primary objectives of this study were to define the safety (treatment-related complications, mortality rate, and neurologic outcomes) and the efficacy (technical success rate, angiographic occlusion) of AcomA aneurysms treated with flow diversion. The

secondary objectives were to define the influence of aneurysm, patient, and treatment characteristics on the analyzed outcomes.

Quality Scoring

The Newcastle-Ottawa Scale⁸ was used for the quality assessment of the included studies (details in On-line Tables 3 and 4). The quality assessment was performed by 2 authors independently, and a third author solved discrepancies.

Statistical Analysis

We estimated, from each cohort, the cumulative prevalence (percentage) and 95% confidence interval for each outcome. Heterogeneity of the data was assessed by the Higgins index (I^2), and subsequently, the DerSimonian and Laird random-effects model was applied. The graphic representation was performed with a forest plot. The meta-regression and funnel plot followed by the Egger linear regression test were analyzed, respectively, to evaluate the heterogeneity and bias. To compare the percentages and to calculate the P values, we used a Z -test for 2 proportions. Differences were considered significant at $P < .05$. Meta-analysis was performed with ProMeta-2 (Internovi, Cesena, Italy) and Open-Meta[Analyst] (<http://www.cebm.brown.edu/openmeta/>).

RESULTS

Literature Review

Studies included in our meta-analysis are summarized in On-line Table 2. The search flow diagram is shown in On-line Fig 1.

Fourteen studies and 148 AcomA aneurysms treated with flow-diverter stents were included in our review.

Quality of Studies

Studies included in our review were the following: Eleven studies were retrospective single-center series, whereas 3 studies were prospective multicentric series. The latter studies were rated as “high-quality” studies. Details of the rating of the included studies are reported in On-line Tables 3 and 4.

Patient Population and Aneurysm Characteristics

Overall, 148 patients with unruptured saccular AcomA aneurysms were treated with flow-diverter stents (On-line Table 5). The mean age of patients was 57 years (range, 24–80 years), and the proportion of male patients was 46% (95% CI, 34%–58%). Mean aneurysm size was 6.2 mm (median, 5.5 mm; interquartile range [IQR], 5–7 mm; range, 3–18 mm). The proportion of previously ruptured aneurysms treated with other techniques in the acute phase was 60.4% (55/91; 95% CI, 50%–70%), and the proportion of aneurysms recanalized and retreated with flow-diverter stents was 50.4% (54/107; 95% CI, 41%–59%).

Treatment Characteristics

The most common stent used was the Pipeline Embolization Device (PED; Covidien, Irvine, California) (97/148 = 65.6%; 95% CI, 57%–72%), followed by the Flow-Redirection Endoluminal Device (FRED; MicroVention, Tustin, California) (21/148 = 14.2%; 95% CI, 9%–21%), the Silk flow diverter (Balt Extrusion, Montmorency, France) (18/148 = 12.1%; 95% CI, 7%–18%), and the Surpass stent (Stryker Neurovascular, Kalamazoo, Michigan) (12/148 = 8.1%; 95% CI, 4.4%–13%). The proportion of

Treatment-related outcomes after flow-diversion treatment of AcomA aneurysms

Variables	Results of Systematic Review and Meta-Analysis	No. of Articles	Statistic (95% CI) (I^2)
Angiographic outcomes			
Rate of successful stent deployment	142/145 = 95.5%	13	(92–98) (I^2 = 0%)
Immediate aneurysm occlusion rate (OKM C–D)	5/35 = 14%	4	(4–23) (I^2 = 19%)
Long-term complete/near-complete occlusion rate (OKM C–D)	91/105 = 87.4%	10	(81.3–93.6) (I^2 = 0%)
Long-term complete occlusion rate (OKM D)	66/80 = 84.9%	8	(76.8–93) (I^2 = 12.5%)
Treatment-related complications and clinical outcomes			
Overall treatment-related complications	14/126 = 8.6%	11	(4–13.1) (I^2 = 0%)
Periprocedural/early complications (within 30 days)	12/126 = 7%	11	(3–11) (I^2 = 0%)
Delayed complications (after 30 days)	2/126 = 1.8%	11	(1–5) (I^2 = 0%)
Transient complications	9/126 = 6%	11	(2.7–11) (I^2 = 0%)
Permanent complications	5/126 = 3.5%	11	(2–7) (I^2 = 0%)
Treatment-related mortality	2/148 = 2.5%	14	(0.3–5) (I^2 = 0%)
Overall rate of good neurologic outcome	108/114 = 95%	10	(93–98) (I^2 = 0%)
Type of complications			
Thromboembolic complications	10/126 = 6%	11	(2–10) (I^2 = 0%)
Hemorrhagic complications	4/126 = 3%	11	(1–6) (I^2 = 0%)
Acute in-stent thrombosis	5/126 = 4%	11	(1.3–8) (I^2 = 0%)
Aneurysm rupture after treatment	0/138 = 0%	13	
Chronic in-stent stenosis (>50%)	2/75 = 4.8%	8	(2–9) (I^2 = 0%)
Overall flow changes on covered vessels	12/34 = 28%	4	(1.5–5) (I^2 = 76%)
Rate of narrowing of covered vessel ^a	5/34 = 11%	4	(0.7–20) (I^2 = 8%)
Rate of occlusion of covered vessels ^a	7/34 = 16%	4	(3.5–28) (I^2 = 22%)

^a Symptoms related to flow changes on the covered vessels (A2 or the recurrent artery of Heubner) were reported in 3 cases: 1 case of transitory hemiparesis due slow flow on the covered A2; 1 case of transient facial palsy due to the coverage of the artery of Heubner; and 1 case of asymptomatic stroke in the territory of the artery of Heubner 4 months after treatment.

patients treated with flow diversion plus coiling was 10.2% (10/98; 95% CI, 5.4%–17%), and the proportion of patients treated with multiple stents was 6.7% (10/148; 95% CI, 3.5%–12%). The mean radiologic (DSA) follow-up was 11 months (range, 4–18 months; median, 12 months; IQR, 9.7–12 months), and the mean clinical follow-up was 11 months (range, 6–19 months; median, 12 months; IQR, 6–12 months).

Angiographic Outcomes

The technical success rate was 95.5% (142/145; 95% CI, 92%–98%; I^2 = 0%) (Table). Immediate angiographic occlusion (OKM C–D) after treatment was obtained in 14% (5/35; 95% CI, 4%–23%; I^2 = 19%) of aneurysms. The rate of long-term complete/near-complete occlusion (OKM C–D) was 87.4% (91/105; 95% CI, 81.3%–93.6%; I^2 = 0%). Meta-regression showed a nonsignificant variation of the effect size (P = .278), and the funnel plot, followed by the Egger linear regression test, excludes publication bias (P = .056) (On-line Fig 2). The rate of long-term complete occlusion (OKM D) was 84.9% (66/80; 95% CI, 76.8%–93%; I^2 = 12.5%).

Treatment-Related Complications

The overall complication rate was 8.6% (14/126; 95% CI, 4%–13.1%; I^2 = 0%) (Table). Meta-regression showed a significant decrease in the effect size (P = .443) during the analyzed periods (P = .022), whereas the funnel plot, followed by the Egger linear regression test, excludes publication bias (P = .407) (On-line Fig 3). Periprocedural/early complications were 7% (12/126; 95% CI, 3%–11%; I^2 = 0%). Delayed complications were 1.8% (2/126; 95% CI, 1%–5%; I^2 = 0%). Transient and permanent complications were 6% (9/126; 95% CI, 2.7%–11%; I^2 = 0%) and 3.5% (5/126; 95% CI, 2%–7%; I^2 = 0%), respectively.

Overall, ischemic/thromboembolic, and hemorrhagic events were 6% (10/126; 95% CI, 2%–10%; I^2 = 0%) and 3% (4/126; 95% CI, 1%–6%; I^2 = 0%), respectively. Hemorrhagic complications were related to intracerebral hemorrhages during the periprocedural period. In only 1 case was the intraparenchymal hematoma associated with permanent sequelae. The rate of acute in-stent thrombosis was 4% (5/126; 95% CI, 1.3%–8%; I^2 = 0%), whereas chronic in-stent stenosis (>50%) was 4.8% (2/75; 95% CI, 2%–9%; I^2 = 0%). There were no cases of aneurysm rupture after treatment during follow-up.

The overall rate of flow modifications of vessels covered by flow diverters (A2 or artery of Heubner) was 28% (12/34; 95% CI, 1.5%–5%; I^2 = 76%). The rate of occlusion of covered arteries during follow-up was 16% (7/34; 95% CI, 3.5%–28%; I^2 = 22%), whereas the rate of arterial narrowing was 11% (5/34; 95% CI, 0.7%–20%; I^2 = 8%). Symptoms related to flow changes on the covered A2 or the recurrent artery of Heubner were reported in 3 cases: 1 case of transitory hemiparesis due to slow flow on the covered A2 immediately after stent deployment, 1 case of transient facial palsy due to the coverage of the artery of Heubner, and 1 case of an asymptomatic ischemic lesion on the territory of the artery of Heubner that was detected with the MR imaging 4 months after treatment.

Treatment-related mortality was 2.5% (2/148; 95% CI, 0.3%–5%; I^2 = 0%), and the rate of good neurologic outcome was 95% (108/114; 95% CI, 93%–98%; I^2 = 0%).

Factors Related to Aneurysm Occlusion

Overall, the occlusion rate was comparable among patients younger-versus-older than 60 years (P = .7), type of flow-diverter stent, flow diversion as a first treatment or retreatment of recana-

lized aneurysms, and flow diverter alone versus flow diverter plus coiling. There was a trend toward higher occlusion rates for aneurysms of small and medium-sized versus large-giant (32/35 = 90%; 95% CI, 80%–95%; $I^2 = 0\%$ versus 11/14 = 70%; 95% CI, 50%–85%; $I^2 = 42\%$) ($P = .07$).

Factors Related to Complications after Treatment

There was no statistically significant difference in complication rates in relation to patient age, first treatment versus retreatment, and flow diverter with-versus-without coiling. Although not statistically significant, complications were higher for large/giant aneurysms (3/14 = 20%; 95% CI, 5%–30%; $I^2 = 0\%$) compared to small/medium sized lesions (2/35 = 7%; 95% CI, 2%–16%; $I^2 = 0\%$). The PED was associated with 12% complications (9/75; 95% CI, 6%–21%); the FRED stent, with 14% (3/21; 95% CI, 4%–30%); and the Silk stent, with 6% (1/17; 95% CI, 2%–25%). Only 1 series described treatment-related complications after using the Surpass stent, reporting no adverse events (On-line Table 6).

Relationship between Antiplatelet Therapy and Treatment-Related Outcomes

Antiplatelet therapy (AT) before treatment was dichotomized into 2 groups: acetylsalicylic acid (ASA), 81–160 mg, + clopidogrel (CP), 75 mg, and ASA, 250–325 mg, + CP, 75 mg, 3–7 days before treatment. The rate of periprocedural complications was 5% (1/20; 95% CI, 4%–15%; $I^2 = 0\%$) and 6% (3/40; 95% CI, 2%–14%; $I^2 = 0\%$) ($P = .8$), respectively (On-line Tables 7–9).

AT therapy after treatment was dichotomized into the following groups: ASA, 81–100 mg, + CP, 75 mg, and ASA, 160–300 mg, + CP, 75 mg, for 3–6 months. The rates of delayed complications were 0% (0/23) and 3.5% (1/28; 95% CI, 3%–11%; $I^2 = 0\%$) ($P = .36$), respectively. Long-term occlusion rates (OKM grades C–D) were 94.5% (28/29; 95% CI, 86%–98%; $I^2 = 0\%$) and 88% (17/19; 95% CI, 76%–94%; $I^2 = 0\%$) ($P = .41$), respectively.

In addition, treatment-related outcomes were evaluated on the basis of the duration of the dual AT: “short” duration of the dual AT (ASA + CP until 3 months) versus “long” duration of the dual AT (at least until 6 months). In both groups, ASA was continued for about 1 year or for life. Overall, treatment-related complications were 5% (2/30; 95% CI, 3%–12%; $I^2 = 0\%$) and 6.5% (5/54; 95% CI, 4%–13%; $I^2 = 0\%$) among the groups with short and long duration of the dual AT, respectively ($P = .77$). Complete/near-complete occlusion rates were 93% (25/27; 95% CI, 83%–98%; $I^2 = 0\%$) and 91% (20/22; 95% CI, 82%–98%; $I^2 = 0\%$), among the groups with short and long duration of the dual AT, respectively ($P = .8$).

Study Heterogeneity

Heterogeneity was low for all except 1 of the analyzed outcomes (the overall rate of flow changes among covered vessels).

DISCUSSION

When we combined data from 14 studies, our meta-analysis underlined several important findings related to the flow-diversion treatment of aneurysms originating from the AcomA region. In general, our results demonstrated that complex unruptured

AcomA aneurysms can be successfully treated with flow-diverter stents with a high rate of long-term angiographic occlusion and an acceptable rate of treatment-related complications.

Angiographic Outcomes

Successful stent deployment was achieved in 95.5% of cases, demonstrating that flow diversion is a straightforward technique even in complex anatomic situations such as the AcomA region. Given that aneurysm occlusion with flow-diverter stents is a progressive process, only 14% of aneurysms were occluded immediately after treatment, whereas 87% and 85% of the lesions presented with adequate (OKM C–D) and complete (OKM D) occlusion during 1 year of follow-up, respectively. In a large meta-analysis of nearly 1500 AcomA aneurysms treated endovascularly (excluding flow-diverter stents), Fang et al⁹ reported a quite high rate of immediate occlusion (88%). However, although their immediate occlusion rate was higher compared with our results, complete/near-complete occlusion during 6 months of follow-up was 85%, underlining that long-term angiographic outcomes after flow diversion for AcomA aneurysms are comparable with other endovascular techniques.

Recently, intrasaccular flow disruption with the Woven EndoBridge device (WEB; Sequent Medical, Aliso Viejo, California) is increasingly used with promising results. However, series focusing on AcomA aneurysms showed approximately a 60% long-term adequate occlusion after treatment with the WEB.¹⁰ In addition, emerging devices for neck protection, such as pCONus (phenox, Bochum, Germany) stents, have been developed to treat wide-neck bifurcation aneurysms. A recent series of 36 AcomA aneurysms treated with the pCONus showed an 80% complete/near-complete occlusion rate.¹¹ Finally, Y-stent-assisted coiling of AcomA aneurysms appears to be associated with 85%–88%^{12,13} complete/near-complete occlusion, though this technique is, in general, technically more complex. Accordingly, Ko et al¹² reported 9 AcomA aneurysms treated with Y-stent placement. All of them were occluded during follow-up, but 2 patients experienced acute in-stent thrombosis and 1 patient had iatrogenic subarachnoid hemorrhage related to aneurysm perforation.

In our study, flow diversion was also effective for the treatment of recanalized AcomA aneurysms (On-line Table 6). Lin et al¹⁴ reported a small series of 6 AcomA aneurysms with recurrences after clipping; occlusion was achieved in 5 of them without treatment-related complications. This outcome is in accordance with those in larger series analyzing treatment-related outcomes of flow diversion used as a retreatment strategy.¹⁵ In addition, we found comparable angiographic results among AcomA aneurysms treated with flow diverters alone or in conjunction with coiling. When we investigated the literature, this result appears contradictory: Szikora et al,¹⁶ in a series of 19 wide-neck aneurysms, reported no differences in occlusion rates among lesions treated with or without coil packing, whereas Lin et al¹⁷ showed higher rates of complete occlusion in the group of aneurysms treated with the PED + coils. However, most aneurysms included in our review were unruptured, small lesions (mean size, 6 mm), and additional coiling was not mandatory in most cases.

The device configuration was rarely reported in the included series, and outcome comparison between ipsilateral A1–A2 and

ipsilateral A1 to contralateral A2 stent configuration was not possible. In the largest available series of AcomA aneurysms treated with flow-diverter stents, Colby et al² described 41 patients treated with PEDs deployed from the ipsilateral A1 to the ipsilateral A2 in 94% of patients and from the A1 to the contralateral A2 in the remaining 6% of patients. The authors reported 85% complete/near-complete occlusion and a 9% complication rate.

Treatment-Related Complications

Treatment-related morbidity after flow diversion in small or distal vessels is reported to be close to 10%.^{4,5,18} However, flow diversion for aneurysms arising from the AcomA complex should be considered separately due to the angioarchitecture and flow dynamics of this region that present the following: 1) frequent anatomic variations (such as the asymmetry of the A1 segments); 2) several perforating arteries supplying important structures such as the optic chiasm, the anterior hypothalamus, and the anterior perforated substance; and 3) the recurrent artery of Heubner (in general originating from the A1–A2 junction), which perfuses the striatum and the anterior limb of the internal capsule.¹ Accordingly, injury to these arteries may result in a wide range of serious neurologic sequelae, including memory disorders, changes of personality, electrolyte imbalance, and motor deficits.¹ When we investigated the literature, our meta-analysis found 8.6% of complications related to flow-diversion treatment of AcomA aneurysms. Most of them occurred in the periprocedural period after treatment (7%). Permanent deficits and mortality related to the treatment were 3.5% and 2.5%, respectively. Not surprising, ischemic events were the most common complications (6%), together with acute in-stent thrombosis (4%). Gawlitza et al¹⁹ reported 2 cases of transient ischemic complications (1 case of facial palsy and 1 case of lacunar infarct detected at MR imaging) related to the covered artery of Heubner. In a series of 9 AcomA aneurysms, Pierot et al²⁰ reported 1 case of thromboembolism and 1 case of flow-diverter occlusion 4 days after treatment without permanent neurologic deficits.

Another important concern is the patency of the arteries covered with flow diverters.²¹ Despite very few studies focused on the angiographic outcome of the covered A2 segment (or main branching vessels such as the artery of Heubner), we found a 16% occlusion rate of jailed arteries during follow-up. Pistocchi et al²² reported 5 cases of occlusion and 4 cases of slow flow of the covered A2 segment among 14 patients with AcomA aneurysms treated with the Silk stent. In this series, only 1 patient experienced a transitory hemiparesis due to the sluggish flow on the covered A2, which regressed after blood pressure augmentation. Saleme et al,²³ in a series of 9 AcomA aneurysms treated with the PED, described 2 cases of asymptomatic A2 occlusion during follow-up. In a recent meta-analysis of nearly 1200 supraclinoid internal carotid artery vessels covered with flow-diverter stents, the overall rate of occlusion was 7%, with important differences among the ophthalmic artery (6%), anterior choroidal artery (1%), and posterior communicating artery (20%),²¹ with approximately 1% symptomatic occlusions. One of the most important mechanisms related to branch preservation is the pressure gradient between the artery and its covered branches. In general, when the occlusion progresses slowly, the collateral circulation can eff-

iciently supply the territory of the jailed artery and the occlusion can be tolerated in most cases.

Finally, meta-regression showed a significant ($P = .022$) decrease of the complication rate during 7 years (from 2011 to 2018), probably due to improvement of the operator experience, 3D angiographic images, and better case selection and posttreatment patient management.

Treatment-Related Outcomes Based on the AT

We assessed pre- and posttreatment antiplatelet regimens dichotomizing the AT into 2 groups: pretreatment (3–7 days) low dose (ASA, 81–160 mg, + CP, 75 mg) and high dose (ASA, 250–325 mg, + CP, 75 mg) AT. Accordingly, we investigated the rate of intraprocedural/periprocedural complications showing 5% and 6% of treatment-related complications for low-dose and high-dose AT, respectively ($P = .8$).

Similarly, there were not statistically significant differences in complication and occlusion rates among groups with low-dose (ASA, 81–100 mg, + CP, 75 mg) and high-dose (ASA, 160–300 mg, + CP, 75 mg) AT regimens administered during follow-up.

Our results are in accordance with a recent meta-analysis discussing the AT regimen used before and after using the PED. In this study, there was a lack of relationship between patients who received low- versus high-dose pre-PED ASA in terms of thromboembolic and hemorrhagic complications.²⁴

Strengths and Limitations

Our study has several limitations. Series were often retrospective studies and small single-institution experiences. Because of the small number of cases, the comparison among subgroups may not provide power to show a statistically significant difference among the studied outcomes. Outcome comparison between ipsilateral A1–A2 and transcommunicating (from the A1 to the contralateral A2) stent configurations was not possible because of the scanty data. For the same reason, the asymmetry of the A1 segment was not evaluated. However, publication bias was reasonably excluded, and our review is the first and the largest study focusing on the flow-diversion treatment of AcomA aneurysms.

CONCLUSIONS

On the basis of our meta-analysis, flow diversion for unruptured saccular AcomA aneurysms appears to be an effective alternative treatment for lesions difficult to treat with coiling or microsurgical clipping. The treatment-related complication rate was relatively low, considering that flow-diverter stents are, in general, used for complex aneurysms of the AcomA region. However, larger studies are needed to confirm the safety and efficacy of this procedure.

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REFERENCES

1. Hernesniemi J, Dashti R, Lehecka M, et al. **Microneurosurgical management of anterior communicating artery aneurysms.** *Surg Neurol* 2008;70:8–28; discussion 29 CrossRef Medline
2. Colby GP, Bender MT, Lin LM, et al. **Endovascular flow diversion for treatment of anterior communicating artery region cerebral**

- aneurysms: a single-center cohort of 50 cases. *J Neurointerv Surg* 2017;9:679–85 CrossRef Medline
3. Bijlenga P, Ebeling C, Jaegersberg M, et al; @neurIST Investigators. Risk of rupture of small anterior communicating artery aneurysms is similar to posterior circulation aneurysms. *Stroke* 2013;44:3018–26 CrossRef Medline
4. Cagnazzo F, Mantilla D, Lefevre PH, et al. Treatment of middle cerebral artery aneurysms with flow-diverter stents: a systematic review and meta-analysis. *AJNR Am J Neuroradiol* 2017;38:2289–94 CrossRef Medline
5. Cagnazzo F, Cappucci M, Dargazanli C, et al. Treatment of distal anterior cerebral artery aneurysms with flow-diverter stents: a single-center experience. *AJNR Am J Neuroradiol* 2018;39:1100–06 CrossRef Medline
6. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg* 2010;8:336–41 CrossRef Medline
7. O'Kelly CJ, Krings T, Fiorella D, et al. A novel grading scale for the angiographic assessment of intracranial aneurysms treated using flow diverting stents. *Interv Neuroradiol* 2010;16:133–37 CrossRef Medline
8. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Ottawa: Ottawa Hospital Research Institute; 2011. http://www.evidencebasedpublichealth.de/download/Newcastle_Ottawa_Scale_Pope_Bruce.pdf. Accessed September 5, 2018
9. Fang S, Brinjikji W, Murad MH, et al. Endovascular treatment of anterior communicating artery aneurysms: a systematic review and meta-analysis. *AJNR Am J Neuroradiol* 2014;35:943–47 CrossRef Medline
10. Gherasim DN, Gory B, Sivan-Hoffmann R, et al. Endovascular treatment of wide-neck anterior communicating artery aneurysms using WEB-DL and WEB-SL: short-term results in a multicenter study. *AJNR Am J Neuroradiol* 2015;36:1150–54 CrossRef Medline
11. Labeyrie PE, Gory B, Aguilar-Perez M, et al. The pCONus device for treatment of complex wide-neck anterior communicating artery aneurysms. *World Neurosurg* 2017;101:498–505 CrossRef Medline
12. Ko JK, Han IH, Cho WH, et al. Crossing Y-stent technique with dual open-cell stents for coiling of wide-necked bifurcation aneurysms. *Clin Neurol Neurosurg* 2015;132:54–60 CrossRef Medline
13. Limbucci N, Renieri L, Nappini S, et al. Y-stent assisted coiling of bifurcation aneurysms with Enterprise stent: long-term follow-up. *J Neurointerv Surg* 2016;8:158–62 CrossRef Medline
14. Lin LM, Iyer RR, Bender MT, et al. Rescue treatment with Pipeline embolization for postsurgical clipping recurrences of anterior communicating artery region aneurysms. *Interv Neurol* 2017;6:135–46 CrossRef Medline
15. Daou B, Starke RM, Chalouhi N, et al. The use of the Pipeline Embolization Device in the management of recurrent previously coiled cerebral aneurysms. *Neurosurgery* 2015;77:692–97; discussion 697 CrossRef Medline
16. Szikora I, Berentei Z, Kulcsar Z, et al. Treatment of intracranial aneurysms by functional reconstruction of the parent artery: the Budapest experience with the Pipeline Embolization Device. *AJNR Am J Neuroradiol* 2010;31:1139–47 CrossRef Medline
17. Lin N, Brouillard AM, Krishna C, et al. Use of coils in conjunction with the Pipeline embolization device for treatment of intracranial aneurysms. *Neurosurgery* 2015;76:142–49 CrossRef Medline
18. Yan Y, Zhu D, Tang H, et al. Safety and efficacy of flow diverter treatment for aneurysm in small cerebral vessels: a systematic review and meta-analysis. *World Neurosurg* 2018;115:54–64 CrossRef Medline
19. Gawlitza M, Januel AC, Tall P, et al. Flow diversion treatment of complex bifurcation aneurysms beyond the circle of Willis: a single-center series with special emphasis on covered cortical branches and perforating arteries. *J Neurointerv Surg* 2016;8:481–87 CrossRef Medline
20. Pierot L, Spelle L, Berge J, et al. Feasibility, complications, morbidity, and mortality results at 6 months for aneurysm treatment with the Flow Re-Direction Endoluminal Device: report of SAFE study. *J Neurointerv Surg* 2018;10:765–70 CrossRef Medline
21. Cagnazzo F, Lefevre PH, Mantilla D, et al. Patency of the supraclinoid internal carotid artery branches after flow-diversion treatment: a meta-analysis. *J Neuroradiol* 2018 Aug 9. [Epub ahead of print] CrossRef Medline
22. Pistocchi S, Blanc R, Bartolini B, et al. Flow diverters at and beyond the level of the circle of Willis for the treatment of intracranial aneurysms. *Stroke* 2012;43:1032–38 CrossRef Medline
23. Saleme S, Iosif C, Ponomarjova S, et al. Flow-diverting stents for intracranial bifurcation aneurysm treatment. *Neurosurgery* 2014;75:623–31; quiz 631 CrossRef Medline
24. Texakalidis P, Bekelis K, Atallah E, et al. Flow diversion with the Pipeline Embolization Device for patients with intracranial aneurysms and antiplatelet therapy: a systematic literature review. *Clin Neurol Neurosurg* 2017;161:78–87 CrossRef Medline
25. Toma AK, Robertson F, Wong K, et al. Early single centre experience of flow diverting stents for the treatment of cerebral aneurysms. *Br J Neurosurg* 2013;27:622–28 CrossRef Medline
26. Clarencon F, Di Maria F, Gabrieli J, et al. Flow diverter stents for the treatment of anterior cerebral artery aneurysms: safety and effectiveness. *Clin Neurol Neurosurg* 2017;27:51–56 CrossRef Medline
27. Dabus G, Grossberg JA, Cawley CM, et al. Treatment of complex anterior cerebral artery aneurysms with Pipeline flow diversion: mid-term results. *J Neurointerv Surg* 2017;9:147–51 CrossRef Medline
28. Möhlenbruch MA, Kizilkilic O, Killer-Oberpfalzer M, et al. Multi-center experience with FRED Jr flow re-direction endoluminal device for intracranial aneurysms in small arteries. *AJNR Am J Neuroradiol* 2017;38:1959–65 CrossRef Medline
29. Wakhloo AK, Lylyk P, de Vries J, et al; Surpass Study Group. Surpass flow diverter in the treatment of intracranial aneurysms: a prospective multicenter study. *AJNR Am J Neuroradiol* 2015;36:98–107 CrossRef Medline
30. Lin LM, Bender MT, Colby GP, et al. Use of a next-generation multi-durometer long guide sheath for triaxial access in flow diversion: experience in 95 consecutive cases. *J Neurointerv Surg* 2018;10:137–42 CrossRef Medline
31. Sultan-Qurraie A, Sattar A, Wazni W, et al. Anterior communicating artery aneurysm treatment with the Pipeline Embolization Device: a single-center experience with long-term follow-up. *Interv Neurol* 2017;6:126–34 CrossRef Medline
32. Lin LM, Jiang B, Bender MT, et al. 47 consecutive cases of Pipeline Flex flow diversion utilizing a novel large-bore intracranial intermediate catheter: nuances and institutional experience with the Syphontrak. *Interv Neurol* 2018;7:153–63 CrossRef Medline

Endovascular Treatment of Unruptured MCA Bifurcation Aneurysms Regardless of Aneurysm Morphology: Short- and Long-Term Follow-Up

F. Hagen, C.J. Maurer, and A. Berlis



ABSTRACT

BACKGROUND AND PURPOSE: The optimal treatment of unruptured middle cerebral aneurysms is still under debate. Although today almost any aneurysm can be treated endovascularly, there is a lack of data comparing endovascular and microsurgical repair of MCA aneurysms. The aim of our analysis is to provide data on the efficacy, clinical outcome, complications and re-treatment rates of endovascular treatment of this subtype of aneurysms.

MATERIALS AND METHODS: Between May 2008 and July 2017, endovascular treatment of 1184 aneurysms in 827 patients was performed in our department. Twenty-four percent of these aneurysms were located at the MCA, and 150 unruptured MCA bifurcation aneurysms treated with coiling, stent-assisted-coiling, or endovascular flow diverter (WEB device) were identified for this retrospective data analysis. Ninety-six percent of all aneurysms, ruptured and unruptured, were treated by an endovascular approach, which yields a low selection bias for aneurysms suitable for endovascular treatment. Follow-up examinations were performed after 12 and 36 months and then every 1–3 years after embolization. Procedures were analyzed for periprocedural complications, outcome, and retreatment rate of the WEB ($n = 38$) and coiling with ($n = 45$) or without stent assistance ($n = 67$).

RESULTS: The procedure-associated good clinical outcome ($mRS \leq 2$) was 89.9%, and the mortality rate was 2.7%. Short-term follow-up good clinical outcome/mortality rates were 91.3%/0.7%. At discharge, 137 patients had an mRS of 0–2 (91.3%) and 13 had an mRS of 3–6 (8.7%). The retreatment rate was significantly higher in the WEB group (21.1%) compared with the coiling group with (5.9%) or without (2.2%) stent placement ($P < .05$).

CONCLUSIONS: Regardless of the architecture of MCA bifurcation aneurysms, the endovascular treatment can be performed with low morbidity/mortality rates. The higher retreatment rate in the WEB group correlates with the learning curve in choosing the right device size.

ABBREVIATION: ASA = acetylsalicylic acid

Since the publication of the results of the International Subarachnoid Aneurysm Trial (ISAT), in 2002, endovascular treatment of ruptured intracranial aneurysms has been regarded as the treatment of choice.¹ Later, the International Study of Unruptured Intracranial Aneurysms confirmed that the treatment of unruptured aneurysms is feasible by endovascular treatment as well.² Because MCA aneurysms were underrepresented in the ISAT study, debate remains about the best way to treat these aneurysms, whether ruptured or not. Additionally, a prospective randomized study of the treatment of unruptured aneurysms,

which objectively evaluates outcomes, does not exist, to our knowledge.

To date, microsurgical clipping of unruptured middle cerebral artery aneurysms is the treatment of choice. One reason in favor of clipping versus coiling is that the use of additional devices such as microstents requires platelet inhibition, which can lead to long-term complications. Recent publications demonstrate good clinical outcomes and low complication rates for both methods.^{3,4}

An essential point is that when we compared the 2 methods, the investigation objective is the same. Therefore, we present our endovascular treatment data of MCA bifurcation aneurysms from 2 hospitals (Klinikum Augsburg and Schoen Klinik, Vogtareuth, Germany). The treatment in both hospitals was performed by the neurointerventionalists from Klinikum Augsburg, since our neurointerventional department has a cooperation with the Schoen Klinik in Vogtareuth. Because in our setting almost all aneurysms (>96%), ruptured or not, were treated by endovascular means, there is a low

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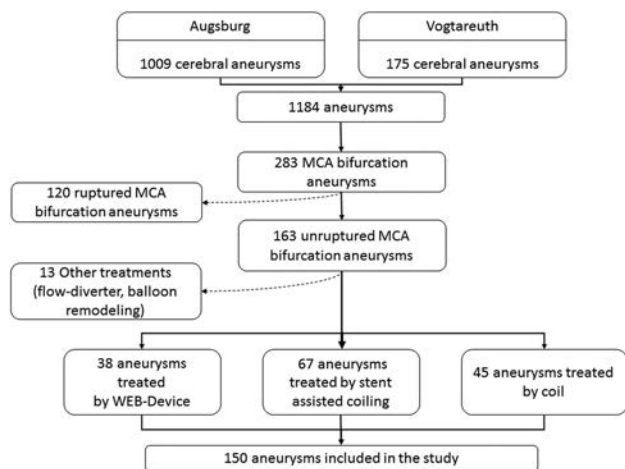


FIG 1. Study design.

selection bias for aneurysms suitable for endovascular therapy. We present our real-world data of endovascular treatment of MCA aneurysms during a 9-year period using coils, stent-assisted coiling, and an endosaccular flow diverter (Woven EndoBridge, WEB; Sequent Medical, Aliso Viejo, California). Specifically, the WEB device was designed to effectively treat wide-neck, symmetric, cylindriciform, or spheric aneurysms by an endovascular approach.

Additionally, the aim of our analysis was to evaluate whether the use of the WEB versus coils may shorten the intervention time and improve the outcome with regard to long-term occlusion and/or the retreatment rate.

MATERIALS AND METHODS

In this retrospective analysis, patients treated for an unruptured bifurcation aneurysm of the middle cerebral artery between May 2008 and July 2017 were included. A total of 1184 aneurysms in 827 patients had been treated by an endovascular technique during this time in our institution. This number corresponds to 96% of all aneurysms treated in both centers during this period. The other 4%, corresponding to 50 aneurysms (12 MCA aneurysms), were patients with intracerebral hemorrhage and emergency evacuation of space-occupying parenchymal hemorrhage and simultaneous clipping of the aneurysms. In elective cases, the patient's choice of clipping was the reason for nonendovascular treatment. There was no treatment failure or crossover from endovascular therapy to clipping.

About 24% (242/1009 in Augsburg and 42/175 in Vogtareuth) of all endovascularly treated aneurysms were located at the MCA bifurcation. All patients were treated by neuroradiologists from the neuroradiology department of Augsburg (Germany) (Fig 1).

Aneurysms were qualified as the coil group if they had been treated by coils or by stent-assisted coiling. Aneurysms were included to the WEB group if ≥ 1 WEB device had been used. Patients treated with other devices such as flow diverters or remodeling balloons were excluded due to the low number, as well as aneurysms that were not located at the MCA bifurcation such as the proximal M1 or distal M2–M4 segments. According to our follow-up protocol, 3–6 months after treatment a combination of MR imaging and MR angiography, including TOF and contrast-enhanced MRA (Avanto/Aera, 1.5T for both; Siemens, Erlangen, Germany) and/or conven-

tional digital subtraction angiography (biplane Artis zee, Siemens; or biplane Allura Xper FD20/20, Philips Healthcare, Best, the Netherlands), was performed. If no treatment was necessary, standard follow-up imaging consisted of MR imaging and MRA 18 months, 3 years, and 5 years after treatment.

Aneurysm Treatment

Total treatment time includes the period from general anesthesia to extubation of the patient, including complete diagnostic angiography of all cerebral supplying vessels. Heparin (5000 IU IV) was given immediately before the start of endovascular treatment to prevent thromboembolic events. Most of the patients were pretreated 5 days before the procedure with double antiaggregation with aspirin (ASA) (100 mg) and an adenosine-diphosphate receptor inhibitor (clopidogrel, 75 mg). The day before treatment, platelet inhibition was tested using the Multiplate Analyzer (Roche Diagnostics, Mannheim, Germany). Patients with an insufficient platelet inhibition by clopidogrel in the Multiplate Analyzer test received a loading dose of ticagrelor (180 mg) followed by ticagrelor (90 mg) 2 times daily.

Retreatment

If relevant recanalization was detected at follow-up imaging, a retreatment strategy was proposed to our patients. All of them accepted endovascular retreatment.

Complications

The electronic medical files were screened for complications related to the intervention, such as vessel dissections, thromboembolic events, vasospasms, hemorrhages, and infarctions, as well as mRS, death on discharge, and follow-up.

Statistical Analysis

Statistical analysis was performed using SPSS (Release 22.0.0; IBM, Armonk, New York). Analyses included descriptive statistics, χ^2 and Fisher exact tests, and the Kruskal-Wallis H test with 3 independent samples. Graphics were designed by Excel 2017 (Microsoft, Redmond, Washington).

According to the guidelines of the local ethics committee, no further approval was necessary for this retrospective analysis.

RESULTS

We included 150 unruptured aneurysms at the MCA bifurcation in our final analysis. Thirty-eight aneurysms were treated by WEB devices, and 112 aneurysms, by coiling or stent-assisted coiling. In the coiling group, 45 aneurysms were treated by coils alone and 67 aneurysms were treated by stent-assisted coiling using 1 ($n = 55$) or >1 self-expanding microstent ($n = 12$). There was no significant difference in the distribution of age, sex, and comorbidities such as arterial hypertension, diabetes, or smoking (Table 1).

All treated aneurysms were <25 mm. Aneurysm size was significantly larger in the WEB group. Fifty percent of all aneurysms in the WEB group measured between 8 and 15 mm, whereas in the coil group, only 25% were >7 mm. Accordingly, the mean neck size in the WEB group (4.46 ± 1.26 mm) was larger than that in the coiling group (2.90 ± 1.00 mm) and in the stent-assisted coiling group (3.9 ± 1.5 mm) ($P < .05$) (Table 2).

Table 1: Demographic data

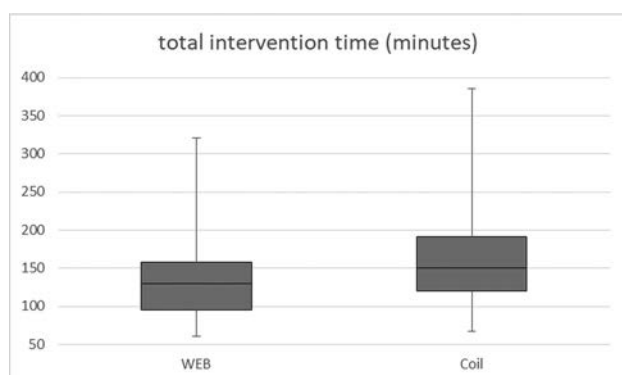
	Coil Group			Significance
	Coiling (n = 45)	Stent-Assisted Coiling (n = 67)	WEB Group (n = 38)	
Age (mean) (yr)	54.6 ± 10.5	55.7 ± 10.8	59.8 ± 11.7	.071 ^a
Sex (No.)				
Male	12 (26.7%)	17 (25.4%)	13 (34.2%)	.638 ^b
Female	33 (73.3%)	50 (74.6%)	25 (65.8%)	
Hypertension (No.)	24 (53.3%)	38 (65.7%)	25 (65.8%)	.497 ^b
Diabetes (No.)	1 (2.2%)	7 (10.4%)	2 (5.3%)	.254 ^b
Smoker (No.)	16 (35.6%)	30 (44.8%)	17 (44.3%)	.611 ^b

^a Kruskal-Wallis H test.^b Fisher exact test.**Table 2: Aneurysm characteristics**

	Coil Group			Significance
	Coiling (n = 45)	Stent-Assisted Coiling (n = 67)	WEB Group (n = 38)	
Aneurysm size (No.)				
0–7 mm	37 (82.2%)	47 (70.1%)	19 (50.0%)	.014 ^a
8–15 mm	7 (15.6%)	16 (23.9%)	19 (50.0%)	
16–25 mm	1 (2.2%)	4 (6.0%)	0 (0.0%)	
>25 mm	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Aneurysm neck (mean) (mm)	2.9 ± 1.0	3.9 ± 1.5	4.46 ± 1.26	.000 ^b
Aspect ratio (dome/neck) (mean)	3.29 ± 1.48	2.60 ± 0.98	2.55 ± 1.00	.005 ^b
Side (No.)				
Right	20 (44.4%)	36 (53.7%)	27 (71.1%)	.050 ^b
Left	25 (55.6%)	31 (46.3%)	11 (28.9%)	
Partially thrombosed (No.)	2 (4.4%)	2 (3.0%)	3 (7.8%)	1.000 ^c

^a χ^2 linear by linear.^b Kruskal-Wallis H test.^c Fisher exact test.**Table 3: Procedural and related complications**

	Coil Group			Significance
	Coiling (n = 45)	Stent-Assisted Coiling (n = 67)	WEB Group (n = 38)	
Procedural time (mean) (min)	155.5 ± 68.2	165.1 ± 54.3	136.3 ± 55.8	.018 ^a
Total device per aneurysm implanted (mean)	3.8 ± 2.4	7.3 ± 5.8	1.0 ± 0.0	.000 ^a
Complication rate (No.) according to Table 4	3 (6.7%)	5 (7.4%)	3 (7.9%)	1.000 ^b

^a Kruskal-Wallis H test.^b Fisher exact test.**FIG 2.** Total intervention time by technique.

The procedural time differed significantly in the 3 groups (136.3 ± 55.8 minutes in the WEB group versus 155.5 ± 68.2 minutes in the coiling group versus 165.1 ± 54.3 minutes in the stent-assisted coiling group; Table 3 and Fig 2). A total of 578 coils and 85 stents (Neuroform 3, Neuroform Atlas, Stryker Neurovascular, Kalamazoo, Michigan; and LVIS Jr, MicroVention, Tustin, California) were used in the treatment of the MCA bifurcation aneurysms.

Seven Multiplate Analyzer tests were missing in the electronic medical files. Eleven complications occurred during or immediately after the intervention. Seven (63.6%) were thromboembolic events, 3 of which occurred despite double antiaggregation and a sufficient platelet inhibition as tested by the Multiplate Analyzer. One infarction without thrombus detection during angiography occurred despite positive findings on the Multiplate Analyzer test. Two MCA ruptures and 1 hemodynamically relevant vasospasm took place in the coil group. No significant differences were found in the clinical outcome indicated by the modified Rankin Scale on discharge or in the complication rate (Table 4). The mRS at discharge had mean values of 0.66 (WEB), 1.50 (coils), and 4.25 (stent-assisted coiling) in the 11 patients with procedure-related complications (Table 4).

The mean follow-up period was 22.3 ± 16.7 months in the WEB group, 38.9 ± 26.8 months for the coiling group, and 29.9 ± 23.4 months for the stent-assisted coiling group ($P = .024$). A significantly higher reintervention rate in the WEB group was noticed; 21.1% of the aneurysms had to be retreated in the WEB group compared with 4.5% in the coil

group ($P = .002$). Twelve incompletely treated aneurysms were detected 6 months after the intervention. One aneurysm was detected and retreated after 24 months. At discharge, 126 patients had an mRS of 0 (84%); 11, an mRS of 1–2 (7.3%); and 13, an mRS of 3–6 (8.7%). No statistical significance was found for delay of the procedure, mRS at discharge, or the long-term mRS scores among the 3 groups. A significant difference was found for the follow-up period and retreatment rate (Table 5).

Thirteen aneurysms were retreated after an endovascular intervention; 8 aneurysms, after a WEB device employment; and 5 aneurysms, after coiling or stent-assisted coiling. The mean neck size was 4.35 ± 1.97 mm in the coil-group and 5.38 ± 1.14 mm in the WEB group (Table 6).

Thirty-eight unruptured MCA bifurcation aneurysms were

Table 4: Complications and outcome

Patient No.	Complication	Hospitalization Time (days)	mRS at Discharge	mRS Long-Term/months	Antiaggregation
WEB group					
65	Ischemia due to local thrombus	8	0	0/12	Simple
92	Occlusion of external iliac artery	9	0	3/48	Simple
121	Ischemia due to local thrombus	2	2	1/6	Simple
Coil group					
Coiling					
6	Aneurysm rupture	17	0	0/36	Simple
37	Ischemia due to local thrombus	11	3	2/12	Double
179	Ischemia due to local thrombus	4	0	1/3	Simple
Stent-assisted coiling					
36	Ischemia due to local thrombus	11	3	2/12	Double
45	Aneurysm rupture	24	6	–	Double
99	Infarction without thrombus detection	8	4	3/12	Double
116	Ischemia due to local thrombus	8	4	4/36	Double
158	Relevant vasospasm	8	3	0/12	Double

Table 5: Follow-up and reintervention rate

	Coil Group		WEB Group (n = 38)	Significance
	Coiling (n = 45)	Stent-Assisted Coiling (n = 67)		
Follow-up-period (mean) (mo)	38.9 ± 26.8	29.9 ± 23.4	22.3 ± 16.7	.024 ^a
Rate of retreatment (No.)	1 (2.2%)	4 (5.9%)	8 (21.1%)	.014 ^b
Delay of retreatment after procedure (mean) (mo)	12 ± 0.0	9.8 ± 9.6	4.5 ± 1.6	.187 ^a
mRS (discharge) (mean)	0.3 ± 0.8	0.6 ± 1.4	0.2 ± 0.6	.283 ^a
Good clinical outcome at discharge (mRS ≤ 2) (No.)	42 (93.3%)	58 (86.6%)	37 (97.4%)	.186 ^b
Death (No.)	0	1	0	1.000 ^b
Clinical outcome (No.)				
mRS at last follow-up (No.)				
0	33 (84.6%)	38 (73.1%)	32 (88.9%)	.164 ^b
1	3 (7.7%)	2 (3.9%)	2 (5.6%)	
2	1 (2.6%)	3 (5.8%)	0 (0.0%)	
3–5	1 (2.6%)	6 (11.5%)	2 (5.6%)	
6	1 (2.6%)	3 (5.8%)	0 (0.0%)	
Follow-up period (No.)				
mRS improvement or consistent	34 (87.2%)	40 (77.0%)	33 (91.6%)	.109 ^b
mRS degradation	5 (12.8%)	12 (23.0%)	3 (8.3%)	

^a Kruskal-Wallis H test.^b Fisher exact test.**Table 6: Characteristics of retreated aneurysms**

	Coil Group		WEB Group (n = 8)	Significance
	Coiling (n = 1)	Stent-Assisted Coiling (n = 4)		
Aneurysm size (No.)				
0–7 mm	1 (100%)	1 (25%)	2 (25.0%)	.734 ^a
8–15 mm	0 (0.0%)	2 (50%)	6 (75.0%)	
16–25 mm	0 (0.0%)	1 (25%)	0 (0.0%)	
>25 mm	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Side (No.)				
Right	1 (100%)	4 (100%)	3 (37.5%)	.046 ^b
Left	0 (0%)	0 (0%)	5 (62.5%)	
Aneurysm neck (mean) (mm)	1.68 ± 0.0	5.03 ± 1.49	5.38 ± 1.14	.273 ^c
Aspect ratio (dome/neck) (mean)	4.17 ± 0.0	3.25 ± 2.01	2.45 ± 0.71	.406 ^c

^a χ^2 linear by linear.^b Fisher exact test.^c Kruskal-Wallis H test.

DISCUSSION

To our knowledge, this is the first study comparing the WEB device with coiling or stent-assisted coiling in a single center setting. We analyzed our data with regard to intervention time, follow-up (after discharge and long-term), and procedure-related complications to assess the effectiveness of endovascular treatment of aneurysms located at the MCA bifurcation. Approximately 25% of all aneurysms treated in Augsburg and Vogtareuth by endovascular means were MCA aneurysms. The incidence is consistent with the published literature of MCA aneurysms ranging from 14% to 29% of all aneurysms, depending on

treated between 2013 and July 2017 using the WEB device. The retreatment rate decreased continuously across the years from initially 50% (2012) to 0% (2017) (Fig 3).

whether unruptured or ruptured aneurysms were included in the particular study.^{1,2} This finding shows that MCA bifurcation aneurysms were treated in our institution regardless of aneurysm

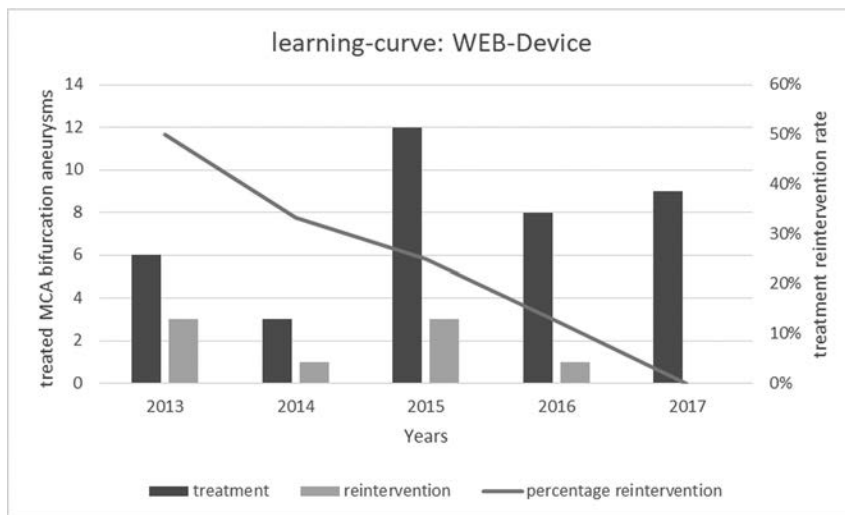


FIG 3. Retreatment rate of aneurysms treated with the WEB device (2013–2017).

morphology and vessel anatomy, leading to a treatment rate of >96% of all intracranial aneurysms by an endovascular technique. The major reason for the nonendovascular approach, corresponding to 50 intracranial aneurysms (14 MCA aneurysms), was the necessity of decompression of a space-occupying intracranial hematoma or the explicit patient request. Hence, we have virtual no selection of the easily accessible aneurysms, which reduces the potential selection bias to a minimum.

Comparison between Surgical Clipping and Endovascular Technique

The proper treatment of intracranial aneurysms is still controversial. Only 66% of all unruptured aneurysms in Germany were treated by endovascular techniques,⁵ despite the results of the ISAT study 2002 and its recommendation of endovascular treatment. One point of criticism of endovascular aneurysm treatment is the higher reintervention rate compared with clipping. However, since the publication of ISAT, the stent design has significantly improved, allowing the use of stents in smaller vessels; new devices such as intra- and extrasaccular flow diverters have appeared on the market; and finally, the coil structure has developed even further with softer coils and the introduction of bioactive coils such as HydroCoils (MicroVention). The higher packing density of HydroCoils seems to be translated into a lower reintervention rate compared with first-generation coils.⁶

With a total mortality rate of 0.6% directly after discharge and 2.7% in long-term follow-up, our results are in the range of published outcomes.⁷ In direct comparison with surgical clipping, the mortality rate after the endovascular technique was at least equal to recent published data (1.9%–2.0%).^{8,9} We found a good clinical outcome ($mRS \leq 2$) in 91.3% directly after discharge and in 89.8% after long-term follow-up. In their comparative analysis, McDonald et al⁷ found a similar in-hospital mortality risk, but in long-term follow-up, the outcome in surgical treatment was significantly worse than after endovascular technique. Compared with published surgical data of unruptured MCA aneurysms ($mRS \leq 2$ in 92%),⁸ our results seem to be comparable. Especially, intraprocedural aneurysm rupture is considered an important complication in clipping intervention. Rodriguez-Hernan-

dez et al⁸ found a 2 times higher risk for such a complication during clipping compared with endovascular aneurysm repair (3.4% versus 1.7%). With an intraprocedural rupture rate of 1.3%, our data are comparable with these findings. The major complication in endovascular treatment is still a thromboembolic event. With a rate of 5.3%, our data slightly exceeded the released findings (3.2%) of Rodriguez-Hernandez et al.⁸

Complications

We found no significant difference in the complication rates between the WEB and the coil and the stent-assisted coiling groups. Overall, 11 periprocedural complications occurred in all 150 patients (7.3%). Five events had a throm-

boembolic origin. Two aneurysms ruptured during the intervention, and 1 relevant vasospasm, 1 stent thrombosis, and 1 infarction occurred in the coil group. We had 8 complications in the coil group. In relation to the total coiled aneurysms ($n = 112$), this meant a 7.1% complication rate, which is much lower compared with other findings.⁹

Compared with the published literature on intrasaccular flow diverters, we had a lower complication rate after using the WEB device (7.9% versus 11.8%).¹⁰ Thromboembolic events occurred twice after double antiaggregation with ASA, 100 mg, and clopidogrel, 75 mg, and 3 times after single antiaggregation with ASA, 100 mg, alone. There was a trend toward risk reduction, but it was not significant.¹¹ However, when a complication occurred, the short-term mRS and the long-term mRS of the WEB-treated aneurysms ($mRS = 0.67$ and 1.33 , respectively) were much lower than those in the coil-treated aneurysms ($mRS = 2.88$ and 2.25). The outcome after coil and stent intervention, especially, caused grave complications compared with the single use of coils or a WEB device. This outcome is also reflected in the hospitalization time. The mean hospitalization time after the WEB device use was about 6 days compared with 11 days (coiling only) and 12 days (stent-assisted-coiling) (Table 4). However, the aneurysms treated by stent-assisted coiling were much larger than the aneurysms treated by coils alone. Furthermore, the average neck size was 1 mm larger in the stent-assisted coiling group compared with the coiling-alone group (Table 2). The higher complexity of these aneurysms probably explains the higher complication rate.

Antiaggregation

The day before elective treatment of the aneurysms, we performed a platelet test. If the patient was a responder to clopidogrel and a stent was used during treatment, a daily dose of 75 mg of clopidogrel was given until 6 weeks after the intervention. In case of a nonresponder to clopidogrel, the patient received a loading dose of 180 mg of ticagrelor before treatment and a dose of 90 mg of ticagrelor twice daily for 6 weeks. Wide-neck aneurysms or protruded coils were usually treated afterward by 100 mg of ASA for 6 weeks. Patients treated with a WEB device had to take 100 mg of

ASA for 6 weeks. ASA was only administered for 6 months if signs of atherosclerosis had been observed during intervention. Subsequent medication administration was stopped without influencing the long-term outcome on follow-up. Thromboembolic events occurred 5 times under simple antiaggregation and 3 times under double antiaggregation. We found a lower thromboembolic event rate in double antiaggregation ($n = 3/78$, 3.8%) than in simple antiaggregation ($n = 5/72$, 7%). Double antiaggregation seems to be a safe way to reduce thromboembolic events without increasing the hemorrhagic risk (Table 5). Three thromboembolic events occurred after positive findings on the Multiplate Analyzer test. In 4, no Multiplate Analyzer test was documented in the electronic medical files. These events can probably be prevented by a switch from clopidogrel to ticagrelor.

Treatment Time

We found a significantly lower total treatment time in the WEB group compared with the coil group or the stent-assisted coiling group (136 versus 155 versus 165 minutes, respectively). One major point seems to be the number of devices used. De Gast et al¹² concluded that coiling of MCA aneurysms takes considerably more time than other intracranial aneurysms. They described a mean treatment time of 57 minutes without preprocedural diagnostic angiography and anesthesiology procedures. We defined our treatment time as the period from intubation to extubation, including the panangiography, the current treatment, and the postinterventional DynaCT (Siemens). In a clinical setting, these points are relevant for the slot planning in daily activity and explain the great difference between de Gast et al¹² and our study.

Reintervention Rate

We observed a learning curve using the WEB device because we saw a decreasing reintervention rate compared with the increasing number of cases (Fig 3). Behme et al¹⁰ found that in 2 years after their first use of a WEB device, the occlusion rate increased to 87.5% in the 3-month follow-up. Nonetheless, in our cohort, the retreatment rate was significantly higher in the WEB group (21.1%) compared with the coiling-alone (2.2%) or the stent-assisted coiling (5.9%) group. Published data for the reintervention rate of coiled aneurysms range between 4.7%¹³ and 12.3%.¹⁴ One major point outlined in the literature is that in thrombosed or partially thrombosed aneurysms, the WEB device could not achieve contact with the aneurysm wall and therefore posed a high risk of recurrence. The WEB device is probably not feasible for this special subtype of aneurysm. Also, device compaction could induce treatment failure as seen in other endovascular techniques such as coiling.

We found no differences in both groups regarding the rate of thrombotic events. One major problem of comparing the reintervention rate with that in other studies is the subjective classification and experience of the interventionalists. Darflinger et al¹⁵ described the differences between reperfusion of an aneurysm and the retreatment. He proposed that only aneurysms that are graded as II or III according to the Raymond-Roy classification should be treated. If <69% of the treated aneurysm volume is reopened, then the rupture risk seems to be equal to that in untreated aneurysms. Aneurysms classified as Raymond-Roy I or II,

however, might be successfully treated.¹⁶ Pierot et al¹⁷ discovered that the recanalization of aneurysms treated by the WEB device was 20.9%, but the reintervention rate was much lower (6.9%). Further investigation seems to be warranted to clarify treatment success in aneurysms treated with the WEB device.

Our reintervention rate was not higher than the numbers mentioned in the literature. However, in our data, the follow-up period differed significantly between both groups. One reason is that the WEB device was released in 2011 and was only used for the first time in Augsburg in 2012. Naturally, an endovascular reintervention means mental stress for the patient. However, a reintervention by an endovascular technique presents a safe and good way to treat patients.¹⁸ We found that nearly all reinterventions were completed in 6 months after the first therapy. Most of the studies mention a mean of 8 months after intervention as being the highest risk time.¹⁹ Additionally, Ferns et al²⁰ reported that a longer follow-up period does not increase the reopening rate or reintervention rate in treated intracranial aneurysms. In our series, 92.3% of all decisions to retreat an already treated aneurysm were made within 6 months. Thus, a postinterventional angiographic control within 3–6 months seems indispensable.

Limitations

Our study has several limitations. First, it is a single-center, non-randomized retrospective cohort. Comparison, especially with clipping, can only be made via published literature. Particularly with regard to the Web group, we observed a clear learning curve, so our data may underestimate the potential of the WEB device in this challenging subgroup of aneurysms. Otherwise in contrast to other studies,³ we have a very limited selection bias for endovascular treatment. This shows that a wide variety of complex MCA bifurcation aneurysms can be treated using endovascular means alone.

CONCLUSIONS

Endovascular treatment of MCA bifurcation aneurysms seems to be a safe option regardless of the aneurysm morphology and vascular anatomy, with low morbidity and mortality rates. The WEB device might have the potential to facilitate treatment of this challenging subtype of aneurysms even further.

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REFERENCES

1. Molyneux A, Kerr R, Stratton I, et al. **International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial.** *Lancet* 2002;360:1267–74 [CrossRef](#) [Medline](#)
2. Wiebers DO. **Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment.** *Lancet* 2003;362:103–10 [CrossRef](#) [Medline](#)
3. Schwartz C, Aster HC, Al-Schameri R, et al. **Microsurgical clipping and endovascular treatment of middle cerebral artery aneurysms in**

- an interdisciplinary treatment concept: comparison of long-term results. *Interv Neuroradiol* 2018;24:608–14 [CrossRef Medline](#)
4. Nussbaum ES, Madison MT, Goddard JK, et al. Microsurgical treatment of unruptured middle cerebral artery aneurysms: a large, contemporary experience. *J Neurosurg* 2018;1–7 [CrossRef Medline](#)
 5. Janssen H, Berlis A, Lutz J, et al. State of practice: endovascular treatment of acute aneurysmal SAH in Germany. *AJNR Am J Neuroradiol* 2017;38:1574–79 [CrossRef Medline](#)
 6. Taschner CA, Chapot R, Costalat V, et al. Second-generation hydrogel coils for the endovascular treatment of intracranial aneurysms: a randomized controlled trial. *Stroke* 2018;49:667–74 [CrossRef Medline](#)
 7. McDonald JS, McDonald RJ, Fan J, et al. Comparative effectiveness of unruptured cerebral aneurysm therapies: propensity score analysis of clipping versus coiling. *Stroke* 2013;44:988–94 [CrossRef Medline](#)
 8. Rodríguez-Hernández A, Sughrue ME, Akhavan S, et al. Current management of middle cerebral artery aneurysms: surgical results with a “clip first” policy. *Neurosurgery* 2013;72:415–27 [CrossRef Medline](#)
 9. Choi JH, Park JE, Kim MJ, et al. Aneurysmal neck clipping as the primary treatment option for both ruptured and unruptured middle cerebral artery aneurysms. *J Korean Neurosurg Soc* 2016;59:269–75 [CrossRef Medline](#)
 10. Behme D, Berlis A, Weber W. Woven EndoBridge intrasaccular flow disrupter for the treatment of ruptured and unruptured wide-neck cerebral aneurysms: report of 55 cases. *AJNR Am J Neuroradiol* 2015;36:1501–06 [CrossRef Medline](#)
 11. Hwang G, Huh W, Lee JS, et al. Standard vs modified antiplatelet preparation for preventing thromboembolic events in patients with high on-treatment platelet reactivity undergoing coil embolization for an unruptured intracranial aneurysm: a randomized clinical trial. *JAMA Neurol* 2015;72:764–72 [CrossRef Medline](#)
 12. de Gast AN, Soepboer A, Sluzewski M, et al. How long does it take to coil an intracranial aneurysm? *Neuroradiology* 2008;50:53–56 [CrossRef Medline](#)
 13. Cognard C, Weill A, Spelle L, et al. Long-term angiographic follow-up of 169 intracranial berry aneurysms occluded with detachable coils. *Radiology* 1999;212:348–56 [CrossRef Medline](#)
 14. Henkes H, Fischer S, Liebig T, et al. Repeated endovascular coil occlusion in 350 of 2759 intracranial aneurysms: safety and effectiveness aspects. *Neurosurgery* 2006;58:224–32; discussion 224–32 [CrossRef Medline](#)
 15. Darflinger R, Thompson LA, Zhang Z, et al. Recurrence, retreatment, and rebleed rates of coiled aneurysms with respect to the Raymond-Roy scale: a meta-analysis. *J Neurointerv Surg* 2016;8:507–11 [CrossRef Medline](#)
 16. Johnston SC, Dowd CF, Higashida RT, et al; CARAT Investigators. Predictors of rehemorrhage after treatment of ruptured intracranial aneurysms: the Cerebral Aneurysm Rerupture After Treatment (CARAT) study. *Stroke* 2008;39:120–25 [CrossRef Medline](#)
 17. Pierot L, Moret J, Barreau X, et al. Safety and efficacy of aneurysm treatment with WEB in the cumulative population of three prospective, multicenter series. *J Neurointerv Surg* 2018;10:553–59 [CrossRef Medline](#)
 18. Ries T, Siemonsen S, Thomalla G, et al. Long-term follow-up of cerebral aneurysms after endovascular therapy prediction and outcome of retreatment. *AJNR Am J Neuroradiol* 2007;28:1755–61 [CrossRef Medline](#)
 19. Teleb MS, Pandya DJ, Castonguay AC, et al. Safety and predictors of aneurysm retreatment for remnant intracranial aneurysm after initial endovascular embolization. *J Neurointerv Surg* 2014;6:490–94 [CrossRef Medline](#)
 20. Ferns SP, Sprengers MES, van Rooij WJ, et al. Coiling of intracranial aneurysms: a systematic review on initial occlusion and reopening and retreatment rates. *Stroke* 2009;40:e523–29 [CrossRef Medline](#)

Local Hemodynamic Conditions Associated with Focal Changes in the Intracranial Aneurysm Wall

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ABSTRACT

BACKGROUND AND PURPOSE: Aneurysm hemodynamics has been associated with wall histology and inflammation. We investigated associations between local hemodynamics and focal wall changes visible intraoperatively.

MATERIALS AND METHODS: Computational fluid dynamics models were constructed from 3D images of 65 aneurysms treated surgically. Aneurysm regions with different visual appearances were identified in intraoperative videos: 1) “atherosclerotic” (yellow), 2) “hyperplastic” (white), 3) “thin” (red), 4) rupture site, and 5) “normal” (similar to parent artery). They were marked on 3D reconstructions. Regional hemodynamics was characterized by the following: wall shear stress, oscillatory shear index, relative residence time, wall shear stress gradient and divergence, gradient oscillatory number, and dynamic pressure; these were compared using the Mann-Whitney test.

RESULTS: Hyperplastic regions had lower average wall shear stress ($P = .005$) and pressure ($P = .009$) than normal regions. Flow conditions in atherosclerotic and hyperplastic regions were similar but had higher average relative residence time ($P = .03$) and oscillatory shear index ($P = .04$) than thin regions. Hyperplastic regions also had a higher average gradient oscillatory number ($P = .002$) than thin regions. Thin regions had lower average relative residence time ($P < .001$), oscillatory shear index ($P = .006$), and gradient oscillatory number ($P < .001$) than normal regions, and higher average wall shear stress ($P = .006$) and pressure ($P = .009$) than hyperplastic regions. Thin regions tended to be aligned with the flow stream, while atherosclerotic and hyperplastic regions tended to be aligned with recirculation zones.

CONCLUSIONS: Local hemodynamics is associated with visible focal wall changes. Slow swirling flow with low and oscillatory wall shear stress was associated with atherosclerotic and hyperplastic changes. High flow conditions prevalent in regions near the flow impingement site characterized by higher and less oscillatory wall shear stress were associated with local “thinning” of the wall.

ABBREVIATIONS: avg = average; GON = gradient oscillatory number; IA = intracranial aneurysm; max = maximum; min = minimum; OSI = oscillatory shear index; PRE = dynamic pressure; RRT = relative residence time; UIA = unruptured intracranial aneurysm; WSS = wall shear stress

Unruptured intracranial aneurysms (UIAs) are relatively frequent in the population older than middle age, with a prevalence of approximately 3%.¹ Although most UIAs are asymptomatic and are found incidentally, when diagnosed, they cause significant concern because some may eventually rupture, causing aneurysmal subarachnoid hemorrhage, which has a mortality rate

of approximately 40%.² Due to this sinister outcome of aneurysmal SAHs, many diagnosed UIAs are treated to prevent rupture. The currently available treatment options are, however, all invasive interventions that carry a significant risk of morbidity (5%–7%) and even a low risk of mortality (1%).^{3,4} Interventions to prevent UIA rupture should therefore be focused on those UIAs that are indeed at risk of rupture, especially because many UIAs remain unruptured during the entire lifetime of their carrier.⁵

An aneurysms ruptures when the mechanical load imposed on

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its wall exceeds the strength of the wall. This mechanical load may vary depending on physical activity; hence, the most important factor to consider when determining the risk of aneurysm rupture is the strength of the aneurysm wall, which can vary substantially across even UIAs.⁶ Histologic studies have shown that UIAs can have very different wall structures^{7,8}; this feature is often clear during an operation when the UIA is exposed.⁹ At the moment, there are no diagnostic tools available to determine the structure of a UIA without direct visualization at an operation.

Flow interacts with the vessel wall and activates signaling pathways that regulate vessel wall remodeling.¹⁰ Flows within aneurysms are not physiologic and are influenced by the aneurysm and parent artery geometry, the position of the orifice on the parent artery, and the local angioarchitecture, among other factors.¹¹ However, flow conditions are statistically different between UIAs and ruptured IAs.^{12–14} Recently, we have shown an association between flow conditions and the overall wall histology of the intracranial aneurysm (IA), as well as with the degree of inflammatory cell infiltration in the IA wall.¹⁵ Because our prior results suggest that global flow inside the IA fundus regulates the remodeling of the IA wall, we now investigate whether local flow conditions are associated with the focal variations in the IA wall structure observed during an operation.

MATERIALS AND METHODS

Patients and Data

Sixty-six patients with intracranial aneurysms treated with surgical clipping were studied. Patients gave informed consent, and the study was approved by the institutional review boards of Helsinki University Hospital, Allegheny General Hospital, and the University of Illinois at Chicago. Video recordings obtained during the surgical procedures were collected. Only aneurysms that were visibly exposed in the videos were included in the study. In the videos of 8 patients, the aneurysm surface could not be reliably visualized, and these cases were discarded. One further case was excluded because it was observed to be heavily thrombosed. The remaining 57 patients had 65 aneurysms that were further studied. Before the operation, 37 of these patients were imaged with 3D CT angiography, and 20, with 3D rotational angiography. The aneurysm and patient characteristics are summarized in On-line Table 1.

Hemodynamics Modeling

Computational fluid dynamics models were constructed from the presurgical 3D images using previously described techniques.¹⁶ Blood was mathematically modeled as an incompressible Newtonian fluid, and the 3D unsteady Navier-Stokes equations were numerically solved using finite elements with in-house software.¹⁷ Pulsatile inflow boundary conditions were prescribed using flow waveforms measured in healthy subjects and scaled with a power law of the area of the inflow vessel.¹⁸ Outflow boundary conditions consistent with the Murray law were prescribed at the outlets.¹⁹ Wall compliance was neglected, and no-slip boundary conditions were prescribed at the walls. Numeric simulations were run for 2 cardiac cycles using a timestep of 0.01 seconds, and data from the second cycle were saved for

analysis. From the results of the second cycle, the following quantities were computed at the aneurysm wall: oscillatory shear index (OSI), mean wall shear stress (WSS), mean wall shear stress divergence, mean wall shear stress gradient, mean gradient oscillatory number (GON), mean pressure (PRE), and relative residence time (RRT). Here, “mean” refers to the time average of these quantities over the cardiac cycle. The mathematic definitions of these quantities and their meanings are listed in On-line Table 2.

Regional Analysis

Five types of aneurysm wall regions were considered according to their appearance in the surgical videos: 1) atherosclerotic walls characterized by a yellow appearance; 2) hyperplastic walls that appear white; 3) thin walls with a red translucent appearance; 4) rupture (site visible as a hole in the wall or a hematoma attached to the rupture site [more details in On-line Fig 1]); and 5) normal, the remainder of the wall that had no remarkable features. Note that the exact connection between the visual appearance and the histologic characteristics of these regions remains to be established. Using a recently developed 3D virtual marking tool (ChePen3D),²⁰ we rotated the patient-specific vascular geometry to the same orientation as the surgical view in a superposed semitransparent video frame where the aneurysm is exposed. The different wall regions visible in the video were then marked directly onto the computational fluid dynamics model with different color labels, enabling direct analysis of the relationship between flow and wall features. On average, the areas of the aneurysm not visible in the videos were $28.9\% \pm 25.6\%$ of the total aneurysm area. Subsequent analysis was restricted to the visible regions. We performed the marking blinded to hemodynamic results. Examples of aneurysm markings are presented in Fig 1.

Once the aneurysm regions were labeled, the maximum (max), minimum (min), and average (avg) of each hemodynamic variable, normalized with the mean value over the aneurysm sac, was computed for each simply connected region of a given wall type. Subsequently, the median and lower and upper quartiles of each variable over the 5 different wall types were computed, and the medians were statistically compared using the nonparametric Mann-Whitney *U* test. Pair-wise differences were considered significant with $P < .05$, and the *P* values were adjusted for multiple testing.

Next, 3 multivariate statistical models were constructed using a regularized logistic regression (Lasso) approach, which reduces overfitting errors. The regularization parameters were computed using a 10-fold cross-validation strategy. In the first model, the atherosclerotic and hyperplastic regions were combined into a single group and compared with the group of normal-appearing walls. In the second model, the thin regions were compared with the normal-appearing walls, and in the third model, the atherosclerotic and hyperplastic regions combined were compared with the thin regions.

Finally, the locations of the different wall regions were visually compared with global flow features such as the inflow jet, regions of flow recirculation and swirling flow, and so forth.

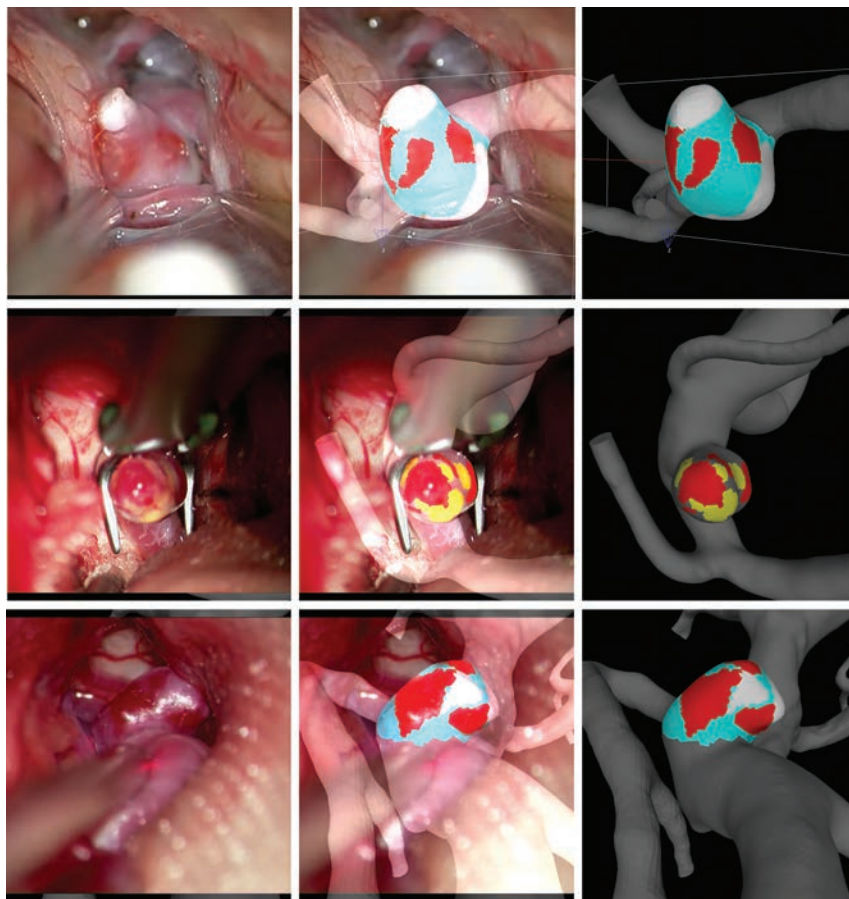


FIG 1. Marking aneurysm regions in 2 sample aneurysms. *Left column*, Selected frames of intraoperative videos displaying the aneurysm wall. *Center column*, Superposition of semitransparent video frame and marked 3D vascular model. *Right column*, Final virtual marking of aneurysm wall regions (red indicates thin; yellow, atherosclerotic; white, hyperplastic; cyan, normal-appearing).

Table 1: P values of pair-wise comparisons of pathologic and normal-appearing aneurysm regions^a

Variable	A vs N	H vs N	T vs N	R vs N
OSI _{max}	<.001 ^b (N)	<.001 ^b (N)	<.001 ^b (N)	<.001 ^b (N)
OSI _{avg}	.8	.98	0.006 ^b (N)	.33
OSI _{min}	<.001 ^b (A)	<.001 ^b (H)	<.001 ^b (T)	<.001 ^b (R)
WSS _{max}	<.001 ^b (N)	<.001 ^b (N)	<.001 ^b (N)	<.001 ^b (N)
WSS _{avg}	.01 ^b (N)	.005 ^b (N)	.54	.005 ^b (N)
WSS _{min}	.01 ^b (A)	<.001 ^b (H)	<.001 ^b (T)	.1
PRE _{max}	<.001 ^b (N)	<.001 ^b (N)	<.001 ^b (N)	.05 ^c (N)
PRE _{avg}	.06	.009 ^b (N)	.59	.03 ^c (R)
PRE _{min}	<.001 ^b (A)	.001 ^b (H)	<.001 ^b (T)	<.001 ^b (R)
RRT _{max}	.004 ^b (N)	<.001 ^b (N)	<.001 ^b (N)	.005 ^b (N)
RRT _{avg}	.67	.36	<.001 ^b (N)	.47
RRT _{min}	<.001 ^b (A)	<.001 ^b (H)	<.001 ^b (T)	.04 ^c (R)
GON _{max}	<.001 ^b (N)	.001 ^b (N)	<.001 ^b (N)	<.001 ^b (N)
GON _{avg}	.54	.85	<.001 ^b (N)	.04 ^c (N)
GON _{min}	<.001 ^b (A)	<.001 ^b (H)	<.001 ^b (T)	.008 ^b (R)
WSSDIV _{max}	.06	.03 ^b (N)	<.001 ^b (N)	.06
WSSDIV _{avg}	.93	.79	.93	.93
WSSDIV _{min}	.21	.21	.06	.21
WSSGRD _{max}	<.001 ^b (N)	<.001 ^b (N)	<.001 ^b (N)	<.001 ^b (N)
WSSGRD _{avg}	.38	.09	.82	.07
WSSGRD _{min}	.007 ^b (A)	.007 ^b (H)	<.001 ^b (T)	.1

Note:—A indicates atherosclerotic; H, hyperplastic; T, thin; R, ruptured; N, normal-appearing; WSSDIV, WSS divergence; WSSGRD, WSS gradient.

^a The region with the larger value is indicated in parentheses next to the significant P values.

^b Significant values after a further adjustment for testing multiple hemodynamic variables.

^c Significant values (adjusted for multiple regional tests).

RESULTS

The median and lower and upper quartiles of each hemodynamic variable over each of the 5 wall regions as well as the entire aneurysm sac are presented in On-line Table 3. The P values of pair-wise comparisons between the pathologic and normal-appearing wall regions are listed in Table 1 and those between the different pathologic wall regions, in Table 2. For these comparisons, the hemodynamic variables were normalized with their values over the entire aneurysm sac, to facilitate the comparisons of regions from different aneurysms at different locations. Statistically significant differences adjusted for multiple regions testing are indicated with a “b”, and the region with the higher median is indicated in parenthesis. Variables that remain significant after further adjusting for multiple variable testing are indicated with a “c”.

Focal Wall Changes Are Associated with Local Flow Conditions

Heterogeneous wall was observed in 59/65 (91%) of the studied IAs during the operation. Compared with wall regions that did not appear hyperplastic, atherosclerotic, or thin during surgical exposure, the local flow conditions at the regions of remodeled wall were different (On-line Table 4).

In general, normal-appearing walls had larger ranges (higher maximum and lower minimum) for all hemodynamic variables compared with pathologic regions (either atherosclerotic, hyperplastic, thin, or ruptured).

Characteristics of Flow in Hyperplastic (White) and Atherosclerotic (Yellow) Regions

Compared with normal-appearing regions, hyperplastic regions had lower mean wall shear stress (WSS_{avg}, $P = .005$) and mean pressure (PRE_{avg}, $P = .009$). Mean variables were not significantly different between atherosclerotic and normal-appearing regions, except for mean wall shear stress, which was lower (WSS_{avg}, $P = .01$). Atherosclerotic and hyperplastic regions (Table 2) had statistically similar flow features; only minimum pressure was higher in the atherosclerotic regions (PRE_{min}, $P = .01$). Additionally, atherosclerotic and hyperplastic regions had flow features statistically similar to those in rupture regions except that the mean pressure was higher in the ruptured regions (PRE_{avg}, atherosclerotic versus rupture: $P = .01$; hyperplastic versus rupture: $P = .009$). In contrast, compared with thin regions, atherosclerotic and hyperplastic regions had slower flows (higher RRT_{avg}, atherosclerotic versus thin: $P = .03$; hyperplastic versus thin: $P < .001$), more oscillatory wall shear stress (OSI_{avg}, atherosclerotic versus thin: $P = .05$; hyperplastic versus thin: $P = .04$), and

Table 2: P values of pair-wise comparisons of pathologic aneurysm regions^a

Variable	A vs H	A vs T	A vs R	H vs T	H vs R	T vs R
OSImax	.77	.03 ^b (A)	.35	.002 ^c (H)	.32	.45
OSIavg	.66	.05 ^b (A)	.33	.04 ^b (H)	.33	.86
OSImin	.09	.46	.46	.29	.52	.98
WSSmax	.74	.74	.4	.96	.14	.14
WSSavg	.81	.06	.47	.006 ^c (T)	.2	.01 ^b (T)
WSSmin	.76	.003 ^b (T)	.76	<.001 ^c (T)	.66	.01 ^b (T)
PREmax	.55	.42	.47	.69	.69	.69
PREavg	.5	.1	.01 ^b (R)	.009 ^c (T)	.009 ^b (R)	.09
PREmin	.01 ^b (A)	.79	.01 ^b (R)	.003 ^c (T)	<.001 ^c (R)	.01 ^b (R)
RRTmax	.98	.007 ^b (A)	.5	<.001 ^c (H)	.42	.42
RRTavg	.8	.03 ^b (A)	.47	<.001 ^c (H)	.36	.67
RRTmin	.82	.82	.82	.82	.82	.82
GONmax	.24	.24	.55	<.001 ^c (H)	.12	.7
GONavg	.6	.19	.6	.002 ^c (H)	.19	.8
GONmin	.49	.66	.57	.85	.92	.75
WSSDIVmax	.93	.46	.54	.28	.54	.93
WSSDIVavg	.8	.93	.93	.93	.93	.96
WSSDIVmin	.83	.96	.96	.54	.83	.96
WSSGRDmax	.75	.89	.31	.75	.08	.08
WSSGRDavg	.82	.39	.38	.07	.38	.07
WSSGRDmin	.6	.02 ^c (T)	.64	<.001 ^b (T)	.88	.01 ^b (T)

Note:—A indicates atherosclerotic; H, hyperplastic; T, thin; R, ruptured; WSSDIV, WSS divergence; WSSGRD, WSS gradient.

^a The region with the larger value is indicated in parentheses next to the significant P values.

^b Significant values (adjusted for multiple regional tests).

^c Significant values after a further adjustment for testing multiple hemodynamic variables.

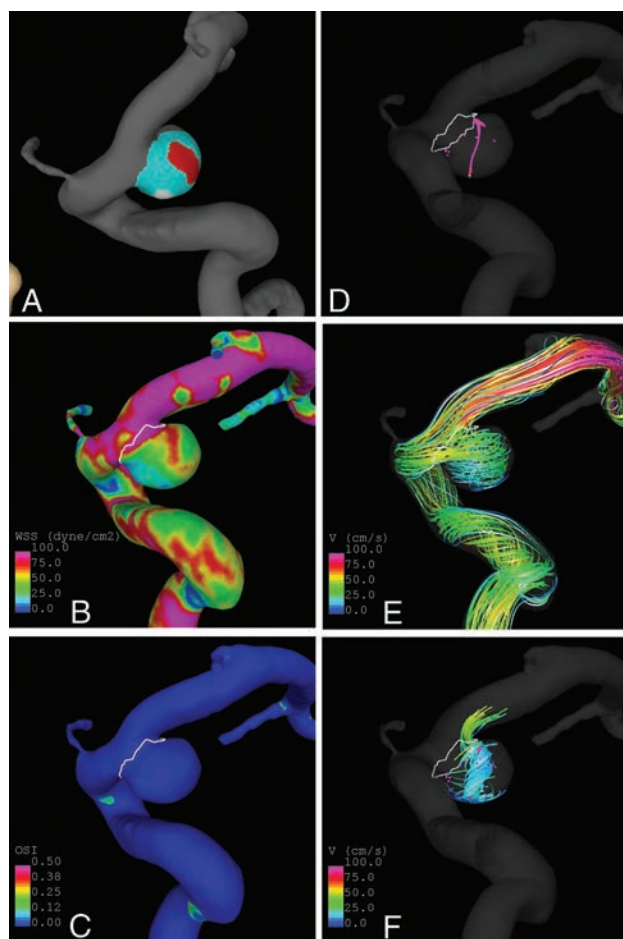


FIG 2. Sample aneurysm with thin and hyperplastic regions. A, Wall regions (red indicates thin; white, hyperplastic; cyan, normal-appearing). B, Wall shear stress. C, Oscillatory shear index. D, Vortex core lines. E, Flow streamlines. F, Swirling around vortex core lines.

more oscillatory shear stress gradients (hyperplastic versus thin: GONavg, $P = .002$).

Characteristics of Flow in Thin (Red) Regions

Compared with normal-appearing regions, thin (red) regions had faster flows (RRTavg, $P < .001$), less oscillatory wall shear stress (OSIavg, $P = .006$), and less oscillatory shear stress gradient (GONavg, $P < .001$). Additionally, thin regions had higher wall shear stress (WSSavg) than hyperplastic ($P = .006$) and ruptured regions ($P = .01$), and they had higher pressure than hyperplastic regions (PREavg, $P = .009$) but not compared with ruptured regions ($P = .09$). Compared with ruptured regions, thin regions also had larger wall shear stress (WSSavg, $P = .01$).

Characteristics of Flow at the Sites of Rupture

Compared with normal regions, the rupture sites had lower wall shear stress (WSSavg, $P = .005$) and higher pressure (PREavg, $P = .03$). Most interesting, the pressure (PREavg) was higher in ruptured regions compared with atherosclerotic ($P = .01$) and hyperplastic ($P = .009$) regions, but lower than in thin regions ($P = .009$).

Qualitative Flow Characteristics and Wall Appearance

Qualitatively, thin wall regions tend to be aligned with the flow stream in the aneurysm (approximately 86% of thin regions are aligned with the inflow jet). Thus, they tend to be in regions of faster flow that have higher wall shear stress (approximately 90% of thin regions are observed in regions of high or moderate WSS) and pressure (closer to flow impingement). In contrast, thick (atherosclerotic and hyperplastic) regions tend to be aligned with the ends of the intrasaccular vortices (approximately 61% of thick regions), which are perpendicular to the flow stream. Thus, thick regions tend to coincide with locations of slow swirling flow (approximately 78% of these regions) that have low wall shear stress (approximately 85% of thick regions are observed in regions of low WSS), high residence time, and higher oscillatory wall shear stress and shear stress gradients.

An example is presented in Fig 2. In this case, the aneurysm has a thin (red) region aligned with the inflow jet and under higher wall shear stress and a hyperplastic (white) region under lower wall shear stress that coincides with the end of a vortex core line around which the flow swirls within the aneurysm. Further examples of aneurysms are presented in On-line Figs 2–5.

Discrimination of Aneurysm Wall Characteristics Based on Local Flow Conditions

Results of multivariate statistical models built to discriminate among the different aneurysm wall regions are presented in On-line Fig 6. This figure shows receiver operating characteristic

curves and calibration plots for the 3 models: 1) atherosclerotic and hyperplastic versus normal regions, 2) thin versus normal regions, and 3) atherosclerotic and hyperplastic versus thin regions. The corresponding areas under the curve were 0.92, 0.97, and 0.70, respectively. These areas under the curve indicate very good discrimination between the pathologic and normal regions and relatively good discrimination between thin and thickened wall regions. Visually, the calibration plots show reasonable fits to the data, with small deviations of the fitted lines from the 45° straight line, which correspond to a perfect goodness of fit.

The coefficients of each hemodynamic variable in each of the 3 models ordered by their importance (influence on the outcome and frequency of inclusion in the model during cross-validation) are presented in On-line Tables 4–6. The most important variables to discriminate atherosclerotic and hyperplastic regions from normal regions were GONmin, RRTavg, maximum wall shear stress gradient, and OSImin,avg. The most important variables to discriminate between thin and normal regions were wall shear stress gradient (min, max), GONavg, RRTmin, max, and PREmax. Finally, the most important variables to discriminate atherosclerotic and hyperplastic from thin regions were RRTavg,max, GONmax, and WSSmin.

DISCUSSION

Flow and Wall Remodeling

The flow characteristics prevalent in atherosclerotic and hyperplastic thick regions of the aneurysm wall are similar to those previously associated with atherosclerosis in arteries,^{21,22} namely low and oscillatory wall shear stress in regions of slow and recirculating flow. In IAs, these regions tend to be located near the end of intrasaccular vortex core lines and toward the sides of the intra-aneurysmal flow stream. These observations suggest that such low-flow conditions promote wall remodeling that results in local thickening of the wall. This conjecture needs to be further investigated to prove that, indeed, atherosclerotic (yellow) and hyperplastic (white) regions are thicker than normal-appearing walls as suggested by previous studies^{23,24} and that their histologic characteristics include lipid accumulation, cell proliferation, and so forth. Furthermore, although these regions may be thicker, this characteristic does not automatically imply that they are mechanically stronger. On the contrary, it is plausible that the wall structure and, in particular, the collagen fiber reinforcements in these regions are degraded, resulting in an overall weaker wall region.

In contrast to atherosclerotic and hyperplastic regions, thin wall regions tend to be aligned with the flow stream and located toward the region where the inflow jet impacts the aneurysm wall. These results agree with previous studies in which the authors reported the correlation between the thin region and impingement flow.²⁵ The local flow conditions in these regions seem similar to those that predispose arteries to aneurysm formation,¹⁴ (ie, faster flow and wall shear stress and WSS gradient with larger magnitudes and less oscillations). Another study of unruptured aneurysm walls found de-endothelialization as a consistent feature in thinned regions.²³ Perhaps these are indications of impaired remodeling of these regions because the time of the aneurysm inception or of degenerative remodeling is associated with abnormally high flow conditions.

Flow as a Trigger of Aneurysm Rupture

Rupture sites share some characteristics with thin wall regions and other characteristics with atherosclerotic and hyperplastic wall regions. Similar to thin regions, rupture sites tend to be aligned with the inflow and have higher pressure (an indication of proximity to the flow-impingement site) than thick wall regions. These features are consistent with previous work in which thin wall regions of unruptured aneurysms coincided with the diverging WSS vector and a local rise in the pressure, again as an indicator of flow impingement.^{23,26} An earlier study of pathologic changes in the aneurysm wall found that thin, hypocellular, de-endothelialized walls were always ruptured.²⁷ On the other hand, similar to atherosclerotic and hyperplastic regions, ruptured regions tend to have lower wall shear stress, higher oscillatory shear index, and higher oscillations of the shear stress gradient than thin regions. These similarities and differences may suggest that there could be >1 failure mode of the aneurysm wall, one associated with thickened walls and another associated with thinned walls. They are a subject of ongoing investigation.

Diagnostic Application of Computational Fluid Dynamics?

Local hemodynamics-based statistical models seem capable of discriminating between normal-appearing regions of the wall and regions of wall thinning or atherosclerotic thickening. On one hand, this capability suggests that local flow conditions have an important influence on the local evolution and remodeling of the aneurysm wall and, on the other hand, that in principle, they could be used as a surrogate biomarker of the wall status when evaluating patients with cerebral aneurysms.

Comparison with Previous Studies and Limitations

Several previous studies have investigated the relationship between hemodynamics and wall characteristics observed during an operation.^{9,28–33} Comparisons with our findings are presented in On-line Table 7. In all 3 studies that compared the hemodynamics at the site of rupture and elsewhere in the IA fundus, low WSS was characteristic of the site of rupture. Similarly, higher pressure was characteristic of thin regions in all 3 studies investigating pressures, and prolonged relative residence time was characteristic of a hyperplastic or atherosclerotic wall in all 4 studies investigating thick or atherosclerotic walls. The observation that there are hemodynamic variables that are consistently associated with IA wall characteristics in different studies despite slightly different methodology, study design, and different patient populations implies that these associations are real and potentially causal. Whether the other hemodynamic variables reported to be associated with IA wall type in some of the studies that have not been replicated by others are, in fact, associated with IA wall remodeling or perhaps just covariates or coincidental findings remains to be determined by large studies with sufficient statistical power. These large studies comparing the flow dynamics and the characteristics of the IA wall are also needed to replicate our finding that IA wall type can be relatively accurately predicted with computational fluid dynamics models.

This study has several limitations. Arterial walls were approximated as rigid, and blood was approximated as a Newtonian

fluid. Patient-specific flow conditions were not available; therefore, typical flows from healthy subjects were used. Flow variables were normalized with the average values over the aneurysm sac to compare the local hemodynamics of the different regions of aneurysms at different locations. In general, normalized values are more robust with respect to uncertainties in the inflow conditions. Minimum and maximum values of hemodynamic variables computed over tissue regions are less robust than mean values and require finer meshes for a more precise calculation. The identification of the different wall regions was performed subjectively by visual inspection of the intraoperative videos and markings of the corresponding 3D models. Inaccuracies in the definition of small regions in places where the hemodynamic variables are highly heterogeneous can have an effect on the values computed over these regions. The reproducibility of region delineation was not assessed because the regions of each aneurysm were marked by 1 observer. Additionally, the assumptions that yellow regions correspond to atherosclerotic changes, white regions to hyperplastic changes, and red regions to thin decellularized regions needs to be further demonstrated. Finally, the sample size limited the significance of some comparisons, such as those involving rupture sites ($n = 13$). The trends identified in this study should be confirmed with larger samples.

CONCLUSIONS

Local flow conditions are associated with local remodeling of the aneurysm wall. Low flow conditions prevalent in regions of slow-swirling flow characterized by low and oscillatory shear stress are associated with atherosclerotic and hyperplastic changes of the wall. High flow conditions prevalent in regions near the flow impingement site characterized by higher and less oscillatory wall shear stress are associated with local thinning of the wall. Local hemodynamics could, in principle, be used to identify local regions of the wall with different histologic and structural properties. This study demonstrates the value of intraoperative data for understanding the role of intrasaccular hemodynamics in IA wall changes.

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REFERENCES

1. Vlak MH, Algra A, Brandenburg R, et al. **Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis.** *Lancet Neurol* 2011;10:626–36 CrossRef Medline
2. Nieuwkamp DJ, Setz LE, Algra A, et al. **Changes in case fatality of aneurysmal subarachnoid haemorrhage over time, according to age, sex, and region: a meta-analysis.** *Lancet Neurol* 2009;8:635–42 CrossRef Medline
3. Kotowski M, Naggara O, Darsaut TE, et al. **Safety and occlusion rates of surgical treatment of unruptured intracranial aneurysms: a systematic review and meta-analysis of the literature from 1990 to 2011.** *J Neurol Neurosurg Psychiatry* 2013;84:42–48 CrossRef Medline
4. Naggara ON, White PM, Guilbert F, et al. **Endovascular treatment of intracranial unruptured aneurysms: systematic review and meta-analysis of the literature on safety and efficacy.** *Radiology* 2010;256:887–97 CrossRef Medline
5. Korja M, Lehto H, Juvela S. **Lifelong rupture risk of intracranial aneurysms depends on risk factors: a prospective Finnish cohort study.** *Stroke* 2014;45:1958–63 CrossRef Medline
6. Robertson AM, Duan X, Aziz K, et al. **Diversity in the strength and structure of unruptured cerebral aneurysms.** *Ann Biomed Eng* 2015; 43:1502–15 CrossRef Medline
7. Kataoka K, Taneda M, Asai T, et al. **Structural fragility and inflammatory response of ruptured cerebral aneurysms: a comparative study between ruptured and unruptured cerebral aneurysms.** *Stroke* 1999;30:1396–401 CrossRef Medline
8. Frösen J, Tulamo R, Paetau A, et al. **Saccular intracranial aneurysm: pathology and mechanisms.** *Acta Neuropathol* 2012;123:773–86 CrossRef Medline
9. Kadasi LM, Dent WC, Malek AM. **Colocalization of thin-walled dome regions with low hemodynamic wall shear stress in unruptured cerebral aneurysms.** *J Neurosurg* 2013;119:172–79 CrossRef Medline
10. Meng H, Tutino VM, Xiang J, et al. **High WSS or Low WSS? Complex interactions of hemodynamics with intracranial aneurysm initiation, growth, and rupture: toward a unifying hypothesis.** *AJNR Am J Neuroradiol* 2014;35:1254–62 CrossRef Medline
11. Sforza DM, Putman CM, Cebal JR. **Hemodynamics of cerebral aneurysms.** *Annu Rev Fluid Mech* 2009;41:91–107 CrossRef Medline
12. Xiang J, Natarajan SK, Tremmel M, et al. **Hemodynamic-morphologic discriminants for intracranial aneurysm rupture.** *Stroke* 2011; 42:144–52 CrossRef Medline
13. Cebal JR, Mut F, Weir J, et al. **Quantitative characterization of the hemodynamic environment in ruptured and unruptured brain aneurysms.** *AJNR Am J Neuroradiol* 2011;32:145–51 CrossRef Medline
14. Can A, Du R. **Association of hemodynamic factors with intracranial aneurysm formation and rupture: systematic review and meta-analysis.** *Neurosurgery* 2016;78:510–20 CrossRef Medline
15. Cebal JR, Ollikainen E, Chung BJ, et al. **Flow conditions in the intracranial aneurysm lumen are associated with inflammation and degenerative changes of the aneurysm wall.** *AJNR Am J Neuroradiol* 2017;38:119–26 CrossRef Medline
16. Cebal JR, Castro MA, Appanaboyina S, et al. **Efficient pipeline for image-based patient-specific analysis of cerebral aneurysm hemodynamics: technique and sensitivity.** *IEEE Trans Med Imaging* 2005;24:457–67 CrossRef Medline
17. Mut F, Aubry R, Löhner R, et al. **Fast numerical solutions of patient-specific blood flows in 3D arterial systems.** *Int J Num Meth Biomed Eng* 2010;26:73–85 CrossRef Medline
18. Cebal JR, Castro MA, Putman CM, et al. **Flow-area relationship in internal carotid and vertebral arteries.** *Physiol Meas* 2008;29:585–94 CrossRef Medline
19. Painter PR, Edén P, Bengtsson HU. **Pulsatile blood flow, shear force, energy dissipation and Murray's Law.** *Theor Biol Med Model* 2006; 3:31 CrossRef Medline
20. Cebal JR, Mut F, Gade P, et al. **Combining data from multiple sources to study mechanisms of aneurysm disease: tools and tech-**

- niques. *Int J Numer Methods Biomed Eng* 2018;34:e3133 [CrossRef Medline](#)
21. Taylor CA, Hughes TJ, Zarins CK. **Finite element modeling of three-dimensional pulsatile flow in the abdominal aorta: relevance to atherosclerosis.** *Ann Biomed Eng* 1998;26:975–87 [CrossRef Medline](#)
 22. Peiffer V, Sherwin SJ, Weinberg PD. **Does low and oscillatory wall shear stress correlate spatially with early atherosclerosis? A systematic review.** *Cardiovasc Res* 2013;99:242–50 [CrossRef Medline](#)
 23. Tobe Y, Yagi T, Iwabuchi Y, et al. **Combined analysis of pathology and hemodynamics of human unruptured cerebral aneurysm with thin-walled region.** In: *ASME 2013 Summer Bioengineering Conference*. Sunriver, Oregon; June 26–29, 2013
 24. Tobe Y. *Pathological Engineering for Predicting Transition of Human Cerebral Aneurysms* [dissertation]. Tokyo: Waseda University; 2016:1–165
 25. Suzuki T, Takao H, Suzuki T, et al. **Determining the presence of thin-walled regions at high-pressure areas in unruptured cerebral aneurysms by using computational fluid dynamics.** *Neurosurgery* 2016;79:589–95 [CrossRef Medline](#)
 26. Tobe Y, Yagi T, Iwabuchi Y, et al. **Relationship between pathology and hemodynamics of human unruptured cerebral aneurysms.** In: Goh J, ed. *IFMBE Proceedings: The 15th International Conference on Biomedical Engineering*. Cham: Springer; 2014:44–47
 27. Frösen J, Piippo A, Paetau A, et al. **Remodeling of saccular cerebral artery aneurysm wall is associated with rupture: histological analysis of 24 unruptured and 42 ruptured cases.** *Stroke* 2004;35:2287–93 [CrossRef Medline](#)
 28. Omodaka S, Sugiyama S, Inoue T, et al. **Local hemodynamics at the rupture point of cerebral aneurysms determined by computational fluid dynamics analysis.** *Cerebrovasc Dis* 2012;34:121–29 [CrossRef Medline](#)
 29. Fukazawa K, Ishida F, Umeda Y, et al. **Using computational fluid dynamics analysis to characterize local hemodynamic features of middle cerebral artery aneurysm rupture points.** *World Neurosurg* 2015;83:80–86 [CrossRef Medline](#)
 30. Sugiyama S, Niizuma K, Nakayama T, et al. **Relative residence time prolongation in intracranial aneurysms: a possible association with atherosclerosis.** *Neurosurgery* 2013;73:767–76 [CrossRef Medline](#)
 31. Sugiyama SI, Endo H, Niizuma K, et al. **Computational hemodynamic analysis for the diagnosis of atherosclerotic changes in intracranial aneurysms: a proof-of-concept study using 3 cases harboring atherosclerotic and nonatherosclerotic aneurysms simultaneously.** *Comput Math Methods Med* 2016;2016:2386031 [CrossRef Medline](#)
 32. Talari S, Kato Y, Shang H, et al. **Comparison of computational fluid dynamics findings with intraoperative microscopy findings in unruptured intracranial aneurysms: an initial analysis.** *Asian J Neurosurg* 2016;11:356–60 [CrossRef Medline](#)
 33. Furukawa K, Ishida F, Tsuji M, et al. **Hemodynamic characteristics of hyperplastic remodeling lesions in cerebral aneurysms.** *PLoS One* 2018;13:e0191287 [CrossRef Medline](#)

Aneurysm Characteristics, Study Population, and Endovascular Techniques for the Treatment of Intracranial Aneurysms in a Large, Prospective, Multicenter Cohort: Results of the Analysis of Recanalization after Endovascular Treatment of Intracranial Aneurysm Study

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ABSTRACT

BACKGROUND AND PURPOSE: The Analysis of Recanalization after Endovascular Treatment of Intracranial Aneurysm (ARETA) prospective study aims to determine factors predicting recurrence after endovascular treatment for intracranial aneurysms. In this publication, we review endovascular techniques and present the study population. Characteristics of treated and untreated unruptured aneurysms were analyzed.

MATERIALS AND METHODS: Sixteen neurointerventional departments prospectively enrolled patients treated for ruptured and unruptured intracranial aneurysms between December 2013 and May 2015. Patient demographics, aneurysm characteristics, and endovascular techniques were recorded.

RESULTS: A total of 1289 patients with 1761 intracranial aneurysms, 835 (47.4%) ruptured, were enrolled. Of these, 1359 intracranial aneurysms were treated by endovascular means. Ruptured intracranial aneurysms were treated by coiling and balloon-assisted coiling in 97.8% of cases. In unruptured intracranial aneurysms, the rates of flow diversion, flow disruption, and stent-assisted coiling were 11.6%, 6.9%, and 7.8%, respectively. Rupture status and aneurysm location, neck diameter, and sac size significantly influenced the chosen technique. Treated unruptured intracranial aneurysms, compared with untreated counterparts, had larger aneurysm sacs (7.6 ± 4.0 versus 3.4 ± 2.0 mm; $P < 0.001$) and neck dimensions (4.1 ± 2.2 versus 2.4 ± 1.3 mm; $P < 0.001$) and more frequently an irregular form (84.6% versus 44.4%; $P < 0.001$). Also, its location influenced whether an unruptured intracranial aneurysm was treated.

CONCLUSIONS: Our study provides an overview of current neurointerventional practice in the ARETA cohort. The technique choice was influenced by aneurysm morphology, location, and rupture status. Flow diversion, flow disruption, and stent-assisted coiling were commonly used in unruptured intracranial aneurysms, while most ruptured intracranial aneurysms were treated with coiling and balloon-assisted coiling.

ABBREVIATIONS: BAC = balloon-assisted coiling; IA = intracranial aneurysm; RIA = ruptured intracranial aneurysm; SAC = stent-assisted coiling; UIA = unruptured intracranial aneurysm; WFNS = World Federation of Neurosurgical Societies

Endovascular embolization is an accepted and, in many cases, the preferred technique for the treatment of ruptured (RIA) and unruptured intracranial aneurysms (UIA). In large prospective multicenter studies, the last patients enrolled were in 2002 in the International Subarachnoid Aneurysm Trial,¹ in 2006 in the

Analysis of Treatment by Endovascular approach of Nonruptured Aneurysms (ATENA),² and in 2007 in the Clinical and Anatomical Results in the Treatment of Ruptured Intracranial Aneurysms (CLARITY) trials.³ While the results of these studies are not outdated, it remains unclear whether they continue to reflect current neurointerventional practice, particularly in light of major technical advances that have become available during the past decade, first and foremost the advent of flow diverters⁴⁻⁶ and intrasaccular flow disrupters,⁷⁻¹³ which have broadened the spectrum of aneurysms amenable to reconstructive endovascular treatment. Unfortunately, little is known regarding the use of these devices in common neurointerventional practice. Furthermore, while the “remodeling technique”¹⁴ (also known as balloon-assisted coiling

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Study group (to be listed as collaborators) is presented in the On-line Appendix.

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[BAC]) and stent-assisted coiling (SAC),¹⁵ were already available in the late 1990s and the early 2000s, respectively, it is probable that these techniques are currently more widely applied than a decade ago.

Different factors may influence the neurointerventionist's choice of materials for treatment of an intracranial aneurysm (IA), for example, the aneurysm rupture status, its sac and neck diameter, and location. More important, due to the relative absence of evidence-based guidelines, chosen techniques are guided by personal preferences, resulting in disparate treatment practices. Other factors influencing these practices are regulatory agencies by limiting the reimbursement of novel devices. Publications defining modern treatment strategies are thus rare.¹⁶

In this study, we report on the endovascular modalities used to treat RIA and UIA in the Analysis of Recanalization after Endovascular Treatment of Intracranial Aneurysm (ARETA) study, a large prospective, multicenter cohort study. Furthermore, we are seeking to present the demographics of the study population and to gain insight into current practices of neurointerventional aneurysm treatment.

MATERIALS AND METHODS

The ARETA Study Protocol

ARETA was conceptualized to systematically evaluate factors that affect aneurysm recanalization after endovascular treatment during a follow-up of 12 months. The study was sponsored by the French Ministry of Health in a Programme Hospitalier de Recherche Clinique, No. 12-001-0372, and was registered on www.clinicaltrials.gov (NCT01942512). ARETA received national regulatory authorizations: approval from the Reims Institutional Review Board, the Consultative Committee of Information Processing in Health Care Research Program, and the National Commission for Data Processing and Freedom. The study objective and its protocol with inclusion and exclusion criteria have previously been described.¹⁷

Patients were prospectively enrolled in 16 centers in France between December 2013 and May 2015. Consecutive enrollment was not mandatory. The following baseline patient characteristics were reported by the participating study sites: age; sex; current or previous use of cigarettes (including the number of pack-years for current and previous smokers), alcohol, cannabis and other recreational drugs; arterial hypertension (defined as blood pressure >140/90 mm Hg, based on medical history); hypercholesterolemia and hypertriglyceridemia; diabetes mellitus; Ehlers-Danlos syndrome or other connective tissue diseases; polycystic kidney disease; and familial history of IA. Furthermore, centers reported the initial World Federation of Neurosurgical Societies (WFNS) grade for patients with RIA and the preprocedural modified Rankin Scale score (mRS) for patients with UIA.

Recorded aneurysm characteristics were aneurysm sac diameter (including trichotomization into <10, 10–25, and >25 mm); neck size (wide-neck being defined as ≥ 4 mm); aneurysm location (extradural ICA, intradural ICA, including the posterior communicating artery, middle cerebral artery, anterior communicating/anterior cerebral artery, or vertebrobasilar artery; territory branch aneurysms were included in the respective category); aneurysm rupture status (ruptured or unruptured); aneurysm

morphology (regular or irregular); and number of IAs (single or multiple).

Treatment modalities were at the discretion of the treating interventional neuroradiologist and categorized into coils, BAC, SAC, flow diversion, intrasaccular flow-disruption, and parent vessel sacrifice. The use of techniques like dual microcatheter coiling, Y-stent placement, or double BAC did not represent an exclusion criterion. Patients treated by these modalities were grouped into the respective categories (for example, double BAC was analyzed as BAC).

Notably, patients with UIAs who did not undergo endovascular treatment of at least 1 aneurysm, including patients who underwent clipping, were not included in the ARETA study.

Data Management and Statistics

Participating centers reported patient, aneurysm, and treatment characteristics on a standardized form. The centers also collected preoperative DSA and immediate postoperative DSA and transferred the results in an anonymized form to Reims University Hospital. Aneurysm characteristics and treatment modalities of all patients were reviewed, checked for accuracy, and, if necessary, revised by 2 neuroradiologists (M.G., S.S.) at the managing site. Data management and statistical analysis were conducted by the Department of Research and Public Health of Reims University Hospital (C.B.). We applied descriptive statistics: Data are presented with mean and SD for quantitative variables and number and percentage for qualitative variables. Comparisons among groups were analyzed using a χ^2 or Student *t* test. No imputation method was used for missing data. Statistical analysis was performed using SAS (Version 9.4; SAS Institute, Cary, North Carolina). A *P* value < .05 was considered significant.

RESULTS

Population Characteristics

In total, 1289 patients with 1761 IA remained for analysis (Figure). Table 1 details the demographic aspects of the study population. Of 1289 patients, 811 (62.9%) presented with at least 1 RIA. Multiple aneurysms (ie, >1) were detected in 319 patients (24.7%); the maximum number of IAs in a single patient was 8.

Among the 811 patients presenting with RIAs, 808 had available data for a World Federation of Neurosurgical Societies score at admission. Distribution of WFNS scores at admission was as follows: I in 390 (48.3%), II in 171 (21.2%), III in 40 (5.0%), IV in 115 (14.2%), and V in 92 (11.4%) patients. Among the 478 patients presenting with UIAs, 467 had available data for pretreatment mRS scores. The distribution of pretreatment mRS was as follows: mRS 0 in 344 (73.7%), mRS 1 in 114 (24.4%), mRS 2 in 5 (1.1%), mRS 3 in 2 (0.4%), and mRS 4 in 2 (0.4%) patients.

Aneurysm Characteristics

Of 1761 observed IAs, 835 (47.4%) were ruptured and 926 (52.6%) were unruptured. Mean aneurysm diameter was 6.1 ± 3.6 mm: 1524 IAs (87.5%) had diameters <10 mm, 214 IAs (12.3%) had diameters between 10 and 25 mm, and 4 IAs (0.2%) had diameters of >25 mm. The mean aneurysm neck diameter was 3.2 ± 1.8 mm. Wide-neck aneurysms with a neck diameter of ≥ 4 mm accounted for 486 IAs (28.3%). Irregular configurations were

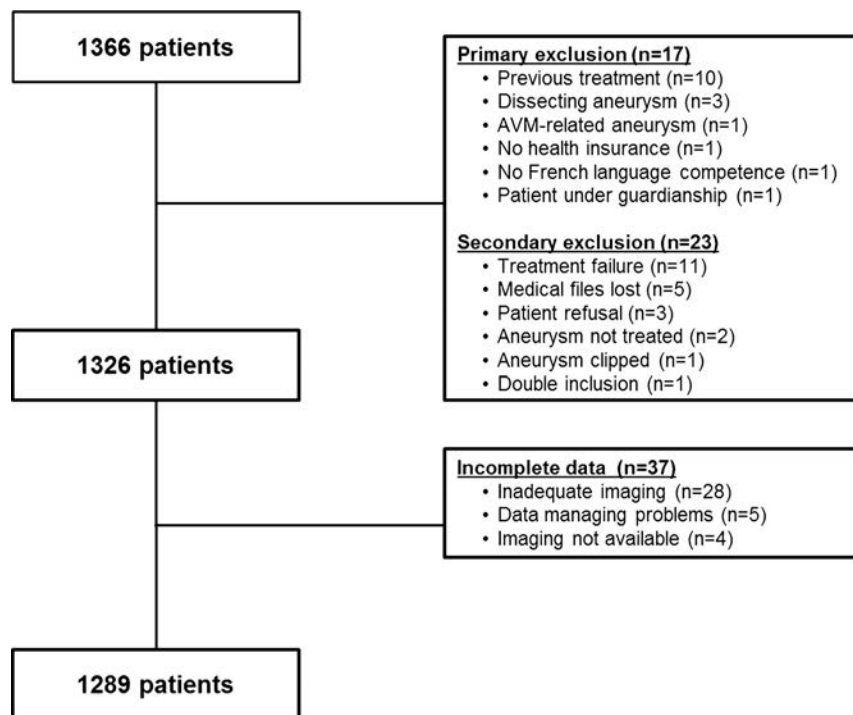


FIGURE Flow chart of the study population. “Treatment failure” refers to an endovascular treatment attempt that was aborted before a device was implanted.

observed in 1022 IAs (60.4%). Locations of the IAs are shown in Table 2.

Endovascular treatment was performed for 1359 of 1761 aneurysms (77.2%). Among treated aneurysms, 835 (61.4%) were ruptured. More than 1 aneurysm was treated during 1 session in 67 patients (5.2%); 24 of 478 (5.0%) patients with UIAs and 43 of 811 (5.3%) patients with RIAs.

Locations of the treated IAs are shown in Table 2. Treated aneurysms had a mean diameter of 6.8 ± 3.5 mm. Diameters of <10 mm were seen in 1149 IAs (84.5%), 206 IAs (15.2%) had diameters between 10 and 25 mm, and 4 IAs (0.3%) had diameters of >25 mm. The mean neck size was 3.5 ± 1.8 mm. Wide-neck accounted for 434 IAs (31.9%). Irregular shapes were found in 967 treated aneurysms (71.2%).

Comparison of Treated and Untreated Unruptured Aneurysms

Of 926 UIAs, 524 (56.6%) were treated. Treated UIAs had significantly greater dimensions both of the aneurysm sac (7.6 ± 4.0 versus 3.4 ± 2.0 mm; $P < 0.001$) and the aneurysm neck (4.1 ± 2.2 versus 2.4 ± 1.3 mm; $P < 0.001$) than UIAs that were left untreated. Of note, 375 untreated UIAs (97.9%) were significantly smaller than 10 mm versus 413 treated UIAs (78.8%) ($P < 0.001$), and 311 untreated UIAs (81.2%) were significantly smaller than 5 mm versus 113 treated UIAs (21.6%) ($P < 0.001$). Treatment rates of UIAs varied among aneurysm locations: Overall, 67.4% of anterior cerebral artery/anterior communicating artery aneurysms (124 of 184), 68.7% of intradural ICA aneurysms (202 of 294), 68.1% of vertebrobasilar aneurysms (47 of 69), 41.4% of extradural ICA aneurysms (36 of 87), and 39.7% of MCA aneurysms (115 of 290) were treated by endovascular means. UIAs of the extradural ICA were significantly less frequently treated than

aneurysms in other locations (36 of 87 [41.4%] versus 488 of 837 [58.3%]; $P = .002$). Likewise, UIAs of the MCA were less frequently treated endovascularly than UIAs in other locations (115 of 290 [39.7%] versus 409 of 634 [64.4%]; $P < 0.001$). Moreover, UIAs with irregular configurations were significantly more frequently treated than UIAs with regular configurations (303 of 358 [84.6%] versus 221 of 498 [44.4%]; $P < 0.001$). The 55 irregular untreated UIAs were significantly smaller than their treated counterparts (4.6 ± 2.4 versus 7.0 ± 3.4 mm, $P < 0.001$).

Endovascular Techniques

Endovascular techniques that were applied are shown in Table 3. UIAs were significantly more frequently treated with intrasaccular flow disruption (36 of 524 [6.9%] versus 5 of 835 [0.6%]; $P < 0.001$), flow diversion (61 of 524 [11.5%] versus 4 of 835 [0.5%]; $P < 0.001$), and SAC (41 of 524 [7.8%] versus 8 of 835 [1.0%]; $P < 0.001$) than

RIAs. Altogether, these 3 techniques were used for 26.1% of UIAs. One giant UIA was treated with a detachable balloon for parent vessel occlusion, and 1 RIA was treated by parent vessel occlusion using coils. RIAs were more frequently treated by coiling (461 of 835 [55.2%] versus 189 of 524 [36.1%]; $P < 0.001$) and BAC (356 of 835 [42.6%] versus 196 of 524 [37.4%]; $P = .06$) than UIAs, but the difference was not statistically significant for BAC. Of note, 97.8% (817 of 835) of RIAs were treated by coiling or BAC.

Treatment modalities varied depending on the aneurysm sac dimensions (Table 4). Aneurysms of >10 mm were more frequently treated with flow diverters than aneurysms <10 mm (30 of 210 [13.8%] versus 35 of 1149 [3.1%]; $P < 0.001$). However, 54.7% (35 of 64) of flow-diverting procedures were performed for treatment of aneurysms of <10 mm. Aneurysms of <10 mm were more frequently treated with standard coiling than aneurysms of >10 mm (569 of 1149 [49.5%] versus 81 of 210 [38.6%]; $P = .003$). An additional analysis, further dividing small aneurysms (<10 mm) into aneurysms of <5 and ≥ 5 mm, was conducted and is shown in On-line Table 1. Most important, interclass differences with the fourth size category did not change for most treatment modalities (ie, coiling, BAC, flow diversion, SAC, and parent vessel occlusion) compared with the initial analysis with 3 size categories (<10 , 10–25, >25 mm). The only new significant difference was found for flow disruption ($P < 0.001$), which is explained by the infrequent use of the Woven EndoBridge (WEB aneurysm embolization system; Sequent Medical, Aliso Viejo, California) for aneurysms of <5 mm (2 of 399 [0.5%] versus 39 of 960 [4.1%]; $P < 0.001$).

Treatment modalities also varied depending on the aneurysm neck diameter (Table 5). Stent-assisted coiling, intrasaccular flow

Table 1: Demographic characteristics of 1289 patients

Variables	
Female (No.) (%)	866 (67.2%)
Age (mean)	54.1 ± 12.7 years
Single IA (No.) (%)	970 (75.3%)
Multiple IAs (No.) (%)	319 (24.7%)
2 IAs (No.) (%)	214 (67.1%)
3 IAs (No.) (%)	73 (22.9%)
4 IAs (No.) (%)	23 (7.2%)
5 IAs (No.) (%)	5 (1.6%)
6 IAs (No.) (%)	2 (0.6%)
7 IAs (No.) (%)	1 (0.3%)
8 IAs (No.) (%)	1 (0.3%)
Tobacco (No.) (%) ^a	768 (60.4%)
Active smoking (No.) (%) ^b	559/762 (73.4%)
Pack-years (mean) ^c	26.0 ± 21.0
Regular alcohol consumption (No.) (%) ^d	255 (20.2%)
Cannabis use (No.) (%) ^e	45 (3.6%)
Other recreational drugs (No.) (%) ^d	15 (1.2%)
Hypertension (No.) (%) ^f	462 (36.1%)
With treatment (No.) (%) ^g	363/449 (80.9%)
Normalized blood pressure (No.) (%) ^h	304/429 (70.9%)
Dyslipidemia (No.) (%) ⁱ	226 (17.8%)
Hypercholesterolemia (No.) (%) ^j	195/207 (94.2%)
Hypertriglyceridemia (No.) (%) ^k	47/198 (23.7%)
With treatment (No.) (%) ^l	151/206 (73.3%)
Family history of IA (No.) (%) ^m	90 (7.2%)
Diabetes mellitus (No.) (%) ^f	63 (4.9%)
Dietary treatment only ⁿ	17/60 (28.3%)
Oral antidiabetic treatment ^o	40/62 (64.5%)
Insulin treatment ^p	9/61 (14.8%)
Polycystic kidney disease (No.) (%) ^q	17 (1.3%)
Connective tissue disease (No.) (%) ^f	1 (0.1%)

^a The following are missing data: 17 (1.3%).

^b 6 (0.8%).

^c 120 (15.6%).

^d 24 (1.9%).

^e 22 (1.7%).

^f 9 (0.7%).

^g 13 (2.8%).

^h 33 (7.1%).

ⁱ 16 (1.2%).

^j 19 (8.4%).

^k 28 (12.4%).

^l 20 (8.8%).

^m 30 (2.3%).

ⁿ 3 (4.8%).

^o 1 (1.6%).

^p 2 (3.2%).

^q 8 (0.6%).

Table 2: All aneurysms in the study collective and treated aneurysms

Location	All Aneurysms ^a		Treated Aneurysms	
	No.	%	No.	%
ACA/AcomA	557	31.7	497	36.6
MCA	458	26.0	283	20.8
Intradural ICA	530	30.1	438	32.2
Extradural ICA	88	5.0	37	2.7
Vertebrobasilar	126	7.2	104	7.6
Total	1751	100	1359	100

Note:—ACA indicates anterior cerebral artery; AcomA, anterior communicating artery.

^a Two missing data.

disrupters, and flow diverters were significantly more frequently deployed in wide-neck aneurysms (32 of 434 [7.4%] versus 17 of 925 [1.8%]; $P < 0.001$; 36 of 434 [8.3%] versus 5 of 925 [0.5%];

$P < 0.001$; and 48 of 434 [11.1%] versus 17 of 925 [1.8%]; $P < 0.001$, respectively) than in narrow-neck IAs. Simple coiling was significantly more frequently used in narrow-neck IAs (511 of 925 [55.2%] versus 139 of 434 [32.0%]; $P < 0.001$). Most interesting, BAC was not used more frequently in wide-neck than in narrow-neck aneurysms (177 of 434 wide-neck [40.8%] versus 375 of 925 narrow-neck IAs [40.6%]; $P = .93$).

Aneurysm location affected the chosen treatment technique, as shown in On-line Table 2. Notably, BAC was performed more often for aneurysms of the intradural segment of the ICA than in other aneurysm locations (204 of 438 [46.6%] versus 348 of 921 [37.8%]; $P = .002$). Conversely, flow diverters were deployed more often in aneurysms of the intra- and extradural ICA than in other aneurysm locations (41 of 438 [9.4%] versus 24 of 921 [2.6%]; $P < 0.001$; and 15 of 37 [40.5%] versus 50 of 1322 [3.8%]; $P < 0.001$, respectively). Also, SAC was used more often for extradural ICA aneurysms (6 of 37 [16.2%] versus 43 of 1322 [3.2%]; $P = .002$). Furthermore, these extradural ICA aneurysms were less frequently treated by standard coiling than IAs in other locations (7 of 37 [18.9%] versus 643 of 1322 [48.6%]; $P < 0.001$). Intra-aneurysmal flow disruption was used more often in MCA and vertebrobasilar aneurysms than in other aneurysm locations (19 of 283 [6.7%] versus 22 of 1076 [2.0%]; $P < 0.001$; and 7 of 104 [6.7%] versus 34 of 1255 [2.7%]; $P = .03$, respectively).

DISCUSSION

Relevance of Flow Diversion, Intracapsular Flow Disruption, and Stent-Assisted Coiling

In ARETA, 11.6% of UIAs were treated by flow diversion, representing a significant proportion in this cohort. The US FDA approved the use of flow diverters for patients with unruptured large or giant wide-neck intracranial aneurysms in the ICA from the petrous to the superior hypophyseal segments.¹⁸ The ARETA results are in line with current recommendations because flow diverters were used for wide-neck large and giant aneurysms at a proportionally higher rate than for small and narrow-neck aneurysms. Flow diverters were also used more frequently in aneurysms of the intradural (9.4%) and extradural (40.5%) ICA. However, the extension of treatment indications to ruptured, small, narrow-neck, or distal bifurcation aneurysms is increasingly reported by some groups.¹⁹ Of note, in the present study, 53.8% of flow diverters were used in aneurysms of <10 mm, and 26.2% of aneurysms treated with a flow diverter had a neck diameter of <4 mm. A limited number of flow-diverting stents were also used for the treatment of MCA and anterior communicating artery aneurysms, a treatment concept that is currently under discussion.^{20,21} These numbers thus reflect a flexible application of current recommendations for the use of flow diversion if judged necessary by the interventionist. Because an endoluminal implant is left in place, dual antiplatelet therapy is usually necessary and the aneurysm is at least temporarily left circulating (if no coils are added during the procedure). Flow diverters were thus very rarely used in RIAs (4 of 835 ruptured aneurysms [0.5%]); however, these results may be biased by the exclusion of dissecting, fusiform, and blisterlike aneurysms, where flow diversion is sometimes the only treatment option when parent vessel sacrifice is not possible.^{22,23}

Table 3: Techniques used for embolization of ruptured and unruptured aneurysms

Treatment Modality	All IAs		RIAs		UIAs		P Value
	No.	%	No.	%	No.	%	
Coiling alone	650	47.8	461	55.2	189	36.1	<0.001
Balloon-assisted coiling	552	40.6	356	42.6	196	37.4	.06
Stent-assisted coiling	49	3.6	8	1.0	41	7.8	<0.001
Flow diversion ^a	65	4.8	4	0.5	61	11.6	<0.001
Flow disruption ^b	41	3.0	5	0.6	36	6.9	<0.001
Parent vessel occlusion	2	0.2	1	0.1	1	0.2	.74
Total	1359	100	835	100	524	100	

^a Thirty aneurysms were treated in conjunction with coils.

^b Two aneurysms were treated in conjunction with coils; 3 aneurysms, in conjunction with a remodeling balloon; and 1 aneurysm, with an ancillary stent.

Table 4: Treatment modality with regard to aneurysm sac diameter

Treatment Modality	All IAs		<10 mm		10–25 mm		>25 mm		P Value
	No.	%	No.	%	No.	%	No.	%	
Coiling alone	650	47.8	569	49.5	81	39.3	0	0	.003
Balloon-assisted coiling	552	40.6	472	41.1	80	38.8	0	0	.24
Stent-assisted coiling	49	3.6	37	3.2	12	5.8	0	0	.20
Flow diversion	65	4.8	35	3.1	27	13.1	3	75.0	<0.001
Flow disruption	41	3.0	35	3.1	6	2.9	0	0	.93
Parent vessel occlusion	2	0.2	1	0.1	0	0	1	25.0	.006
Total	1359	100	1149	100	206	100	4	100	

Table 5: Treatment modality with regard to aneurysm neck diameter

Treatment Modality	All IAs		<4 mm		≥4 mm		P Value
	No.	%	No.	%	No.	%	
Coiling alone	650	47.8	511	55.2	139	32.0	<0.001
Balloon-assisted coiling	552	40.6	375	40.5	177	40.8	.93
Stent-assisted coiling	49	3.6	17	1.8	32	7.4	<0.001
Flow diversion	65	4.8	17	1.8	48	11.1	<0.001
Flow disruption	41	3.0	5	0.5	36	8.3	<0.001
Parent vessel occlusion	2	0.2	0	0	2	0.5	.10
Total	1359	100	925	100	434	100	

Intrasaccular flow disruption by the WEB device was used to treat 3.0% of patients. This device was introduced in 2011, primarily for treatment of complex wide-neck bifurcation aneurysms of the MCA and basilar artery in particular.^{7–13} If we grouped these aneurysms, 6.7% of both MCA and basilar artery aneurysms were treated by this technique; 87.8% of WEB devices were used in wide-neck aneurysms with neck diameters of ≥4 mm. In ARETA, intrasaccular flow disruption was often used in UIAs (6.9% were treated by the WEB) and only in 0.6% of RIAs. This may be because a wide range of WEB devices suitable for various aneurysm configurations were not permanently available in all departments; furthermore, the learning curve in WEB application might be a limiting factor as well as a possible reluctance to use this novel device in a ruptured aneurysm. Whereas the current literature indicates that it may be safe and effective to treat RIAs with flow disrupters²⁴—particularly because postinterventional antiplatelet therapy is not imperative—large prospective controlled data are not available and are subject to the CLinical Assessment of WEB Device in Ruptured aneurYSms (CLARYS) study, which recently completed recruitment (NCT02687607: www.clinicaltrials.gov).

In the ARETA study, SAC was used in 3.6% of all aneurysms. The use of dedicated self-expanding endoluminal devices for SAC was first reported in 2002¹⁵ and is now a standard technique. SAC was primarily designed for the treatment of unruptured wide-neck aneurysms, and in ARETA, it was used in 7.8% of these aneurysms: Wide-neck aneurysms accounted

for 65.3% of SAC procedures. Stents usually necessitate a dual-antiplatelet regimen and are associated with a higher complication rate in RIAs compared with UIAs.²⁵ Conversely, only 8 patients (1%) with RIAs were treated with stent assistance; moreover, it is not clear in how many of these patients SAC was used as a rescue treatment.

Overall, our study confirms that in patients presenting with a ruptured saccular aneurysm, flow diversion, flow disruption, and SAC currently play a minor role, given that 97.8% of RIAs were amenable to treatment with simple coiling or BAC in our study.

Balloon-Assisted Coiling

BAC, also known as a remodeling technique, was used in 40.6% of aneurysms in the present series (42.6% of RIAs and 37.4% of UIAs). Since its initial description by Moret et al¹⁴ in 1997, BAC has emerged as a standard treatment option. Apart from the ability to treat wide-neck aneurysms and offer improved immediate and follow-up anatomic results,²⁶ it has 2 additional potential advantages over simple coiling, with a similar safety profile²⁶: 1) The microcatheter is stabilized during embolization, making it easier to maintain access; and 2) in case of aneurysm perforation during coiling, the balloon can be inflated while detaching several coils to immediately protect and seal the rupture site. These potential advantages are also reflected by the fact that BAC was not more frequently used for the treatment of wide-neck than narrow-neck aneurysms in the present study. Aneurysm location in-

fluenced the frequency of BAC: Notably, it was used more often for aneurysms of the intradural ICA (ie, posterior communicating artery and paraophthalmic aneurysms).

In CLARITY, BAC was used in 20.5% of cases (versus 40.6% in the present cohort); our study confirms the wider application of BAC in cases of RIAs. The rationale behind this development is likely linked to the increased risk of perforation in RIAs.^{3,27} While the rates of BAC between ARETA and ATENA for UIAs are comparable (37.3% in ATENA versus 37.4% in the present series), we observed a decline in simple coiling approaches (54.5% in ATENA versus 36.1% in ARETA).² Flow diversion, flow disruption, and SAC were used in 26.2% of UIAs in the present series, whereas neither flow diversion nor intrasaccular flow disruption was available during the recruitment period of ATENA; 7.8% of patients were treated by SAC in that study. Our results indicate that treatment modalities of UIAs are currently shifting toward more complex and novel approaches, away from the simple coiling technique.

Comparison of Treated and Untreated Unruptured Aneurysms

The rupture risk of UIAs depends on aneurysm size, location, and shape and is generally low, especially in small aneurysms.^{28,29} Preventive treatment is generally justified if the benefit of treatment outweighs the anticipated treatment risks. Therefore, it is not surprising that untreated UIAs in ARETA were smaller than treated counterparts and presented less frequently with an irregular form. Furthermore, extradural ICA aneurysms, in which subarachnoid hemorrhage is usually not a concern, were less frequently treated than UIAs of the anterior cerebral artery/anterior communicating artery, the intradural ICA segment (which included the posterior communicating artery in this study), and the vertebrobasilar territory. Also, unruptured MCA aneurysms were less frequently treated than UIAs in other locations, which may be because they are less likely to rupture.²⁸

Limitations of the Study

Our study has limitations. Because patients who underwent clipping were not included in the study, a selection bias may exist, in particular with MCA aneurysms in which clipping is still widely used. However, endovascular treatment is currently the treatment of choice for RIAs and UIAs in many institutions. Another limitation is that consecutive enrollment of all patients treated in 1 center was not mandatory for the participation in the study. Because the study inclusion period ended in 2015, modifications of the current practice with an even broader implementation of novel techniques are probable, particularly intrasaccular flow disruption. The low percentage of novel techniques could also be partly explained by regulatory mechanisms because during the study period, there was no reimbursement for intrasaccular flow disruptors or intravascular flow diverters and limited reimbursement for conventional microstents by the French Health Insurance (whereas the devices are, in case of nonreimbursement, paid for by the hospital itself). Moreover, there is certainly a variance of technical approaches among the participating centers. Another limitation is that only the aneurysm rupture status was assessed at inclusion into the ARETA cohort and compressive symptoms

were not evaluated. Our observations of the characteristics of treated and untreated UIAs must be viewed with caution because this study did not focus on the natural course of UIAs and there was no prospective observation of rupture risk. Finally, this article does not present clinical or anatomic outcome data, which will be the subject of future publications.

CONCLUSIONS

Our study presents the demographics of the patient collective of the ARETA study and provides a representative overview of current endovascular treatment strategies for RIAs and UIAs. The technique choice was influenced by the rupture status of the aneurysm, sac size, neck diameter, and location. While the evolving techniques of flow diversion, intrasaccular flow disruption, and stent-assisted coiling were deployed in a significant proportion of UIAs, most RIAs were treated with simple coiling and balloon-assisted coiling. When we compared the present study collective with previously published series, shifting treatment regimens toward more advanced techniques—away from simple coiling—was observed. Moreover, we observed an influence of size, location, and form on the decision of whether to treat UIAs.

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REFERENCES

1. Molyneux A, Kerr R, Stratton I. **International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial.** *Lancet* 2002;360:1267–74 [CrossRef Medline](#)
2. Pierot L, Spelle L, Vitry F. **Immediate clinical outcome of patients harboring unruptured intracranial aneurysms treated by endovascular approach: results of the ATENA study.** *Stroke* 2008;39:2497–504 [CrossRef Medline](#)
3. Pierot L, Cognard C, Ricolfi F, et al. **Immediate anatomic results after the endovascular treatment of ruptured intracranial aneurysms: analysis in the CLARITY series.** *AJNR Am J Neuroradiol* 2010;31:907–11 [CrossRef Medline](#)
4. Kallmes DF, Brinjikji W, Boccardi E, et al. **Aneurysm Study of Pipeline in an Observational Registry (ASPIRe).** *Interv Neurol* 2016;5: 89–99 [CrossRef Medline](#)
5. Kallmes DF, Hanel R, Lopes D, et al. **International retrospective study of the Pipeline Embolization Device: a multicenter aneurysm treatment study.** *AJNR Am J Neuroradiol* 2015;36:108–15 [CrossRef Medline](#)
6. Becske T, Kallmes DF, Saatci I, et al. **Pipeline for uncoilable or failed aneurysms: results from a multicenter clinical trial.** *Radiology* 2013; 267:858–68 [CrossRef Medline](#)
7. Pierot L, Spelle L, Molyneux A, et al. **Clinical and anatomical follow-up in patients with aneurysms treated with the WEB device: 1-year follow-up report in the cumulated population of 2 prospective, multicenter series (WEBCAST and French Observatory).** *Neurosurgery* 2016;78:133–41 [CrossRef Medline](#)
8. Pierot L, Klich J, Cognard C, et al. **Endovascular WEB flow disruption in middle cerebral artery aneurysms: preliminary feasibility, clinical, and anatomical results in a multicenter study.** *Neurosurgery* 2013;73:27–34; discussion 34–35 [CrossRef Medline](#)
9. Pierot L, Moret J, Turjman F, et al. **WEB treatment of intracranial**

- aneurysms: clinical and anatomic results in the French Observatory. *AJNR Am J Neuroradiol* 2016;37:655–59 CrossRef Medline
10. Pierot L, Moret J, Turjman F, et al. **WEB treatment of intracranial aneurysms: feasibility, complications, and 1-month safety results with the WEB DL and WEB SL/SLS in the French Observatory.** *AJNR Am J Neuroradiol* 2015;36:922–27 CrossRef Medline
 11. Pierot L, Gubucz I, Buhk JH, et al. **Safety and efficacy of aneurysm treatment with the WEB: results of the WEBCAST 2 study.** *AJNR Am J Neuroradiol* 2017;38:1151–55 CrossRef Medline
 12. Asnafi S, Rouchaud A, Pierot L, et al. **Efficacy and safety of the Woven EndoBridge (WEB) device for the treatment of intracranial aneurysms: a systematic review and meta-analysis.** *AJNR Am J Neuroradiol* 2016;37:2287–92 CrossRef Medline
 13. Fiorella D, Molyneux A, Coon A, et al. **Demographic, procedural and 30-day safety results from the WEB Intra-saccular Therapy Study (WEB-IT).** *J Neurointerv Surg* 2017;9:1191–96 CrossRef Medline
 14. Moret J, Cognard C, Weill A, et al. **Reconstruction technic in the treatment of wide-neck intracranial aneurysms: long-term angiographic and clinical results—apropos of 56 cases [in French].** *J Neuroradiol* 1997;24:30–44 Medline
 15. Henkes H, Bose A, Felber S, et al. **Endovascular coil occlusion of intracranial aneurysms assisted by a novel self-expandable nitinol microstent (Neuroform).** *Interv Neuroradiol* 2002;8:107–19 CrossRef Medline
 16. Fargen KM, Soriano-Baron HE, Rushing JT, et al. **A survey of intracranial aneurysm treatment practices among United States physicians.** *J Neurointerv Surg* 2018;10:44–49 CrossRef Medline
 17. Benaissa A, Barbe C, Pierot L. **Analysis of recanalization after endovascular treatment of intracranial aneurysm (ARETA trial): presentation of a prospective multicenter study.** *J Neuroradiol* 2015;42:80–85 CrossRef Medline
 18. U.S. Food and Drug Administration. Premarket Approval (PMA) of the Pipeline Embolization Device. <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P100018>. Accessed August 15, 2018
 19. Patel PD, Chalouhi N, Atallah E, et al. **Off-label uses of the Pipeline Embolization Device: a review of the literature.** *Neurosurg Focus* 2017;42:E4 CrossRef Medline
 20. Gawlitz M, Januel AC, Tall P, et al. **Flow diversion treatment of complex bifurcation aneurysms beyond the circle of Willis: a single-center series with special emphasis on covered cortical branches and perforating arteries.** *J Neurointerv Surg* 2016;8:481–87 CrossRef Medline
 21. Pistocchi S, Blanc R, Bartolini B, et al. **Flow diverters at and beyond the level of the circle of Willis for the treatment of intracranial aneurysms.** *Stroke* 2012;43:1032–38 CrossRef Medline
 22. Fischer S, Perez MA, Kurre W, et al. **Pipeline embolization device for the treatment of intra- and extracranial fusiform and dissecting aneurysms: initial experience and long-term follow-up.** *Neurosurgery* 2014;75:364–74; discussion 374 CrossRef Medline
 23. Lozupone E, Piano M, Valvassori L, et al. **Flow diverter devices in ruptured intracranial aneurysms: a single-center experience.** *J Neurosurg* 2018;128:1037–43 CrossRef Medline
 24. van Rooij SB, van Rooij WJ, Peluso JP, et al. **WEB treatment of ruptured intracranial aneurysms: a single-center cohort of 100 patients.** *AJNR Am J Neuroradiol* 2017;38:2282–87 CrossRef Medline
 25. Bechan RS, Sprengers ME, Majoie CB, et al. **Stent-assisted coil embolization of intracranial aneurysms: complications in acutely ruptured versus unruptured aneurysms.** *AJNR Am J Neuroradiol* 2016;37:502–07 CrossRef Medline
 26. Pierot L, Cognard C, Spelle L, et al. **Safety and efficacy of balloon remodeling technique during endovascular treatment of intracranial aneurysms: critical review of the literature.** *AJNR Am J Neuroradiol* 2012;33:12–15 CrossRef Medline
 27. Cloft HJ, Kallmes DF. **Cerebral aneurysm perforations complicating therapy with Guglielmi detachable coils: a meta-analysis.** *AJNR Am J Neuroradiol* 2002;23:1706–09 Medline
 28. Morita A, Kirino T, Hashi K, et al; UCAS Japan Investigators. **The natural course of unruptured cerebral aneurysms in a Japanese cohort.** *N Engl J Med* 2012;366:2474–82 CrossRef Medline
 29. Wiebers DO. **Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment.** *Lancet* 2003;362:103–10 CrossRef Medline

Comparison of Pipeline Embolization Device Sizing Based on Conventional 2D Measurements and Virtual Simulation Using the Sim&Size Software: An Agreement Study

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ABSTRACT

BACKGROUND AND PURPOSE: The Sim&Size software simulates case-specific intraluminal Pipeline Embolization Device behavior, wall apposition, and device length in real-time on the basis of rotational angiography DICOM data. The purpose of this multicenter study was to evaluate whether preimplantation device simulation with the Sim&Size software results in selection of different device dimensions than manual sizing.

MATERIALS AND METHODS: In a multicenter cohort of 74 patients undergoing aneurysm treatment with the Pipeline Embolization Device, we compared apparent optimal device dimensions determined by neurointerventionalists with considerable Pipeline Embolization Device experience based on manual 2D measurements taken from rotational angiography with computed optimal dimensions determined by Sim&Size experts blinded to the neurointerventionalists' decision. Agreement between manually determined and computed optimal dimensions was evaluated with the Cohen κ . The significance of the difference was analyzed with the Wilcoxon signed rank test.

RESULTS: The agreement index between manual selection and computed optimal dimensions was low (κ for diameter = 0.219; κ for length = 0.149, $P < .01$). Computed optimal device lengths were significantly shorter (median, 14 versus 16 mm, $T = 402$, $r = -0.28$, $P < .01$). No significant difference was observed for device diameters.

CONCLUSIONS: Low agreement between manually determined and computed optimal device dimensions is not proof, per se, that virtual simulation performs better than manual selection. Nevertheless, it ultimately reflects the potential for optimization of the device-sizing process, and use of the Sim&Size software reduces, in particular, device length. Nevertheless, further evaluation is required to clarify the impact of device-dimension modifications on outcome.

ABBREVIATION: PED = Pipeline Embolization Device

Theoretic flow-diversion concepts for aneurysm treatment were originally formulated in the 1990s.^{1,2} Development of metal alloys and delivery systems, however, lagged behind con-

ceptual thought. The first generation of low-porosity endoluminal reconstruction devices therefore became available only in the following decade.³⁻⁵ The Pipeline Embolization Device (PED; Covidien, Irvine, California) is a member of this larger family of endovascular tools that became known as "flow diverters." The PED was initially approved in the United States by the FDA in 2011 for endovascular treatment of adults with large or giant wide-neck intracranial aneurysms of the internal carotid artery from the petrous to the superior hypophyseal segment,⁶ but indications for its use have subsequently been expanded to a wide range of aneurysm locations and morphologies.⁷⁻¹²

Successful intra-arterial placement of the PED ideally produces immediate changes in regional circulation, redirecting blood flow past the aneurysm into the distal normal vasculature. The resultant intra-aneurysmal stasis promotes thrombosis within the aneurysm, which leads to an angiographic appearance of "cure."¹³ Actual cure, however, is achieved when subsequent

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“endothelialization” of the device occurs, leading to permanent aneurysm exclusion from the circulation. A challenge that inevitably arises when using braided-design flow diverters such as the PED is their mechanical behavior when constrained and forced to accommodate a diameter mismatch along the covered arterial segment. For instance, proximal and distal landing zones are most often of different diameters, and device placement, therefore, naturally involves “oversizing” at one end of the recipient vessel. Sizing mismatch, however, leads to heterogeneity in metal coverage, which, in turn, determines the ability of the device to modulate flow and to sustain endothelial overgrowth, a key factor in the success of the treatment.^{14,15}

Deployment of flow diverters is technically far more challenging than conventional stents used as supports for coiling aneurysms. Also, experience with the PED is still increasing, and device behavior during implantation remains somewhat counterintuitive and, at times, challenging to predict.^{14,15} This behavior results in a comparatively flat learning curve and may well contribute to the occurrence of some of the often devastating periprocedural complications.¹⁶ It is, therefore, desirable to facilitate and optimize device sizing and device positioning through preimplantation simulation. Computer-based-simulation modeling tools such as the Sim&Size software (Sim&Cure; Grabels, France) provide the opportunity to simulate and, hence, to anticipate PED behavior of variable dimensions easily and within seconds. In short, this novel technology aims to standardize the PED-sizing process and ultimately promises to increase the neurointerventionalists’ ability to confidently select optimal PED dimensions before implantation.

In this multicenter cohort study of 74 patients who underwent aneurysm treatment with PEDs, we compared the dimensions of devices selected by neurointerventionalists with considerable PED experience based on conventional, manual 2D measurements obtained from rotational angiography with the computed optimal PED dimensions determined by Sim&Size experts, who were blinded to the neurointerventionalists’ choice. The purpose was to evaluate whether virtual preimplantation device simulation with the Sim&Size software results in selection of different PED dimensions compared with conventional (ie, manual) device sizing.

MATERIALS AND METHODS

Seventy-four consecutive patients undergoing aneurysm treatment with PEDs between January 2015 and December 2016 in center A (Hôpital Gui de Chauliac, Centre Hospitalier Universitaire de Montpellier, University of Montpellier, Montpellier, France) and between January 2017 and February 2018 in center B (Basel University Hospital, University of Basel, Basel, Switzerland) were included. Ethics committee approval and patient consent were obtained.

Baseline Characteristics

Baseline characteristics included patient sex and age, as well as aneurysm location and maximal diameter. In addition, we recorded the additional use of embolic material such as coils and whether a single PED or a multi-PED construct was used.

Perioperative Complications and Outcome

Perioperative complications, such as PED deployment failure, occlusion of inadvertently covered branches, and occurrence of hemorrhagic or ischemic stroke, were recorded. Radiologic outcome, including the presence of residual aneurysm perfusion or an endoleak, was recorded for all patients with 1-year imaging follow-up.

Study Variables

Study variables included the nominal dimensions (diameter, length) of both the manually determined and the computed PEDs. In cases in which a multi-PED construct was used, analysis was limited to the first implanted device.

Study Design

The Sim&Size software became available in France and Switzerland for use in routine clinical practice at the end of 2016. For cases performed before the software had become available (all patients from center A), the presumed optimal device dimensions were manually determined on the basis of 2D measurements made on rotational angiography acquired before PED implantation by 1 of 2 local neurointerventionalists with considerable PED experience. The manually determined presumed optimal device was then implanted. In these cases, the computed optimal PED dimensions were retrospectively determined by virtual simulation by a team of Sim&Size experts, which included software engineers and at least 1 local neurointerventionalist with considerable PED experience, all blinded to the operating neurointerventionalists’ manual choice. For cases performed after Sim&Size software had become available (all patients from center B), preimplantation virtual device simulation was routinely performed before implantation by a team of Sim&Size experts that included software engineers and at least 1 local neurointerventionalist with considerable PED experience. In these cases, the manually determined presumed optimal device dimensions were retrospectively determined on the basis of 2D measurements made on rotational angiography acquired before PED implantation by 1 of 2 local neurointerventionalists with considerable PED experience who was blinded to the results of virtual simulation.

Data Collection

Clinical and radiographic baseline data as well as the manually determined presumed optimal and computed optimal PED dimensions were collected by the local teams in both participating centers. Anonymized data were then collected centrally and prepared for analysis at the Department of Radiology, Basel University Hospital, University of Basel, Basel, Switzerland.

Statistical Analysis

Descriptive statistics for a set of predefined variables of interest are provided (see study variables above). The degree of agreement between the manually determined presumed optimal and computed optimal device dimensions was evaluated with the Cohen κ . The Wilcoxon signed rank test was performed to analyze differences in nominal device length and nominal device diameter between sizing methods. Differences in baseline characteristics were evaluated with a Student t test, Fisher exact test, and Wilcoxon signed rank test, as applicable. Statistical analysis was performed

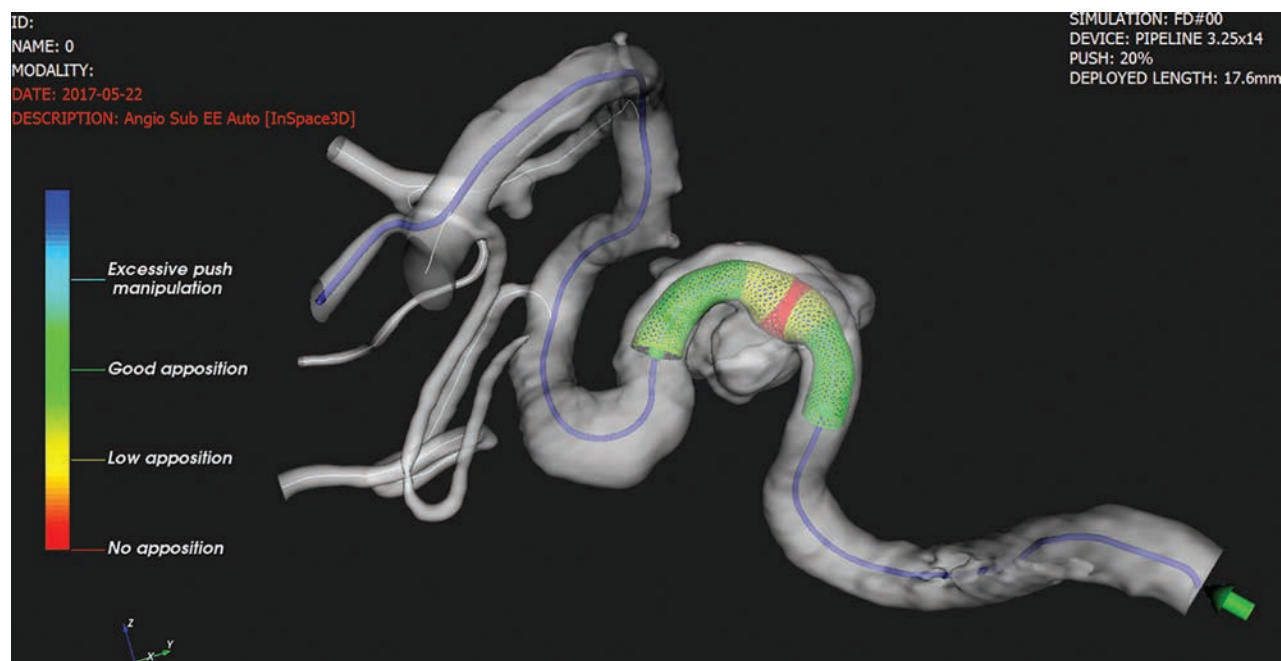


FIG 1. The Sim&Size software anticipates intraluminal PED behavior, wall apposition, and device length after implantation on the basis of preimplantation rotational angiography DICOM data. The planned microcatheter trajectory for PED delivery is indicated in blue. Anticipated wall apposition along the covered segment is color-coded from red (no apposition) to green (good apposition). Courtesy of Cindy Wehrli and Phil Häfliger from Medtronic, Switzerland.

with SPSS (Version 22.0; IBM, Armonk, New York). Statistical significance was defined as $P < .05$.

Software-Based Computation of PED Dimensions

The commercially available Sim&Size software is a fast simulation tool that predicts intravascular behavior of flow diverters such as the PED (Fig 1).¹⁷ On the basis of DSA DICOM data, the software reconstructs the 3D vessel geometry using volume-rendering. The accuracy of the reconstruction can be reviewed in real-time and, if necessary, optimized manually. Potential microcatheter trajectories in the target vessel are then computed on the basis of the vessel centerline. Once trajectory and device type have been selected, the desired distal and proximal landing zones are defined manually. A first proposal is provided instantly for device dimensions compatible with the chosen landing zones. Device deformation, porosity, and degree of wall apposition are simultaneously incorporated and displayed. Different landing zones, device diameters, lengths, and mechanical manipulations (eg, amount of push during PED deployment) can be virtually tested in real-time.

RESULTS

Baseline Characteristics

Seventy-four consecutive patients from 2 tertiary neurovascular centers were included. Center A contributed 63 patients (85.1%), and center B contributed the remaining 11 patients (14.9%). While the mean age distribution between the 2 centers was not different (overall: 58.6 ± 13.3 years; center A: 58.6 ± 14.0 years; center B: 58.5 ± 8.6 years), aneurysms in center A were significantly larger (overall: 8.8 ± 7.2 mm; center A: 9.3 ± 7.7 mm; center B: 6.3 ± 2.9 mm, $P < .05$) and significantly more often extradural in location (overall: 52/74 cases [70.3%]; center A:

Table 1: Baseline characteristics^a

Characteristics	
Sex (No.) (%)	
Male	63 (85.1%)
Female	11 (14.9%)
Patient age (mean) (SD, range) (yr)	58.6 (13.3, 30–83)
Ruptured aneurysms (No.) (%)	5 (6.8%)
Acute dissection (No.) (%)	15 (20.3%)
Location of aneurysms (No.) (%)	
Cervical ICA	10 (13.5%)
Petrous ICA	13 (17.6%)
Cavernous ICA	26 (35.1%)
Paraophthalmic ICA	10 (13.5%)
Communicating ICA	1 (1.4%)
Choroidal ICA	1 (1.4%)
Vertebrobasilar circulation	3 (4.1%)
ACA	4 (5.4%)
MCA	6 (8.1%)
Maximum aneurysm diameter (mean) (SD, range) (mm)	8.8 (7.2, 2.0–40.0)
Multi-PED constructs (No.) (%)	7 (9.5%)
Use of additional coils (No.) (%)	11 (14.9%)

Note:—ACA indicates anterior cerebral artery.

^a Location of ICA aneurysms is provided according to the New York University classification.³⁵ Number of patients = 74.

50/63 cases [79.4%]; center B: 2/11 cases [18.2%], $P < .01$). Baseline characteristics are provided in Table 1.

Treatment Characteristics, Perioperative Complications, and Outcome

Coils were used in addition to the PED in 11 cases (14.9%); and a multi-PED construct, in 7 cases (9.5%). Periprocedural complications occurred in 11 patients (14.9%), including PED deployment failure ($n = 5$ cases, 6.8%), ischemia in the same territory as

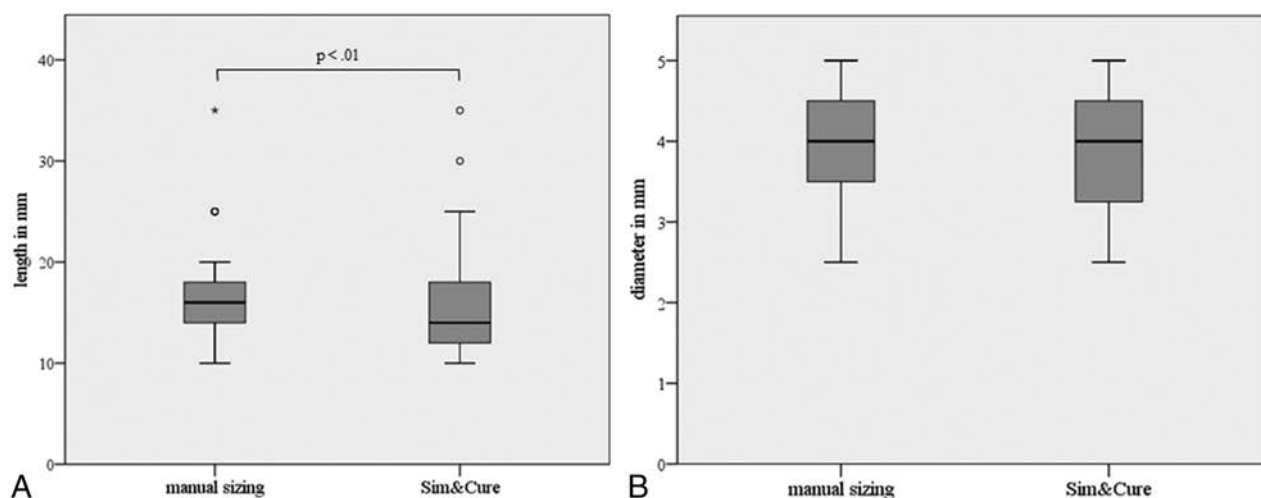


FIG 2. Boxplots illustrating differences between manually determined presumed optimal device dimensions and computed optimal PED dimensions for PED length (A) and for PED diameter (B).

PED deployment ($n = 4$, 5.4%), and hemorrhage in the same territory as the PED deployment ($n = 2$, 2.7%). One-year imaging follow-up was available for 47/74 patients (63.5%) and revealed residual aneurysm perfusion in 6 patients (8.1%). Differences between the 2 participating centers in terms of perioperative complications and outcome were not statistically significant. Details are provided in On-line Table 1.

Degree of Agreement

Sim&Size computation suggested different device dimensions than the manually determined presumed optimal dimensions in 67/74 patients (90.5%). Accordingly, the agreement index between neurointerventionalists and Sim&Size was low (κ for diameter = 0.219; κ for length = 0.149, $P < .01$). Agreement remained low when the cohorts from each contributing center were analyzed separately (center A: κ for diameter = 0.203; κ for length = 0.129, $P < .05$; center B: κ for diameter = 0.294; κ for length = 0.230, $P < .05$) and when patients who received a multi-PED construct were excluded from the analysis (overall: κ for diameter = 0.239; κ for length = 0.125, $P < .01$; center A: κ for diameter = 0.222, κ for length = 0.119, $P < .01$; center B: κ for diameter = 0.349; κ for length = 0.186, $P < .05$).

PED Dimensions

The median length of software-based optimal PEDs was shorter than the median length of manually determined presumed optimal devices (14 versus 16 mm) (Fig 2). This difference did reach statistical significance ($T = 402$, $r = -0.28$, $P < .01$) and remained significant when patients who received a multi-PED construct were excluded from analysis ($T = 375$, $r = -0.24$, $P < .01$). There was no significant difference with regard to the median PED diameter, which was 4 mm in both groups (Fig 2). Accordingly, the mean length of the computed optimal PEDs was shorter (15.22 versus 16.31 mm), while the mean diameter was comparable in both groups (3.94 versus 3.89 mm). Details are provided in Table 2.

The Sim&Size software suggested a shorter nominal PED length than manually determined in 56.8% ($n = 42$), the same

Table 2: Dimensions (diameter, length) of the manually determined presumed optimal and computed optimal PEDs

	Manually Determined	Computed Optimal
PED diameter (mm)		
Mean (SD)	3.89 (0.70)	3.94 (0.69)
Range	2.5–5	2.5–5
Median (IQR)	4 (3.50–4.50)	4 (3.25–4.50)
PED length (mm)		
Mean (SD)	16.31 (3.94)	15.22 (5.21)
Range	10–35	10–35
Median (IQR)	16 (14–18)	14 (11.5–18)

Note:—IQR indicates interquartile range.

length in 25.7% ($n = 19$), and a longer device length in the remaining 17.6% ($n = 13$) of cases (Fig 3). The proportion of cases in which the software proposed a shorter length was higher for intradural compared with extradural aneurysms and was the highest for more distal aneurysms arising from areas such as the anterior or middle cerebral artery. However, the length differences between software-based optimal PEDs and manually determined presumed optimal devices was smaller (most, 0–4 mm) for intracranial aneurysms compared with their extradural counterparts (Fig 4).

DISCUSSION

We analyzed a multicenter cohort of 74 patients undergoing treatment with PEDs for intracranial aneurysms (Table 1) and found low agreement between the neurointerventionalists' manual device selection and the computed optimal PED dimensions determined by a team of Sim&Size experts blinded to the neurointerventionalist's manual-sizing decision. While we believe that this low agreement ultimately reflects the potential for optimization of the device-sizing process, it should not be interpreted per se as proof that virtual simulation performs better than conventional manual selection.

We found that the computed optimal PEDs were significantly shorter (Table 2 and Fig 2), which we attribute to the ability of the software to reliably anticipate implanted length and consequently

accurate landing zones, thereby allowing confident selection of the shortest possible device. Accordingly, the proportion of cases in which the Sim&Size software suggested a shorter device was higher for intradural aneurysms where side-branches and perforators come into play (Fig 4). Even though the true consequences

of this device-length reduction remain to be clarified in dedicated further research, it is intuitive that particularly for intradural aneurysms, the minimal amount of endoprosthetic material required to achieve a goal is desirable, as is the potential to remove uncertainties related to unexpected landing zones and, consequently, unpredictable wall apposition or unanticipated branch vessel coverage.¹⁸⁻²¹ There were also cases in which virtual simulation suggested a longer device or where suggestion of a larger diameter led to an increase in length of the implanted PED (Fig 3). These, at times, very sizeable discrepancies between manually selected and computed optimal device dimensions typically occurred in large, dysplastic, or fusiform aneurysms of the extradural ICA, as well as in aneurysms associated with dissection (On-line Tables 1-3).

Notwithstanding the fact that the diameter difference did not reach statistical significance, we think that the Sim&Size algorithm suggested the smallest diameter necessary to maintain wall apposition along the entire length of the device, which, in theory, would reduce the risk for oversizing and, thereby, promote device efficacy (Table 2 and Fig 2).^{15,22,23} Nevertheless, there were cases in which

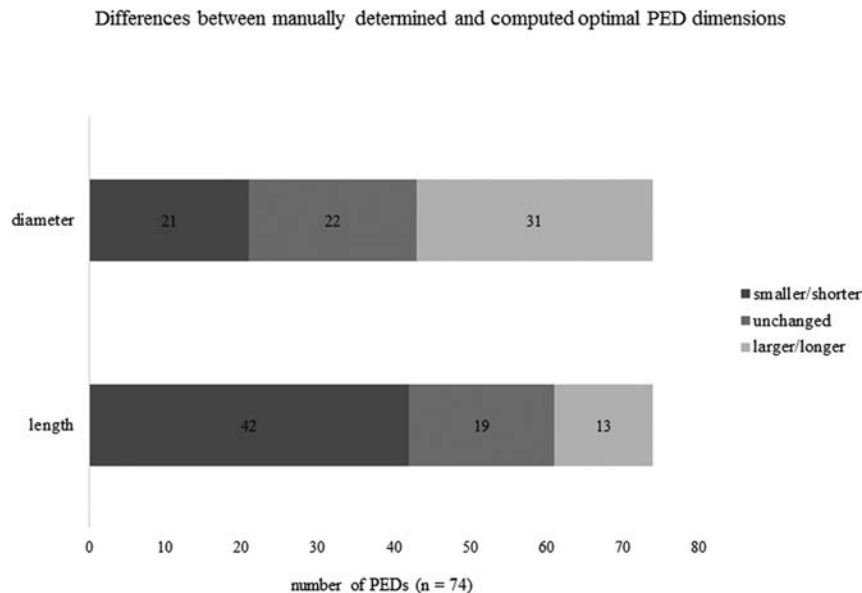


FIG 3. Bar graph illustrating differences between manually determined presumed optimal device dimensions and computed optimal PEDs. Computed optimal device diameter was larger in 31 cases, identical to the neurointerventionalists' manual selection in 22 cases, and smaller in the remaining 21 cases. Computed optimal device length was shorter in 42 cases, identical to the neurointerventionalists' manual selection in 19 cases, and longer in the remaining 13 cases.

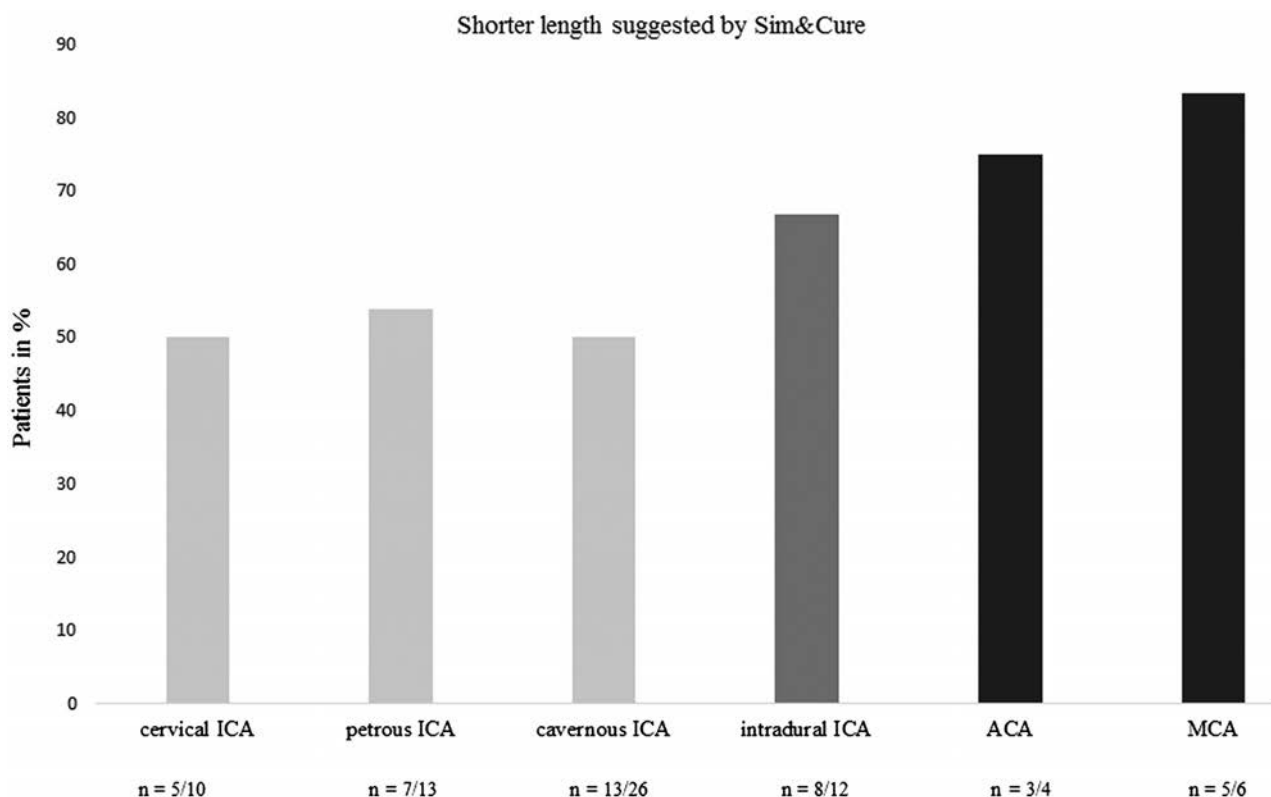


FIG 4. Bar graph illustrating the proportion of cases in which computed PED lengths were shorter than manually determined lengths for the anterior circulation. The proportion of cases in which computed optimal PED lengths were shorter increases from proximal to distal.

virtual simulation suggested a larger device or where suggestion of a longer device required increasing the nominal diameter of the PED (Fig 3). One may speculate that these are cases in which manual device selection would have resulted in inadvertent undersizing or insufficient device length, with the potential consequence of known periprocedural complications such as device migration or endoleak formation.²⁴ Alternatively, as in 1 example from our series, a cervical ICA dissection (patient 27, On-line Table 1) was initially covered using a single PED of 4 mm in diameter and 18 mm in length, as chosen from manual measurements. Virtual simulation, however, revealed that a device of 30 mm in nominal length would be required to optimally cover the entire dissection, which, in turn, would require using a device of 5 mm in nominal diameter to maintain wall apposition at the proximal end. In summary, our study was neither designed nor powered to assess the clinical or radiologic consequences of device length or diameter modifications; thus, the true benefits of preimplantation virtual simulation remain hypothetical until proved in a prospectively conducted and, ideally, randomized trial.

Computer-based planning tools that virtually visualize stent length in situ have been described.^{25–29} Previous work has revealed, for instance, how virtual simulation reduces the error in length prediction compared with the nominal length provided by the manufacturers.^{30,31} Much of this research in the field of virtual device simulation has focused, however, on technical aspects of accurate modeling and prediction of intraluminal device behavior, with only a very few small case series of in vivo use of simulation tools in the field of neurointervention.³² Moreover, previous software solutions generally remain of limited use with regard to their application in a real-world setting, given the constraints such as a lack of information regarding wall apposition and the inability to test, in real-time, multiple device dimensions and positions. Altogether, the present study is, to our knowledge, the first attempt to objectify the impact of preimplantation PED simulation in a real-world setting, and our results, therefore, represent an important step toward translation of this novel technology into routine clinical practice.

Our study has several limitations, and we recommend caution when interpreting the results. First, the 2 participating centers did not contribute an equal number of patients, and their aneurysm population differed significantly in terms of location and size. We, therefore, performed an exploratory subgroup analysis to clarify the particular aneurysm categories that were most affected by simulation. Second, the average number of devices used per aneurysm in the Pipeline for the Intracranial Treatment of Aneurysms³³ and Pipeline for Uncoilable or Failed Aneurysms³⁴ trials was 1.52 and 3.1, respectively. We were obliged to limit our analysis to the first implanted device, given that the Sim&Size algorithm is restricted to simulation of a single device at this time. Third, the purpose of the present study was only to evaluate whether the use of a computer-based simulation model results in the selection of different PED dimensions, and we certainly acknowledge a lack of study design and statistical power for any meaningful outcome analysis. The significance of selecting PEDs of different dimensions in terms of long-term outcome remains, therefore, to be clarified in dedicated future research. Finally, our results are based on a small number of practitioners and patients,

meaning that further studies on larger cohorts will be necessary to confirm our results.

CONCLUSIONS

Experience with PEDs remains characterized by heterogeneity in device sizing and deployment technique. Furthermore, the properties of the PED require not only appropriate but optimal device dimensions to achieve treatment success and minimize complications. It is therefore appealing to facilitate device sizing and positioning through preimplantation virtual simulation techniques. We found, in the present study, robust evidence that preimplantation simulation with the Sim&Size software results in selection of different PED dimensions compared with conventional manual device sizing, and preimplantation device simulation led, in particular, to a measurable decrease in median device length. We believe that the benefits of the Sim&Size software may, therefore, be the greatest for intradural aneurysms, where side branches and perforators are relevant. In summary, we are confident that our findings reveal the potential of the software for optimization of the device-selection process, even if the impact on outcome remains to be clarified in dedicated research.

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REFERENCES

1. Turjman F, Acevedo G, Moll T, et al. **Treatment of experimental carotid aneurysms by endoprosthesis implantation: preliminary report.** *Neurol Res* 1993;15:181–84 CrossRef Medline
2. Geremia G, Haklin M, Brennecke L. **Embolization of experimentally created aneurysms with intravascular stent devices.** *AJNR Am J Neuroradiol* 1994;15:1223–31 Medline
3. Fiorella D, Kelly ME, Albuquerque FC, et al. **Curative reconstruction of a giant midbasilar trunk aneurysm with the Pipeline embolization device.** *Neurosurgery* 2009;64:212–17; discussion 217 CrossRef Medline
4. Fiorella D, Lylyk P, Szikora I, et al. **Curative cerebrovascular reconstruction with the Pipeline embolization device: the emergence of definitive endovascular therapy for intracranial aneurysms.** *J Neurointerv Surg* 2009;1:56–65 CrossRef Medline
5. Lylyk P, Miranda C, Ceratto R, et al. **Curative endovascular reconstruction of cerebral aneurysms with the Pipeline embolization device: the Buenos Aires experience.** *Neurosurgery* 2009;64:632–42; discussion 642–43; quiz N6 CrossRef Medline
6. ADMINISTRATION U.S. FOOD AND DRUG. **Premarket Approval (PMA).** 2011; <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?ID=P100018>. Accessed August 8, 2018
7. Patel PD, Chalouhi N, Atallah E, et al. **Off-label uses of the Pipeline embolization device: a review of the literature.** *Neurosurg Focus* 2017;42:E4 CrossRef Medline
8. Dabus G, Grossberg JA, Cawley CM, et al. **Treatment of complex anterior cerebral artery aneurysms with Pipeline flow diversion: mid-term results.** *J Neurointerv Surg* 2017;9:147–51 CrossRef Medline
9. Fischer S, Perez MA, Kurre W, et al. **Pipeline embolization device for the treatment of intra- and extracranial fusiform and dissecting**

- aneurysms: initial experience and long-term follow-up. *Neurosurgery* 2014;75:364–74; discussion 374 CrossRef Medline
10. Kulcsar Z, Wetzel SG, Augsburger L, et al. **Effect of flow diversion treatment on very small ruptured aneurysms.** *Neurosurgery* 2010;67:789–93 CrossRef Medline
11. Phillips TJ, Wenderoth JD, Phatouros CC, et al. **Safety of the Pipeline embolization device in treatment of posterior circulation aneurysms.** *AJNR Am J Neuroradiol* 2012;33:1225–31 CrossRef Medline
12. Zhang Y, Huang QH, Fang Y, et al. **A novel flow diverter (Tubridge) for the treatment of recurrent aneurysms: a single-center experience.** *Korean J Radiol* 2017;18:852–59 CrossRef Medline
13. Rajah G, Narayanan S, Rangel-Castilla L. **Update on flow diverters for the endovascular management of cerebral aneurysms.** *Neurosurg Focus* 2017;42:E2 CrossRef Medline
14. Shapiro M, Raz E, Becske T, et al. **Building multidevice Pipeline constructs of favorable metal coverage: a practical guide.** *AJNR Am J Neuroradiol* 2014;35:1556–61 CrossRef Medline
15. Shapiro M, Raz E, Becske T, et al. **Variable porosity of the Pipeline embolization device in straight and curved vessels: a guide for optimal deployment strategy.** *AJNR Am J Neuroradiol* 2014;35:727–33 CrossRef Medline
16. Brinjikji W, Murad MH, Lanzino G, et al. **Endovascular treatment of intracranial aneurysms with flow diverters: a meta-analysis.** *Stroke* 2013;44:442–47 CrossRef Medline
17. Sim&Cure RdIV, 34790 Grabels, France. <https://sim-and-cure.com/product>. Accessed August, 29, 2018
18. Kulcsár Z, Ernemann U, Wetzel SG, et al. **High-profile flow diverter (Silk) implantation in the basilar artery: efficacy in the treatment of aneurysms and the role of the perforators.** *Stroke* 2010;41:1690–96 CrossRef Medline
19. van Rooij WJ, Sluzewski M. **Perforator infarction after placement of a Pipeline flow-diverting stent for an unruptured A1 aneurysm.** *AJNR Am J Neuroradiol* 2010;31:E43–44 CrossRef Medline
20. Potts MB, Shapiro M, Zumofen DW, et al. **Parent vessel occlusion after Pipeline embolization of cerebral aneurysms of the anterior circulation.** *J Neurosurg* 2017;127:1333–41 CrossRef Medline
21. Raz E, Shapiro M, Becske T, et al. **Anterior choroidal artery patency and clinical follow-up after coverage with the Pipeline embolization device.** *AJNR Am J Neuroradiol* 2015;36:937–42 CrossRef Medline
22. Makoyeva A, Bing F, Darsaut TE, et al. **The varying porosity of braided self-expanding stents and flow diverters: an experimental study.** *AJNR Am J Neuroradiol* 2013;34:596–602 CrossRef Medline
23. Mut F, Cebal JR. **Effects of flow-diverting device oversizing on hemodynamics alteration in cerebral aneurysms.** *AJNR Am J Neuroradiol* 2012;33:2010–16 CrossRef Medline
24. Zhou G, Su M, Yin YL, et al. **Complications associated with the use of flow-diverting devices for cerebral aneurysms: a systematic review and meta-analysis.** *Neurosurg Focus* 2017;42:E17 CrossRef Medline
25. Bernardini A, Larrabide I, Petrini L, et al. **Deployment of self-expandable stents in aneurysmatic cerebral vessels: comparison of different computational approaches for interventional planning.** *Comput Methods Biomech Biomed Engin* 2012;15:303–11 CrossRef Medline
26. Kim JH, Kang TJ, Yu WR. **Mechanical modeling of self-expandable stent fabricated using braiding technology.** *J Biomech* 2008;41:3202–12 CrossRef Medline
27. Ma D, Dargush GF, Natarajan SK, et al. **Computer modeling of deployment and mechanical expansion of neurovascular flow diverter in patient-specific intracranial aneurysms.** *J Biomech* 2012;45:2256–63 CrossRef Medline
28. Ma D, Dumont TM, Kosukegawa H, et al. **High-fidelity virtual stenting (HiFiVS) for intracranial aneurysm flow diversion: in vitro and in silico.** *Ann Biomed Eng* 2013;41:2143–56 CrossRef Medline
29. Bouillot P, Brina O, Yilmaz H, et al. **Virtual-versus-real implantation of flow diverters: clinical potential and influence of vascular geometry.** *AJNR Am J Neuroradiol* 2016;37:2079–86 CrossRef Medline
30. Fernandez H, Macho JM, Blasco J, et al. **Computation of the change in length of a braided device when deployed in realistic vessel models.** *Int J Comput Assist Radiol Surg* 2015;10:1659–65 CrossRef Medline
31. Narata AP, Blasco J, Roman LS, et al. **Early results in flow diverter sizing by computational simulation: quantification of size change and simulation error assessment.** *Oper Neurosurg (Hagerstown)* 2018;15:557–66 CrossRef Medline
32. Martinez-Galdamez M, Holtmannspöetter M, Isokangas M, et al. **Simulation in clinical practice: first experience with Sim&Size before implantation of flow diverter (Pipeline) or WEB-device for the treatment of intracranial aneurysms.** In: *Proceedings of the Anatomy Biology Clinical Correlations-Working group in Interventional Neuro-radiology Seminar*, Val d'Isère, France. January 15–20, 2017
33. Nelson PK, Lylyk P, Szikora I, et al. **The Pipeline embolization device for the intracranial treatment of aneurysms trial.** *AJNR Am J Neuroradiol* 2011;32:34–40 CrossRef Medline
34. Becske T, Kallmes DF, Saatci I, et al. **Pipeline for uncoilable or failed aneurysms: results from a multicenter clinical trial.** *Radiology* 2013;267:858–68 CrossRef Medline
35. Shapiro M, Becske T, Riina HA, et al. **Toward an endovascular internal carotid artery classification system.** *AJNR Am J Neuroradiol* 2014;35:230–36 CrossRef Medline

Pipeline Sizing Based on Computer Simulation

Flow-diversion treatment of cerebral aneurysms with the Pipeline Embolization Device (Covidien, Irvine, California) has been around for nearly 13 years, yet we are still struggling with some fundamental issues, such as optimal device-size selection and optimal flow diversion (ie, which aneurysms need >1 device for a cure, and how we can identify those aneurysms).

As operators, we all deal with these questions differently. Some of us use as individualized an approach to each patient and aneurysm as possible and spend considerable time ruminating over minute differences in device length and diameter to be implanted, not to mention the guesswork that goes into predicting how much flow diversion is necessary or enough to ensure complete aneurysm occlusion after the first treatment (ie, do we use 1 or multiple devices?). This desire to cure with a single procedure may be rooted in our prior experience and frustration with the predictability of recurrence after more traditional endovascular therapy of complex aneurysms. Others among us have given up the guessing and decided to bring the same approach to each aneurysm we encounter: Always use 1 device, and always use the widest and longest one ("to be safe"). We all hope that one day artificial intelligence will tell us exactly what kind, size, and quantity of devices or materials we need to deliver to optimally treat our target—be it an aneurysm, a brain AVM, and so forth.

At the same time, I think we also fear the arrival of that very same day.

The article written by Ospel et al¹ brings us a bit closer to our dream (but luckily leaves enough left to think about before we get there).

The authors of the article embarked on an experiment to assess the potential use of a virtual-simulation software in planning Pipeline flow diversion in 74 aneurysms. Due to limitations of the simulation software, the simulation was applied to a single Pipeline device (though 7 cases were treated with multiple devices; in these, the software was used for the first device only). One of the 2 participating hospitals, contributing 63 aneurysms, used manual measurements based on standard angiographic evaluation (including 3D images) to select device sizes, and simulation was performed at a later date blinded to the device-size selection of the treating physician. The

other hospital enrolled 11 aneurysms, all treated after the simulation software became available; therefore, they applied the software to determine optimal device size, and manual measurements were obtained at a later time blinded to the results of the simulation.

Overall, the authors found that the simulation software suggested somewhat shorter devices and this difference reached statistical significance. Intradural aneurysms and, within them, more distal aneurysms were especially likely to have a shorter device recommendation by the software, though the length difference between manual and simulation measurements was smaller in intradural aneurysms. On the other hand, they found no statistically significant difference in device diameters suggested by the software versus manual measurements. Nevertheless, not surprisingly, they observed that the largest discrepancies in sizing (both length and diameter) of the devices, as suggested by manual measurements and simulation, occurred in relation to extradural aneurysms that were large, fusiform, or dissecting.

Therefore, the authors concluded that software-based sizing may be most beneficial for intradural aneurysms, in which considerations such as the avoidance of perforators are significantly different from those at extradural sites.

An additional, not unexpected finding is the low rate of agreement in device sizing between the 2 measurement methods. The significance of this is unclear because if we consider all the various lengths and diameters, one can choose from >90 device sizes. It is very likely that the agreement rate on recommended optimal device sizes for a set of aneurysms between 2 experienced operators would also be very low. Therefore, it would be difficult to conclude that the software is better at predicting device sizes purely on the basis of the frequency of this discordance.

The authors should be applauded for this well-written and thoughtful article. The very fact that they are making an effort to improve Pipeline device sizing demonstrates their commitment to advancing our understanding of flow diversion. As shown in numerous articles in the past, optimal device length and diameter selection are critical in providing more appropriate deployment, wall apposition, and device porosity at the aneurysm neck and, as a result, improved flow diversion. Therefore, it logically follows that better pre-

diction of device sizing should theoretically lead to better outcomes. This study is a small step in that direction.

Disclosures: I am a consultant and Pipeline proctor for Medtronic; I have no financial or other interest in the simulation software discussed in this article. One of the authors was, in part, trained by me; however, this was unknown to me at the time of my initial review of the article.

REFERENCE

1. Ospel JM, Gascou G, Costalat V, et al. **Comparison of Pipeline embolization device sizing based on conventional 2D measure-**

ments and virtual simulation using the Sim&Size software: an agreement study. *AJNR Am J Neuroradiol* 2019;40:524–30.

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Predictors and Clinical Impact of Delayed Stent Thrombosis after Thrombectomy for Acute Stroke with Tandem Lesions

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ABSTRACT

BACKGROUND AND PURPOSE: There are very few published data on the patency of carotid stents implanted during thrombectomies for tandem lesions in the anterior circulation. We aimed to communicate our experience of stenting in the acute setting with systematic follow-up of stent patency and discuss predictors and clinical repercussions of delayed stent thrombosis.

MATERIALS AND METHODS: We performed a retrospective study of stroke thrombectomies in a single center between January 2009 and April 2018. Patient files were reviewed to extract patient characteristics, procedural details, imaging studies, and clinical information. Predictors of delayed stent thrombosis and clinical outcome at discharge were analyzed using univariate and multivariate analyses.

RESULTS: We identified 81 patients treated for tandem lesions: 63 (77.7%) atheromas, 17 (20.9%) dissections, and 1 (1.2%) carotid web. TICI 2b–3 recanalization was achieved in 70 (86.4%) cases. Thirty-five patients (43.2%) were independent (mRS score ≤ 2) at discharge. Among 73 patients with intracranial recanalization and patent stents at the end of the procedure, delayed stent thrombosis was observed in 14 (19.1%). Among 59 patients with patent stents, 44 had further imaging controls (median, 105 days; range, 2–2407 days) and 1 (1.6%) had 50% in-stent stenosis with no retreatment. Stent occlusion rates were 11/39 (28.2%) for periprocedural aspirin treatment versus 3/34 (8.8%) for aspirin and clopidogrel ($P = .04$). Delayed stent thrombosis was independently associated with higher admission NIHSS scores (OR, 1.1; 95% CI, 1.01–1.28), diabetes (OR, 6.07; 95% CI, 1.2–30.6), and the presence of in-stent thrombus on the final angiographic run (OR, 6.2; 95% CI, 1.4–27.97). Delayed stent thrombosis (OR, 19.78; 95% CI, 2.78–296.83), higher admission NIHSS scores (OR, 1.27, 95% CI, 1.12–1.51), and symptomatic hemorrhagic transformation (OR, 23.65; 95% CI, 1.85–3478.94) were independent predictors of unfavorable clinical outcome at discharge.

CONCLUSIONS: We observed a non-negligible rate of delayed stent thrombosis with significant negative impact on clinical outcome. Future studies should systematically measure and report stent patency rates.

In around 15% of endovascular procedures for anterior circulation stroke,¹ there is a tight stenosis or occlusion of the cervical carotid artery in addition to the intracranial arterial occlusion. The optimal endovascular management of tandem intra- and extracranial lesions remains subject to debate. The landmark thrombectomy trials either included relatively small numbers of tandem lesions^{2–4} or completely excluded them.^{5,6} Available data

mostly consist of retrospective case series published in recent years.⁷

Regardless of technical variations, most groups communicate high recanalization rates with a favorable safety profile for stenting of the extracranial carotid artery.⁷ However, there are very few data available regarding patency rates for the implanted carotid stents and the impact of stent thrombosis on clinical outcome.

Our aim was to communicate our single-center experience in endovascular management of consecutive cases of tandem lesions with systematic follow-up of stent patency and to discuss predictors and clinical repercussions of stent thrombosis.

MATERIALS AND METHODS

We conducted a retrospective analysis of our prospective data base of acute stroke endovascular procedures between January 1, 2009, and April 1, 2018, using the following inclusion criterion: association of extracranial internal carotid artery occlusion or stenosis of $\geq 70\%$ using the NASCET criteria and an intracranial

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 Indicates article with supplemental on-line tables.

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arterial occlusion in the anterior circulation. Endovascular treatments for complications of surgical carotid endarterectomy were excluded. Images stored on the PACS and radiology reports were reviewed to extract technical details of the endovascular procedure, as well as postprocedural imaging. Patient files were reviewed to extract patient demographics, comorbidities, complications, clinical status at discharge, and clinical follow-up information. The study was approved by the Strasbourg University Hospital's ethics review board. Due to the retrospective nature of the study, the board waived the need for signed informed consent.

Patient Selection and Preprocedural Imaging

Patients with acute stroke were selected for endovascular procedures using MR imaging, except in case of extreme agitation or absolute contraindications. Patients with favorable profiles for recanalization were selected using clinico-radiologic mismatch (discrepancy between the severity of neurologic deficits and the size of acute ischemic lesion on the diffusion sequence) as well as estimation of leptomeningeal collateral status using FLAIR vascular hyperintensities.^{8,9} We did not use a specific collateral scoring system; vascular hyperintensities were evaluated visually and considered indicative of the presence of ischemic penumbra. Patients with acute infarction in more than two-thirds of the middle cerebral artery territory were generally not considered for treatment. Wake-up strokes and patients with unclear time of onset were considered for treatment if last seen well <12 hours before evaluation, using the same imaging-selection criteria.

Endovascular Procedure

All procedures were performed with the patient under general anesthesia. The strategy did not change during the study period and consisted of an antegrade approach in most cases: stent placement and angioplasty of the proximal occlusion first before addressing the intracranial occlusion. Briefly, a 9F balloon-guide catheter was placed in the distal common carotid artery, and the proximal occlusion was explored with a microcatheter and a 0.014-inch guidewire. If the occlusion could not be crossed using the microcatheter, the system was replaced with a long 4F or 5F vertebral catheter and a 0.035-inch guidewire. After crossing the occlusion, we performed a distal angiographic run to assess the distal cervical ICA. Subsequently, a long 0.014-inch guidewire was advanced into the ICA, and using an exchange maneuver, we placed a carotid stent (usually Wallstent; Boston Scientific, Natick, Massachusetts) covering the lesion and extending to the common carotid artery. The guiding catheter was then advanced inside the stent, and postdilation of the stenosis was performed if needed by means of a 6 × 20 mm monorail angioplasty balloon under proximal flow arrest using the balloon of the guiding catheter. The angioplasty balloon was then deflated and removed; the stagnating column of blood was aspirated using a 50-mL syringe before deflation of the balloon-guide catheter. Subsequently, the distal occlusion was treated using a stent retriever, aspiration, or a combination of both methods.

Depending on operator preferences, a minority of cases (mostly carotid dissections) were performed using a retrograde approach. A distal-access catheter or large-bore aspiration catheter was advanced across the proximal lesion, and the distal occlu-

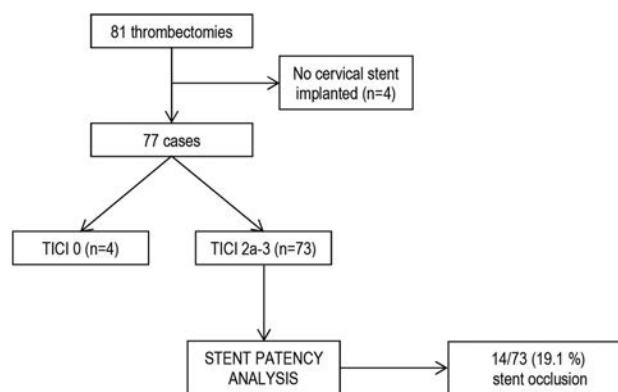


FIG 1. Flow diagram of patient selection for stent-patency analysis.

sion was treated by aspiration or a combination of a stent retriever and distal aspiration. Subsequently, the proximal occlusion was treated with the method previously described, using a long 0.014-inch guidewire advanced through the distal-access catheter.

The antiplatelet and procedural anticoagulation regimen varied across the study period. In the early experience, before carotid stent placement, we administered loading doses of clopidogrel, 300 mg (nasogastric tube), and aspirin, 250 mg (IV); and between 2500 and 4000 U of heparin (IV). Due to an increased rate of hemorrhagic complications, since October 2011, heparin administration was discontinued and the regimen was reduced to IV aspirin (250 mg) with or without a loading dose of clopidogrel (300 mg), depending on operator preferences and case-by-case discussion (estimation of hemorrhagic-transformation risk depending on the size of the acute ischemic lesion and concomitant treatment with IV thrombolysis). If the stent was patent after 24 hours and in the absence of sizeable hemorrhagic transformation, clopidogrel, 75 mg/day, was continued for 3 months in addition to life-long aspirin, 75 mg/day. None of the cases were treated with glycoprotein IIb/IIIa inhibitors.

Postprocedural Imaging and Clinical Follow-Up

All patients underwent cerebral CT 24 hours postprocedure. Hemorrhagic transformation was evaluated using the European Cooperative Acute Stroke Study criteria.¹⁰ In addition, for patients with carotid stents, cervical and transcranial Doppler sonography was performed at 24 hours and before discharge to check for stent patency. If a sonographic examination was not feasible at 24 hours, CT angiography of the carotids was performed along with the 24-hour CT examination.

In addition, whenever possible, patients were recalled for additional clinical and carotid sonography examinations between 3 months and 1 year after the initial event.

Evaluation of Delayed Stent Thrombosis

Delayed stent thrombosis was researched in the subgroup of patients who underwent carotid stent placement, and in whom the procedure resulted in partial or complete recanalization of the cervical and intracranial vasculature. The selection procedure is detailed in Fig 1. Delayed stent thrombosis was defined as carotid stent occlusion diagnosed on follow-up imaging. Predictors of stent thrombosis were researched using univariate and multivariate analyses.

Clinical Impact of Delayed Stent Thrombosis

To assess whether delayed stent thrombosis had any repercussions on clinical outcome, we researched predictors of unfavorable clinical outcome at discharge (mRS score > 2) within the same subgroup of patients using univariate and multivariate analyses.

Statistical Analysis

Continuous variables were presented as median and range and compared using the Mann-Whitney *U* test after assessment of the normality of the distribution. Categorical variables were presented as numbers and percentages and compared using the χ^2 test. To assess independent predictors of stent thrombosis and clinical outcome at discharge, we implemented baseline characteristics associated with a $P < .10$ in univariate analyses into backward-stepwise multivariable binary logistic regression models using a removal criterion of $P > .10$. A logistic regression model using the Firth bias reduction method was fitted to handle separation in our data for the clinical outcome at discharge. Results are presented as odds ratios with their 95% confidence intervals. Statistical data were analyzed using GraphPad Prism, Version 6.0 (GraphPad Software, San Diego, California) and SPSS software, Version 20.0 (IBM, Armonk, New York). The significance level was established at $P < .05$.

RESULTS

Patient Characteristics

We identified 81 patients treated for tandem lesions (77.7% carotid atheromas, 20.9% dissections, and 1 case [1.2%] of a carotid web). Patient demographics and baseline characteristics are detailed in On-line Table 1. The median age was 63 years, and the median admission NIHSS score was 14. Initial imaging consisted of MR imaging in nearly all patients (80/81). Intravenous alteplase was administered in 49.3% of cases. The median time from symptom onset to femoral puncture was 255 minutes. Of note, 19.7% of cases were wake-up strokes or with unclear time of onset (in these cases, time when last seen well was used instead of symptom onset).

Thrombectomy Procedure and Outcome

Technical details of the thrombectomy procedure as well as clinical and imaging outcomes are detailed in On-line Table 2. A carotid stent was implanted in 77 (95%) patients, of which 42/77 (54.5%) received periprocedural aspirin (250 mg IV) and 35/77 (45.4%) received aspirin and clopidogrel (300 mg via a nasogastric tube). Most patients (83.9%) were treated using an antegrade approach. The median procedural time was 80 minutes; intracranial circulation TICI 2b–3 recanalization was achieved in 86.4% of cases. Symptomatic hemorrhagic transformation occurred in 6.1% of cases. Eight patients (9.8%) died during the initial hospitalization. Good clinical outcome (mRS ≤ 2) was observed in 43.2% of patients at discharge. Follow-up was available in 60/81 patients (including deceased patients); after a median interval of 10 months, (range 1–78), 61.6% of patients had mRS ≤ 2 .

Delayed Stent Thrombosis

A subgroup of 73 patients had patent carotid stents and partial/complete intracranial recanalization achieved at the end of the

thrombectomy procedure (see Fig 1 for subgroup selection). Cervical imaging at 24 hours consisted of Doppler sonography for 64/73 patients (87.6%) and CT angiography for 9/73 patients (12.3%).

Delayed stent thrombosis was observed in 14/73 (19.1%). In most cases (13/14), thrombosis occurred in the first 24 hours; in 1 patient, the stent thrombosed 5 days after the procedure despite double-antiplatelet therapy with aspirin and clopidogrel. Testing of clopidogrel resistance was not performed.

Initially, none of the 14 cases of stent thrombosis were associated with intracranial re-embolization, and imaging demonstrated collateral flow to the MCA via the anterior and/or posterior communicating arteries. However, in 5/14 cases (35.7%), transcranial Doppler detected lower flow velocities in the MCA compared with the contralateral side, suggestive of insufficient collateralization. Subsequently, in 1 additional patient (1/14, 7.1%), the MCA reoccluded at 5 days and remained occluded on further follow-up.

On clinical examination, only 3/14 (21.5%) patients presented with a clear aggravation of neurologic deficits that could be attributed to stent occlusion. They all had reduced MCA flow velocities on transcranial Doppler compared with contralateral side.

Among the 59 patients with patent stents, further imaging follow-up was available for 44 patients (median, 105 days; range, 2–2407 days). One patient (1.6%) had 50% in-stent stenosis; there were no retreatments. Among the 14 patients with occluded stents, further stent patency follow-up was available for 11 cases (median, 124 days; range, 5–371 days). The stents remained occluded in all cases.

Stent occlusion rates were significantly higher ($P = .04$) for patients who received aspirin alone (11/39, 28.2%) compared with aspirin and clopidogrel (3/34, 8.8%).

Univariate analysis of predictors for delayed stent thrombosis is presented in On-line Table 3. In backward stepwise multivariable analysis (Table), delayed stent thrombosis was independently associated with a higher admission NIHSS score (OR per 1-point increase, 1.1; 95% CI, 1.01–1.28), diabetes (OR, 6.07; 95% CI, 1.2–30.6), and the presence of in-stent thrombus on the final angiographic run (OR, 6.2; 95% CI, 1.4–27.97).

Administration of intravenous thrombolysis before thrombectomy was not associated with a significantly reduced rate of stent thrombosis in univariate or multivariate analyses.

Impact of Stent Thrombosis on Clinical Outcome

Within the same subgroup of 73 patients, 34 (46.5%) had good clinical outcome at discharge. Among patients with delayed stent occlusion, only 1 (7.1%) was independent at discharge, compared with 33 (55.9%) cases with patent stents ($P = .001$). The distribution of mRS scores for both groups is detailed in Fig 2. Univariate analysis of predictors for clinical outcome is presented in On-line Table 4. In backward stepwise multivariable analysis (Table), delayed stent thrombosis (OR, 19.78; 95% CI, 2.78–296.83), higher admission NIHSS score (OR per 1-point increase, 1.27; 95% CI, 1.12–1.51), and symptomatic hemorrhagic transformation (OR, 23.65; 95% CI, 1.85–3478.94) were independently associated with unfavorable clinical outcome at discharge.

Multivariable regression analysis of predictors for delayed stent thrombosis and clinical outcome at discharge^a

Predictors	OR (95% CI)	P Value
Delayed stent thrombosis		
Admission NIHSS (per 1-point increase)	1.1 (1.01–1.28)	.03
Diabetes	6.07 (1.2–30.6)	.02
In-stent thrombus on final angiographic run	6.2 (1.4–27.97)	.01
Unfavorable clinical outcome at discharge (mRS > 2) ^b		
Delayed stent thrombosis	19.78 (2.78–296.83)	.001
Admission NIHSS (per 1-point increase)	1.27 (1.12–1.51)	<.001
Symptomatic hemorrhagic transformation	23.65 (1.85–3478.94)	.012

^a Candidate predictors for delayed stent thrombosis were the following: antiplatelet treatment (aspirin vs aspirin and clopidogrel), admission NIHSS, diabetes, diffusion ASPECTS of <7, visualization of in-stent thrombus on final angiographic run, presence of cervical thrombus distal to the proximal lesion, and time from onset to recanalization. Candidate predictors for clinical outcome at discharge were the following: delayed stent thrombosis, admission NIHSS, location of distal occlusion (M2 versus ICA/MI), presence of cervical thrombus distal to the proximal lesion, diffusion ASPECTS of <7, symptomatic hemorrhagic transformation, and time from onset to recanalization.

^b Because none of the patients with good clinical outcome had symptomatic hemorrhagic transformation, a logistic regression model using the Firth bias reduction method was fitted to handle separation in our data for the clinical outcome at discharge.

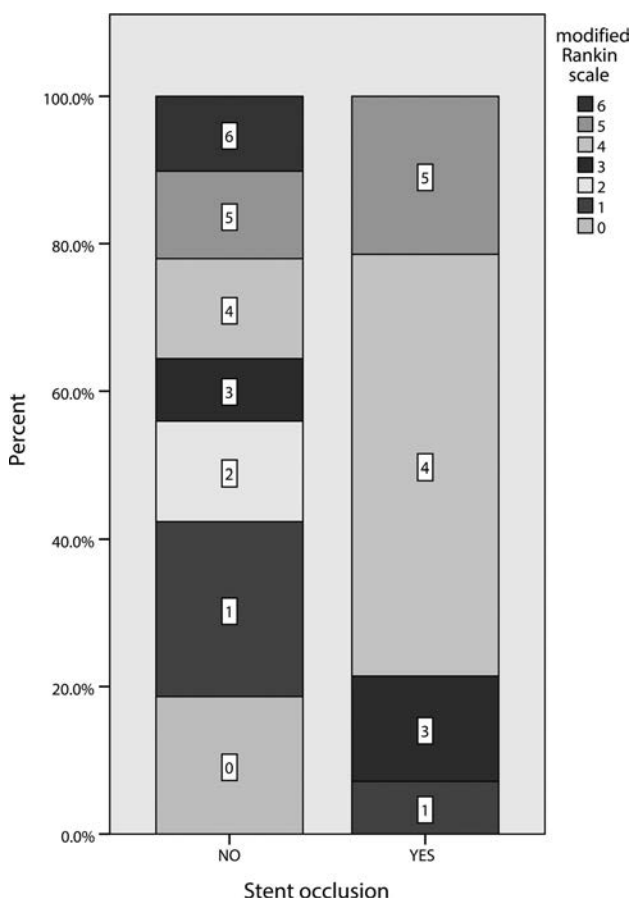


FIG 2. Distribution of mRS scores at discharge in patients with patent-versus-occluded carotid stents. Among patients with delayed stent occlusion, only 1 (7.1%) was independent (mRS ≤ 2) at discharge, compared with 33 (55.9%) patients with patent stents ($P = .001$).

An illustrative case of delayed stent thrombosis from this series is presented in Fig 3.

DISCUSSION

Our study of endovascular treatment for 81 consecutive patients with tandem lesions provides the largest single-center series reported in the literature. By performing systematic imaging fol-

low-up of stent patency, we observed a non-negligible rate of delayed stent thrombosis with a significant impact on clinical outcome.

Numerous retrospective case series of endovascular management for tandem lesions have been published in recent years. The data are synthesized in 2 recently published meta-analyses.^{7,11} Most articles reported high recanalization rates with different technical variations of the procedure and identified predictors of successful recanalization and/or good clinical outcome. Surprisingly, there was very little information on the outcome of implanted carotid stents.

In many publications,^{12–21} there is no mention of postprocedural stent patency. Other groups communicate partial data: Sadeh-Gonik et al¹¹ studied 43 patients; they reported 1 delayed stent thrombosis of 8 cases with available imaging follow-up (12.5%). Lockau et al²² performed imaging controls in 28 of 37 patients; there was delayed stent thrombosis in 6 cases (16.2%) and significant stenosis in another 2 (5.4%). Steglich-Arnholm et al²³ controlled stent patency for 3 months in 43 of a total 47 patients; 4 (9%) had occluded stents. Heck et al²⁴ controlled stent patency in 18 of 23 cases and found 1 (5.5%) delayed stent thrombosis; in 13 patients with follow-up sonography ranging from 90 days to 24 months, there were no subsequent events. In a series of 24 cases, Cohen et al²⁵ reported 4 readmissions for new cerebrovascular ($n = 2$) or cardiovascular events ($n = 2$); the stents were patent in all 4 patients. Stent thrombosis rates in these articles are lower than the ones observed in our series, but their data concern only a proportion of the total number of patients. We have shown, in our series, that in most cases (11/14, 78.5%), stent thrombosis was not associated with overt aggravation of neurologic deficits; clinical examination alone therefore seems to be insufficient for detection of stent thrombosis. In the absence of systematic imaging controls of stent patency in the reported series, their real stent thrombosis rates remain unknown.

We identified a single article²⁶ reporting 24-hour imaging follow-up of stent patency for all 77 patients, with only 1 (1.2%) thrombosed stent. The long-term (30 days or later) in-stent restenosis rate was 2/27 (7.4%) in patients with available follow-up imaging. Of note, patients in this series received either epifibatide or double antiplatelet therapy with clopidogrel, 600 mg, and aspirin, 325 mg, in addition to systemic heparinization. Hemorrhagic transformation occurred in 10.4% of cases.

Several articles discussed intraprocedural stent thrombosis. Mpotsaris et al²⁷ reported periprocedural in-stent thrombosis in 4/63 (6%) procedures. Rangel-Castilla et al²⁸ observed 2/45 (4.4%) cases, both resolved with infusion of epifibatide. In a series of 47 patients, Steglich-Arnholm et al²³ had 8 (17%) cases with acute stent thrombosis during thrombectomy, 7 of which resolved with local administration of glycoprotein IIb/IIIa inhibitor; in 1 patient, recanalization was not attempted because of excellent collateral flow and complete intracranial recanalization.

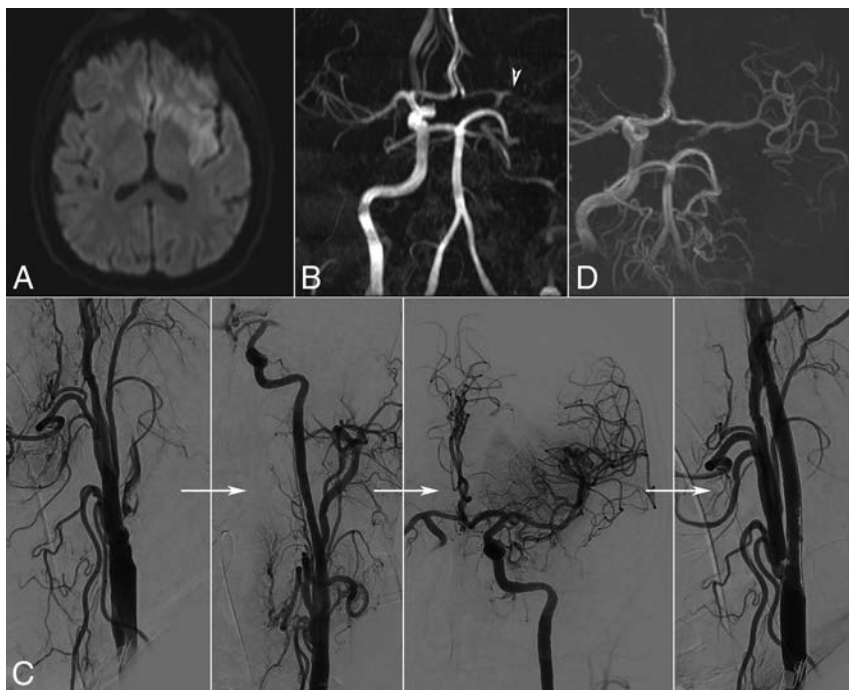


FIG 3. Illustrative case. A patient in his sixties with a history of type 2 diabetes, severe chronic obstructive pulmonary disease, and siderosis was found by his wife hemiplegic and aphasic on wake-up. Initial examination showed depressed consciousness (Glasgow Outcome Score, 7) and signs of respiratory failure for which orotracheal intubation was necessary. Emergency MR imaging showed a relatively small acute ischemic lesion in diffusion imaging (A) not visible in FLAIR imaging, as well as occlusion of the left internal carotid and middle cerebral (arrowhead) arteries (B). Given the important clinicroadiologic mismatch, we proceeded to thrombectomy (C). There was calcified atheroma at the origin of the ICA with floating thrombus. An IV bolus of aspirin, 250 mg, was administered, and a 9×50 mm Wallstent was deployed and postdilated with a 6×20 mm balloon. Then the MCA occlusion was treated by 2 passages of a stent retriever with TICI 3 recanalization. The final cervical angiographic run showed excellent patency of the carotid stent with images suggestive of plaque protrusion but no in-stent thrombus. However, the next day, Doppler sonography demonstrated stent occlusion. The patient remained intubated, with signs of right hemiplegia. Because repeat MR imaging (D) showed flow across the anterior communicating artery and patency of the left MCA, recanalization was not attempted. The patient remains dependent with an NIHSS score of 9 and mRS score of 4 at 3-month follow-up.

Yoon et al²⁹ observed 1 case (2.2%) of acute stent thrombosis in a series of 47 patients. Lockau et al²² had 3/37 (8.1%) acute stent occlusions during the procedure: One was recanalized by aspiration and balloon angioplasty. In the 2 other cases, recanalization attempts remained unsuccessful, but there was sufficient cross-flow from the contralateral site. In our series, 3 cases (3/73, 4.1%) of intraprocedural stent thrombosis were treated successfully with aspiration using a large-bore 6F intracranial aspiration catheter or a guiding catheter.

Several conclusions can be drawn from the available literature. First, because the data are clearly insufficient, there is a clear need for systematic follow-up of stent patency in all future case series or prospective studies. This will provide more robust evidence, which can be used to refine the technical details of the endovascular procedure and periprocedural medication, to reduce stent thrombosis rates. In addition, we have shown that delayed stent thrombosis is an independent predictor of unfavorable clinical outcome. Incorporating stent patency data in future studies could improve understanding of clinical outcomes.

Second, the reported stent thrombosis rates were highly variable. There are several causative factors: variability of the procedural antiplatelet protocol (ranging from rectal aspirin to intra-

venous glycoprotein IIb/IIIa inhibitors), differences of implanted stents (varying percentages of metallic surfaces, mesh size, closed- or open-cell design, stent length), subnominal or nominal diameter dilation, and use of overlapping stents.

Third, there seems to be a link between the occurrence of intraprocedural thrombosis and subsequent patency. Intuitively, the underlying pathophysiologic process is the same and is initiated as soon as the stent is implanted. Not surprisingly, we found that visualization of in-stent thrombus on the final angiographic run was an independent predictor of delayed thrombosis. This is concordant with the observation of Steglich-Arnholm et al,²³ in which all patients with occluded stents at follow-up had also experienced partial or complete stent thrombosis during thrombectomy.

Subsequently, it seems that the risk of thrombosis is highest in the first 24 hours. In our series, almost all (13/14) stent occlusions were diagnosed at 24 hours. Similar results have been reported,²⁴ but the number of studied cases is clearly insufficient to draw a conclusion. Given the negative impact of stent thrombosis on clinical outcome, it would seem reasonable to perform more frequent controls of stent patency during the first 24 hours, especially in cases with additional risk factors for stent thrombosis.

Intervention for Occluded Carotid Stent

Once the diagnosis of delayed stent thrombosis has been made, the decision to attempt recanalization can be problematic. In our experience, stent occlusion was not associated with distal re-embolization in the intracranial branches. Initial CT angiography or transcranial sonography demonstrated collateral flow in the MCA through the anterior and/or posterior communicating arteries. In addition, only 3/14 (21.5%) patients had clear aggravation of neurologic deficits that could be attributed to stent occlusion. The main procedural risk is distal intracranial embolization during carotid recanalization attempts.

To avoid this clinical dilemma and in light of the clear association between stent thrombosis and unfavorable clinical outcome observed in our series, it seems justified to make every possible effort to prevent delayed stent thrombosis. This involves administering dual-antiplatelet treatment whenever possible, angiographic surveillance of the stent at the end of the thrombectomy for 5–10 minutes, and specific treatment of in-stent thrombus (either by thromboaspiration or administration of glycoprotein IIb/IIIa inhibitors).

Predictors of Stent Thrombosis

There was a relatively high rate of delayed stent thrombosis in this study. We believe this is because more than half of the patients with stents (42/77, 54.5%) received a single antiplatelet agent (aspirin) during the first 24 hours.

In addition, most patients in this series were treated using long 50-mm Wallstent stents. In comparison with open-cell designs, the mesh size is smaller and the percentage of metal coverage is higher; these features offer better plaque impaction but are also more thrombogenic in an acute setting.

Delayed stent occlusion was more frequent in patients with diabetes. The association between diabetes and higher rates of stent restenosis and occlusion has been extensively documented in the cardiology literature.³⁰ Moreover, diabetes can be associated with an accelerated platelet turnover time, which leads to reduced efficacy of aspirin treatment.³¹ The circulating quantity of new uninhibited platelets rises more rapidly; thus, platelet aggregation returns to normal more rapidly after aspirin administration. To counter this phenomenon, we can speculate that patients with diabetes may need a second dose of aspirin in the first 24 hours, however, further research is needed to balance efficacy versus the added risk of hemorrhagic transformation.

Patients with high NIHSS scores on initial presentation were also more likely to experience delayed stent thrombosis in this series. We can hypothesize that a larger volume of hypoperfused brain leads to decreased carotid outflow and thus promotes stent thrombosis, analogous with peripheral vascular interventions.

Limitations

This study has several limitations. Patients were identified retrospectively in a single center, and most of the procedures were performed using an antegrade strategy and a single type of stent. Because we included patients during >9 years, endovascular approaches and periprocedural anticoagulant/antiplatelet regimens were heterogeneous. In addition, none of the patients in this cohort received glycoprotein IIb/IIIa inhibitors; subsequently, we cannot provide information on stent patency rates for this subgroup.

CONCLUSIONS

By performing systematic follow-up of stent patency in a consecutive series of thrombectomies for anterior circulation tandem lesions, we observed a non-negligible rate of delayed stent thrombosis in cases with patent stents at the end of the procedure. Stent thrombosis was independently associated with unfavorable clinical outcome at discharge. Stent patency seems to be an important end point that needs to be systematically measured and reported in future studies of tandem lesions.

Disclosures: Johann Sebastian Richter—UNRELATED: Travel/Accommodations/Meeting Expenses Unrelated to Activities Listed: MicroVention, Balt, Medtronic, Stryker, Penumbra.

REFERENCES

1. Rubiera M, Ribo M, Delgado-Mederos R, et al. **Tandem internal carotid artery/middle cerebral artery occlusion: an independent predictor of poor outcome after systemic thrombolysis.** *Stroke* 2006;37:2301–05 [CrossRef Medline](#)
2. Berkhemer OA, Fransen PS, Beumer D, et al. **A randomized trial of intraarterial treatment for acute ischemic stroke.** *N Engl J Med* 2015; 372:11–20 [CrossRef Medline](#)
3. Goyal M, Demchuk AM, Menon BK, et al; ESCAPE Trial Investigators. **Randomized assessment of rapid endovascular treatment of ischemic stroke.** *N Engl J Med* 2015;372:1019–30 [CrossRef Medline](#)
4. Jovin TG, Chamorro A, Cobo E, et al; REVASCAT Trial Investigators. **Thrombectomy within 8 hours after symptom onset in ischemic stroke.** *N Engl J Med* 2015;372:2296–306 [CrossRef Medline](#)
5. Saver JL, Goyal M, Bonafe A, et al; SWIFT PRIME Investigators. **Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke.** *N Engl J Med* 2015;372:2285–95 [CrossRef Medline](#)
6. Bracad S, Ducrocq X, Mas JL, et al; THRACE investigators. **Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial.** *Lancet Neurol* 2016;15:1138–47 [CrossRef Medline](#)
7. Wilson MP, Murad MH, Krings T, et al. **Management of tandem occlusions in acute ischemic stroke: intracranial versus extracranial first and extracranial stenting versus angioplasty alone: a systematic review and meta-analysis.** *J Neurointerv Surg* 2018;10: 721–78 [CrossRef Medline](#)
8. Legrand L, Tisserand M, Turc G, et al. **Do FLAIR vascular hyperintensities beyond the DWI lesion represent the ischemic penumbra?** *AJNR Am J Neuroradiol* 2015;36:269–74 [CrossRef Medline](#)
9. Legrand L, Tisserand M, Turc G, et al. **Fluid-attenuated inversion recovery vascular hyperintensities-diffusion-weighted imaging mismatch identifies acute stroke patients most likely to benefit from recanalization.** *Stroke* 2016;47:424–27 [CrossRef Medline](#)
10. Hacke W, Kaste M, Bluhmki E, et al; ECASS Investigators. **Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke.** *N Engl J Med* 2008;359:1317–29 [CrossRef Medline](#)
11. Sadeh-Gonik U, Tau N, Friehmann T, et al. **Thrombectomy outcomes for acute stroke patients with anterior circulation tandem lesions: a clinical registry and an update of a systematic review with meta-analysis.** *Eur J Neurol* 2018;25:693–700 [CrossRef Medline](#)
12. Behme D, Mpotsaris A, Zeyen P, et al. **Emergency stenting of the extracranial internal carotid artery in combination with anterior circulation thrombectomy in acute ischemic stroke: a retrospective multicenter study.** *AJNR Am J Neuroradiol* 2015;36:2340–45 [CrossRef Medline](#)
13. Maurer CJ, Joachimski F, Berlis A. **Two in one: endovascular treatment of acute tandem occlusions in the anterior circulation.** *Clin Neuroradiol* 2015;25:397–402 [CrossRef Medline](#)
14. Puri AS, Kühn AL, Kwon HJ, et al. **Endovascular treatment of tandem vascular occlusions in acute ischemic stroke.** *J Neurointerv Surg* 2015;7:158–63 [CrossRef Medline](#)
15. Spiotta AM, Lena J, Vargas J, et al. **Proximal to distal approach in the treatment of tandem occlusions causing an acute stroke.** *J Neurointerv Surg* 2015;7:164–69 [CrossRef Medline](#)
16. Fahed R, Redjem H, Blanc R, et al. **Endovascular management of acute ischemic strokes with tandem occlusions.** *Cerebrovasc Dis* 2016;41:298–305 [CrossRef Medline](#)
17. Grigoryan M, Haussen DC, Hassan AE, et al. **Endovascular treatment of acute ischemic stroke due to tandem occlusions: large multicenter series and systematic review.** *Cerebrovasc Dis* 2016;41: 306–12 [CrossRef Medline](#)
18. Gory B, Haussen DC, Pottin M, et al; Thrombectomy In TANdem lesions (TITAN) investigators. **Impact of intravenous thrombolysis and emergent carotid stenting on reperfusion and clinical outcomes in patients with acute stroke with tandem lesion treated with thrombectomy: a collaborative pooled analysis.** *Eur J Neurol* 2018; 25:1115–20 [CrossRef Medline](#)
19. Lescher S, Czeppan K, Porto L, et al. **Acute stroke and obstruction of the extracranial carotid artery combined with intracranial tandem occlusion: results of interventional revascularization.** *Cardiovasc Intervent Radiol* 2015;38:304–13 [CrossRef Medline](#)
20. Stampfl S, Ringleb PA, Möhlenbruch M, et al. **Emergency cervical internal carotid artery stenting in combination with intracranial**

- thrombectomy in acute stroke. *AJNR Am J Neuroradiol* 2014;35:741–46 [CrossRef Medline](#)
21. Kwak HS, Hwang SB, Jin GY, et al. Predictors of functional outcome after emergency carotid artery stenting and intra-arterial thrombolysis for treatment of acute stroke associated with obstruction of the proximal internal carotid artery and tandem downstream occlusion. *AJNR Am J Neuroradiol* 2013;34:841–46 [CrossRef Medline](#)
 22. Lockau H, Liebig T, Henning T, et al. Mechanical thrombectomy in tandem occlusion: procedural considerations and clinical results. *Neuroradiology* 2015;57:589–98 [CrossRef Medline](#)
 23. Steglich-Arnholm H, Holtmannspötter M, Kondziella D, et al. Thrombectomy assisted by carotid stenting in acute ischemic stroke management: benefits and harms. *J Neurol* 2015;262:2668–75 [CrossRef Medline](#)
 24. Heck DV, Brown MD. Carotid stenting and intracranial thrombectomy for treatment of acute stroke due to tandem occlusions with aggressive antiplatelet therapy may be associated with a high incidence of intracranial hemorrhage. *J Neurointerv Surg* 2015;7:170–75 [CrossRef Medline](#)
 25. Cohen JE, Gomori JM, Rajz G, et al. Extracranial carotid artery stenting followed by intracranial stent-based thrombectomy for acute tandem occlusive disease. *J Neurointerv Surg* 2015;7:412–17 [CrossRef Medline](#)
 26. Malik AM, Vora NA, Lin R, et al. Endovascular treatment of tandem extracranial/intracranial anterior circulation occlusions: preliminary single-center experience. *Stroke* 2011;42:1653–57 [CrossRef Medline](#)
 27. Mpotsaris A, Kabbasch C, Borggrefe J, et al. Stenting of the cervical internal carotid artery in acute stroke management: the Karolinska experience. *Interv Neuroradiol* 2017;23:159–65 [CrossRef Medline](#)
 28. Rangel-Castilla L, Rajah GB, Shakir HJ, et al. Management of acute ischemic stroke due to tandem occlusion: should endovascular recanalization of the extracranial or intracranial occlusive lesion be done first? *Neurosurg Focus* 2017;42:E16 [CrossRef Medline](#)
 29. Yoon W, Kim BM, Kim DJ, et al. Outcomes and prognostic factors after emergent carotid artery stenting for hyperacute stroke within 6 hours of symptom onset. *Neurosurgery* 2015;76:321–29 [CrossRef Medline](#)
 30. Wilson SR, Vakili BA, Sherman W, et al. Effect of diabetes on long-term mortality following contemporary percutaneous coronary intervention: analysis of 4,284 cases. *Diabetes Care* 2004;27:1137–42 [CrossRef Medline](#)
 31. Di Minno MN, Lupoli R, Palmieri NM, et al. Aspirin resistance, platelet turnover, and diabetic angiopathy: a 2011 update. *Thromb Res* 2012;129:341–44 [CrossRef Medline](#)

Validating the Automatic Independent Component Analysis of DSA

 J.-S. Hong,  Y.-H. Kao,  F.-C. Chang, and  C.-J. Lin



ABSTRACT

SUMMARY: Time-density curve analysis of DSA provides useful blood flow information. However, manually selecting the ROI is time-consuming. We developed an automatic technique to provide arterial, capillary, and venous vasculatures with corresponding time-density curves. This study retrospectively analyzed the data of 36 patients with unilateral carotid stenosis. We found that the full width at half maximum of the time-density curve for the automatically segmented capillary vasculature is a suitable representation of the cerebral circulation time.

ABBREVIATIONS: CCT = cerebral circulation time; FWHM = full width at half maximum; I1 and I2 = the internal carotid artery at 2 locations; IA = cervical internal carotid artery in the lateral view; IB = cavernous segment of the internal carotid artery in the lateral view; MCP = manually selected capillary phase; PA = posteroanterior; TDC = time-density curve

X-ray DSA images are the criterion standard for diagnosing cerebrovascular diseases. The time-density curve (TDC) measured from an ROI represents the changes in the intensity of the contrast bolus passing through the selected region. TDC analysis is less computationally intensive, and measurement outcomes are immediately available.¹ However, the manual selection of the ROI is time-consuming and is susceptible to interobserver variation. The aim of this study was to develop an automatic analysis method for detecting vascular structures and corresponding TDCs from DSA images. Seven hemodynamic parameters were measured from the TDCs. The automatically measured TDCs and hemodynamic parameters were validated through their comparison with those measured from manually selected ROIs.

MATERIALS AND METHODS

This retrospective study was approved by the institutional review board of Taipei Veterans General Hospital. This study enrolled 36 patients who had extracranial internal carotid stenosis of >70% according to the NASCET criteria and who consequently underwent stent placement. DSA acquisitions were performed on a biplane angiosuite (Axiom Artis dBA; Siemens, Erlangen, Germany). A power injector (Liebel-Flarsheim Angiomat; Illumena, San Diego, California) was used to administer the contrast bolus. The image size was 960 × 960 or 1440 × 1440 pixels, and the FOV was 22 cm. The acquisition rate was 6 frames per second, and the acquisition lasted 8–18 seconds. Each patient was imaged in the posteroanterior (PA) and lateral views before and after treatment. A total of 144 datasets were analyzed.

The scale-invariant feature transform flow technique² was applied to the dynamic x-ray projection images for reducing motion artifacts. After performing the registration process, we used the FastICA technique (<https://cran.r-project.org/web/packages/fastICA/fastICA.pdf>)³ to segment the DSA images into arterial, capillary, and venous vasculature images. The thresholding method of Otsu⁴ was applied to the output independent component images for generating binary mask images. The binary masks of these 3 vessel types were used to measure the actual TDCs.

Each TDC was fitted by a γ -variate function⁵ to reduce random noise and recirculation. The following 4 parameters were calculated from the fitted curve: 1) the area under the fitted TDC (area under curve), 2) the maximum enhancement, 3) TTP, and 4) the width between the 2 time points on the TDC when the density was half the maximum enhancement, full width at half maximum (FWHM).

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Three other parameters were calculated by fitting the γ -variate curve to straight lines. Every set of 4 consecutive temporal points on the γ -variate function was fitted to a straight line described by a linear equation: $C(t) = mt + b$, where m was the slope, using a least-squares error technique. The largest and smallest m values were recorded to represent the wash-in and washout slopes, respectively. The bolus arrival time was the time at which the straight line with the largest slope intercepted the horizontal axis (eg, Bolus Arrival Time = $-b / \text{Wash-In Slope}$).

Fifteen ROIs were manually selected to validate the proposed automatic technique. The locations of these ROIs are indicated in Fig 1. The first 13 ROIs had areas of 3×3 pixels. In the PA view, we selected 7 ROIs: the ICA at 2 locations (I1 and I2), anterior and middle cerebral arteries in the PA view, transverse sinus in the PA view, and ipsilateral and contralateral internal jugular veins (ipsi-

lateral internal jugular vein and contralateral internal jugular vein in the PA view, respectively). In the lateral view, we selected 6 ROIs: the cervical ICA (anterior cerebral artery in the PA view [IA]), the cavernous segment of the ICA in the lateral view (IB), anterior and cerebral arteries in the lateral view, parietal vein, and superior sagittal sinus. The other 2 manually drawn ROIs were used to represent the manually selected capillary phase (MCP) in the PA and lateral views. In the MCP ROIs, pixels with maximum enhancement higher than the average were excluded.

For each DSA dataset, 3 TDCs were obtained using the automatic method, and they were designated group A. A total of 15 TDCs were measured from the manually selected ROIs, and they were designated group B. Seven hemodynamic parameters, namely maximum enhancement, bolus arrival time (BAT), TTP, wash-in slope, wash out slope, FWHM, and area under curve, were calculated from the

TDCs. We used the Pearson product-moment correlation coefficient to compare TDCs and these parameters between groups A and B. The cerebral circulation time (CCT) was defined as the time difference between the TTPs of IB and the parietal vein.¹ We compared the CCT with the FWHM measured from the automatically segmented capillary mask and the MCP ROI.

RESULTS

The 3 output independent-component images related to arterial, capillary, and venous phases and the corresponding TDCs are shown in Fig 2A. The mask images and the corresponding TDCs are shown in Fig 2B.

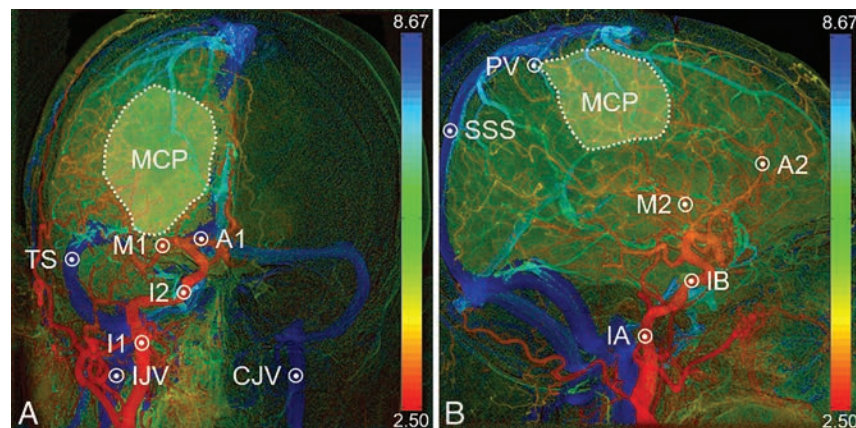


FIG 1. Color-coded DSA images in the PA (A) and lateral (B) views. The numbers on the right-hand side are TTP values. Fifteen ROIs are manually selected to validate the automatic technique.

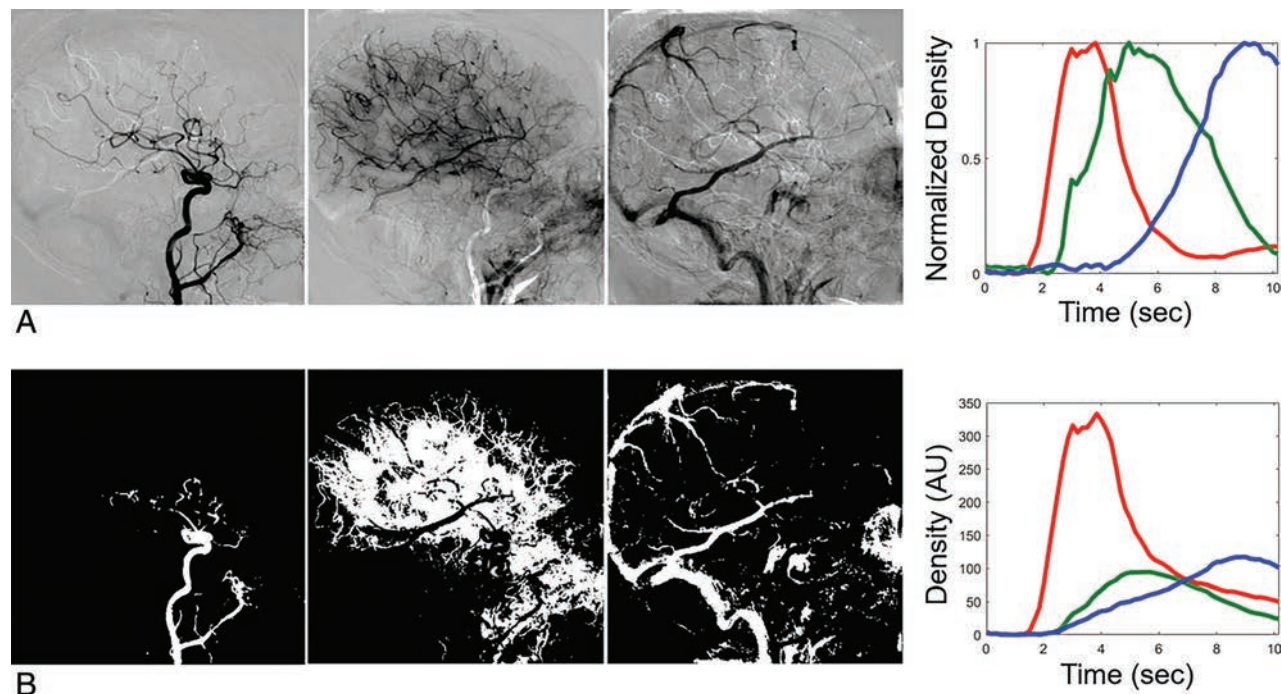


FIG 2. Three output images and corresponding TDCs (A). Mask images for each phase and corresponding TDCs (B). The images are ordered as arterial, capillary, and venous phases from left to right. The red, green, and blue solid lines represent the TDCs of the arterial, capillary, and venous phases. AU indicates arbitrary unit.

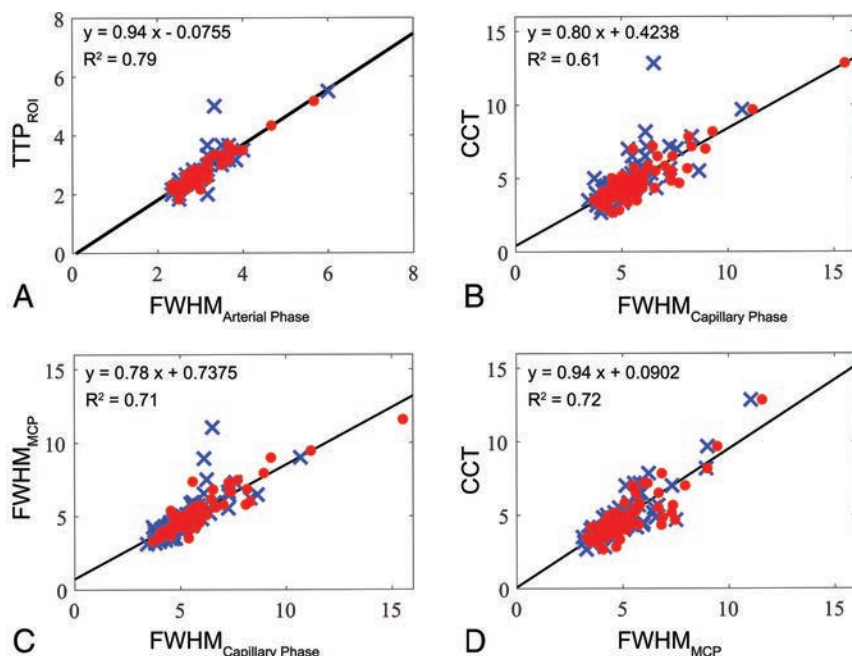


FIG 3. Scatterplot of the TTP between the manually measured I1 (red dots) and IA (blue crosses) and the automatically measured arterial mask (A). Scatterplot between the manually measured CCT and automatically measured FWHM of the capillary mask in the PA (red dots) and lateral (blue crosses) views (B). Scatterplot between the FWHM of MCP and automatically measured FWHM of the capillary mask in the PA (red dots) and lateral (blue crosses) views (C). For comparison, the scatterplot between the manually measured CCT and the FWHM of the MCP in the PA (red dots) and the lateral views (blue crosses) is shown in D.

The Pearson correlation coefficients between the automatically measured TDCs and some manually measured TDCs showed the following: 1) The TDCs of arterial masks were very similar to those of the manually selected large arterial (I1, I2, IA, IB) ROIs (>0.90); 2) the TDCs of capillary masks were very similar to those of the MCP ROI (>0.85); and 3) the TDCs of venous masks were very similar to those of venous (ipsilateral internal jugular vein in the PA view and superior sagittal sinus) ROIs (>0.90).

The 7 parameters calculated from the TDCs of arterial masks were all significantly correlated with the parameters calculated from manually selected large arterial (I1, I2, IA, IB) ROIs ($P < .05$). Those parameters (except wash-in slope) of the capillary masks correlated significantly with those of the MCP ROIs ($P < .05$). The CCT also significantly correlated with the FWHM of capillary masks ($P < .05$). Figure 3 illustrates scatterplots of several hemodynamic parameters measured manually versus those measured automatically. The results indicate that the TDC of the arterial mask is a suitable representation of those for larger ICAs and that the FWHM of the capillary mask is a suitable representation of both CCT and the FWHM of MCP.

DISCUSSION

The proposed automatic postprocessing method obtained robust results for segmenting arterial, capillary, and venous

vasculatures and generated hemodynamic parameters objectively without the manual selection of ROIs. In the era before the capillary phase could be accurately extracted, most morphologic observations focused on arteries and veins. The brain parenchyma itself, comprising capillaries, could not be visualized on an angiogram. A surrogate marker, CCT, was used to indicate the viability of the brain.¹ However, obtaining CCT in a manual manner is inconvenient and has interobserver variation. In the proposed technique, the FWHM of the TDC for the segmented capillary is proportional to the CCT and thus can be considered a useful hemodynamic parameter.

CONCLUSIONS

The proposed technique combines scale-invariant feature transform flow, FastICA, and thresholding techniques to decompose DSA images into arterial, capillary, and venous vasculatures in a completely automatic manner.

The results obtained were highly consistent with those obtained using manually selected ROIs.

Disclosures: Jia-Sheng Hong—RELATED: Patent Pending. UNRELATED: Grant: Siemens, Comments: a grant to develop 2 Matlab programs.* Yi-Hsuan Kao—RELATED: Patent Pending. UNRELATED: Grant: Siemens, Comments: a grant to develop 2 Matlab programs.* Chung-Jung Lin—RELATED: Grant: Ministry of Science and Technology, Taiwan, Comments: grant No. 104-2314-B-010-037*; RELATED: Patent Pending. *Money paid to institution.

REFERENCES

1. Lin CJ, Hung SC, Guo WY, et al. **Monitoring peri-therapeutic cerebral circulation time: a feasibility study using color-coded quantitative DSA in patients with steno-occlusive arterial disease.** *AJNR Am J Neuroradiol* 2012;33:1685–90 [CrossRef Medline](#)
2. Liu C, Yuen J, Torralba A. **SIFT flow: dense correspondence across scenes and its applications.** *IEEE Trans Pattern Anal Mach Intell* 2011; 33:978–94 [CrossRef Medline](#)
3. Hyvärinen A, Oja E. **Independent component analysis: algorithms and applications.** *Neural Netw* 2000;13:411–30 [CrossRef Medline](#)
4. Otsu N. **A threshold selection method from gray-level histograms.** *IEEE Transactions on Systems, Man, and Cybernetics* 1979;9:62–66 [CrossRef](#)
5. Thompson HK Jr, Starmer CF, Whalen RE, et al. **Indicator transit time considered as a gamma variate.** *Circ Res* 1964;14:502–15 [CrossRef Medline](#)

CT Texture Analysis of Cervical Lymph Nodes on Contrast-Enhanced [¹⁸F] FDG-PET/CT Images to Differentiate Nodal Metastases from Reactive Lymphadenopathy in HIV-Positive Patients with Head and Neck Squamous Cell Carcinoma

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ABSTRACT

BACKGROUND AND PURPOSE: Differentiating nodal metastases from reactive adenopathy in HIV-infected patients with [¹⁸F] FDG-PET/CT can be challenging because lymph nodes in HIV-positive patients often show increased [¹⁸F] FDG uptake. The purpose of this study was to assess CT textural analysis characteristics of HIV-positive and HIV-negative lymph nodes on [¹⁸F] FDG-PET/CT to differentiate nodal metastases from disease-specific nodal reactivity.

MATERIALS AND METHODS: Nine HIV-positive patients with head and neck squamous cell carcinoma (7 men, 2 women; 29–62 years of age; median age, 48 years) with 22 lymph nodes (≥ 1 cm) who underwent contrast-enhanced CT with [¹⁸F] FDG-PET followed by pathologic evaluation of cervical lymph nodes were retrospectively reviewed. Twenty-six HIV-negative patients with head and neck squamous cell carcinoma with 61 lymph nodes were evaluated as a control group. Each lymph node was manually segmented, and an in-house-developed Matlab-based texture analysis program extracted 41 texture features from each segmented volume. A mixed linear regression model was used to compare the pathologically proved malignant lymph nodes with benign nodes in the 2 enrolled groups.

RESULTS: Thirteen (59%) lymph nodes in the HIV-positive group and 22 (36%) lymph nodes in the HIV-negative control group were confirmed as positive for metastases. There were 7 histogram features ($P = .017$ – 0.032), 3 gray-level co-occurrence features ($P = .009$ – $.025$), and 9 gray-level run-length features ($P < .001$ – $.033$) that demonstrated a significant difference in HIV-positive patients with either benign or malignant lymph nodes.

CONCLUSIONS: CT texture analysis may be useful as a noninvasive method of obtaining additional quantitative information to differentiate nodal metastases from disease-specific nodal reactivity in HIV-positive patients with head and neck squamous cell carcinoma.

ABBREVIATIONS: AUC = area under receiver operating characteristic curve; HNSCC = head and neck squamous cell carcinoma; GLCM = gray-level co-occurrence matrix; GLGM = gray-level gradient matrix; GLN = gray-level nonuniformity; GLRL = gray-level run-length; HGRE = high gray-level run emphasis; LGRE = low gray-level run emphasis; LRE = long-run emphasis; LRHGE = long-run high gray-level emphasis; max = maximum; RLN = run-length nonuniformity; RP = run percentage; SRE = short-run emphasis; SRLGE = short-run low gray-level emphasis; SUV = standard uptake value

Although patients with HIV have increased life expectancies through the introduction of highly active antiretroviral therapy,¹ there remains significant cancer-specific mortality in these

patients.^{2,3} Many of these patients are now acquiring malignancies that had previously not been associated with HIV or AIDS.^{4,5} The HIV-positive population is at an increased risk of head and neck squamous cell carcinoma (HNSCC) compared with the general population,^{6,7} and HNSCC is an increasingly common disease among individuals with HIV.⁸ HIV-positive HNSCCs have a more aggressive profile that leads to poorer patient outcomes,⁹ and HIV-positive patients have a concurrent increase in HNSCC-related mortality.^{3,4,10}

CT is the initial imaging technique for the diagnosis and staging of HNSCC below the hard palate at many institutions. However, HIV-positive patients often have diffuse bilateral lymph node enlargement consistent with AIDS-associated reactive adenopathy, cystic lesions, necrosis, or infections,^{11,12} and CT is sometimes limited for nodal staging. The introduction of [¹⁸F] FDG-PET/CT has enabled the metabolic assessment of lymph

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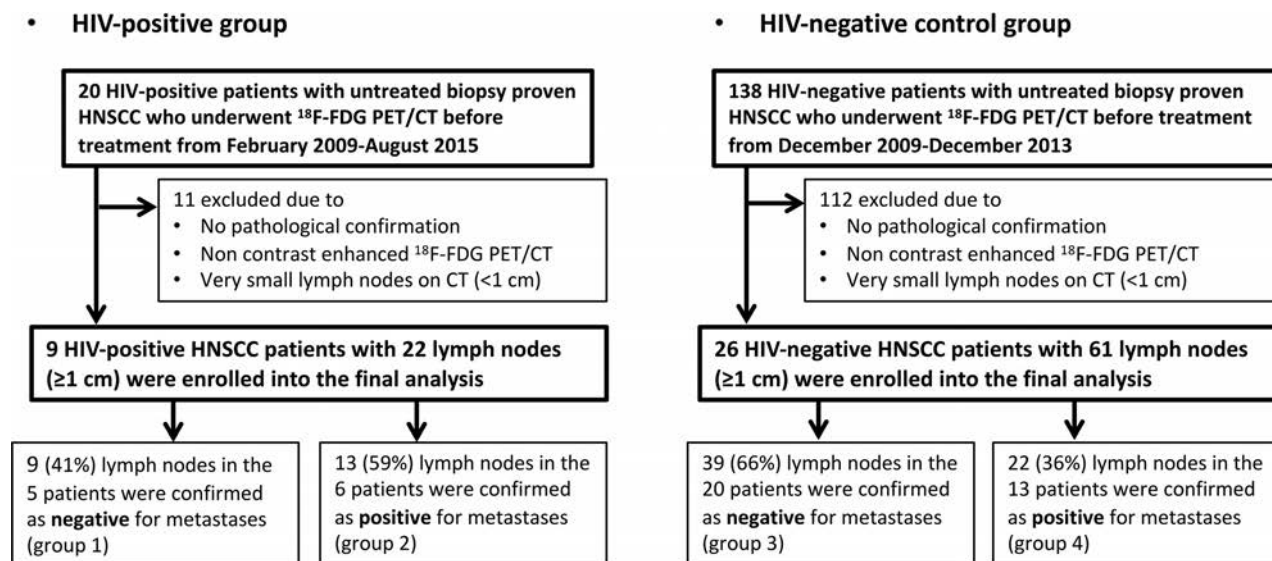


FIG 1. Flowchart shows patient selection for the study.

nodes and is widely used for initially staging, restaging, and monitoring therapeutic responses for patients with head and neck squamous cell carcinoma.¹³⁻¹⁵ However, lymph nodes in HIV-positive patients often show increased [^{18}F] FDG uptake, especially in the setting of high-plasma HIV RNA.¹⁶⁻¹⁸ Activated lymphocytes exhibit increased glucose use, and HIV-positive individuals have a greater accumulation of FDG in their lymph nodes than HIV-negative patients. Both HIV-1 and HNSCC can spread to the primary site of regional deep cervical lymph nodes,^{19,20} which makes metastatic determination and management complex.

There is increasing focus on using texture analysis to determine the features of CT images and elicit characteristics that may adequately describe nodal metastases despite the viral adenopathy.²¹⁻²³ Image texture analysis analyzes complex visual characteristics on the basis of underlying simpler patterns and then conducts quantitative comparisons of these characteristics between 2 images. Considering that these mathematic textural analyses have helped elucidate nuanced differences in pathology, we hypothesized that CT textural features would have the potential to add additional quantitative information in conjunction with [^{18}F] FDG-PET/CT in HIV-positive HNSCC for the evaluation of lymph nodes. In addition, to the best of our knowledge, imaging studies including [^{18}F] FDG-PET/CT of HIV-positive patients with head and neck squamous cell carcinoma related to lymph node adenopathy have not been fully explored in the literature. Hence, the purpose of this study was to assess the CT texture-analysis characteristics of HIV-positive and HIV-negative lymph nodes on [^{18}F] FDG-PET/CT to differentiate nodal metastases from disease-specific nodal reactivity.

MATERIALS AND METHODS

Patients

The institutional review board approved this retrospective study. The requirement to obtain written informed consent was waived. The flowcharts of patient selection for HIV-positive patients and an HIV-negative control group in the study are shown in Fig 1.

HIV-Positive Patient Group

We retrospectively searched our electronic medical records to identify HIV-positive patients with untreated biopsy-proved HNSCCs who also underwent [^{18}F] FDG-PET/CT before treatment between February 2009 and August 2015, and 20 patients were identified in total. Four of the 20 patients were excluded because they received nonsurgical treatment, such as chemoradiotherapy, without biopsy-proved pathologic confirmation of cervical lymph nodes. An additional 7 patients were excluded, 3 of whom were excluded due to non-contrast-enhanced [^{18}F] FDG-PET/CT; and 4 patients, due to very small lymph nodes on CT (maximum size, <1 cm) that were difficult to analyze using the texture-analysis program. The remaining 9 patients (7 men, 2 women; 29–62 years of age; median age, 48 years; with 3 oral cavity, 3 oropharynx, 1 larynx, 1 maxillary sinus, and 1 primary unknown lesion) with 22 lymph nodes (maximum size, ≥ 1 cm) were enrolled in this study.

The electronic medical records were reviewed on all subjects, specifically for the presence of pathologically confirmed cervical lymph node metastasis at first treatment with neck dissection. The dates of the first surgical procedure and patient outcomes such as the presence of metastatic recurrence in a cervical lymph node within 1 year after surgery were also noted.

HIV-Negative Patient Group for Controls

We also identified HIV-negative patients with untreated biopsy-proved HNSCCs as a control group to investigate how HIV infection affects the texture features and standard uptake values (SUVs) of the nodal metastasis and reactive adenopathy. Between December 2009 and December 2013, one hundred thirty-eight consecutive HIV-negative patients with newly diagnosed primary head and neck squamous cell carcinoma underwent [^{18}F] FDG-PET/CT before treatment. Fifty-three of the 138 patients were excluded because they received nonsurgical treatment without pathologic confirmation of cervical lymph nodes. An additional 25 patients were excluded because only non-contrast-enhanced [^{18}F] FDG-PET/CT was performed. In addition, 34 patients with

small lymph nodes on CT (maximum size, <1 cm) were also excluded. The remaining 26 patients (17 men, 9 women; 30–86 years of age; median age, 59 years; with 12 oral cavity, 10 oropharynx, 1 hypopharynx, and 3 larynx lesions) with 61 lymph nodes (node size, ≥ 1 cm) were enrolled in this study as a control group.

PET/CT Imaging Protocol

For image analysis, the pretreatment PET/CT was used to obtain CT texture analysis and FDG uptake. All [^{18}F] FDG-PET/CT studies were performed on an integrated PET/CT scanner combining PET with a 16-slice multidetector row CT (Discovery STE 16; GE Healthcare, Milwaukee, Wisconsin). Patients were injected with an average of 10.59 mCi of [^{18}F] FDG, and it was incubated for an average of 62 minutes. The amount of injected radioactivity was routinely measured by quantification of the radioactivity of the syringe before and after injection. Patients were scanned in a supine position from the skull base to midthigh on a flat table with a head and neck acquisition separate from the body acquisition. All patients were scanned using a dedicated head and neck protocol.

The dedicated head and neck CT studies were helically acquired (120 kV[peak], gantry rotation time = 0.5 seconds, kVp = 120, auto milliamperage, minimum = 299 mA, maximum = 440 mA, noise index = 11, helical pitch factor = 0.937:1, scan FOV = 30 cm, reconstructed slice thickness = 1.25 mm, image matrix = 512×512) extending from the skull base to thoracic inlet following a 60-second delay after intravenous contrast injection (60 mL of ioversol, Optiray 350, Mallinckrodt, St. Louis, Missouri; or iopimidel, Isovue 370, Bracco, Princeton, New Jersey). The images were reviewed in soft-tissue algorithms. The dedicated head and neck PET scans were obtained using 2D imaging with emission scans lasting between 5 and 6 minutes, and an FOV of 30 cm. The matrix size was 128×128 , and slice thickness was 3.3 mm.

Image Segmentation and Texture Analysis on CT

Multiple lymph nodes (up to 5 per patient, selected on the basis of a maximum size of >1 cm) were analyzed for CT texture analysis and FDG uptake. Each lymph node was manually contoured by a neuroradiologist with 10 years of experience. Segmentation of the lymph nodes was performed using OsiriX Imaging Software (<http://www.osirix-viewer.com>). The entire lymph node, including necrotic or cystic areas, was segmented for analysis. For a subanalysis, ROIs without obvious necrotic or cystic areas were also created (On-line Figure). When severe streak artifacts within the lymph node were seen, the slices with severe artifacts were excluded and only artifact-free slices were used for texture analysis. Each contoured image was imported into an in-house-developed Matlab-based (MathWorks, Natick, Massachusetts) texture analysis software.^{24,25} We discuss the extraneous math behind each texture feature in detail in a subsequent On-line Appendix.^{24,26–31} In total, 41 texture features, including 12 histogram features, 5 gray-level co-occurrence matrix (GLCM) features, 11 gray-level run-length (GLRL) features, 4 gray-level gradient matrix (GLGM) features, and 9 Laws features, were computed and averaged over the images per dataset. The mean value of the textural features was estimated. Both the volume and size of each lymph node were also calculated.

[^{18}F] FDG-PET/CT Image Analysis

The PET study and contrast-enhanced CT scan were viewed independently and as coregistered studies using a Vista workstation (MIM Software, Cleveland, Ohio). PET, CT, and fused PET/CT images were reviewed in the axial planes. Standard uptake value maximum (SUVmax), the maximum SUV within the tumor normalized to lean body mass from PET, was measured by drawing an ROI slightly outside each lesion corresponding to those used for texture analysis on the CT image for each patient.

Statistical Analysis

We compared the 41 texture parameters, SUVmax, lymph node size, and volume: 1) the malignant nodes with benign nodes in the HIV-positive group (group 2 versus 1); 2) the malignant lymph nodes with benign nodes in the HIV-negative group (group 4 versus 3); 3) the benign lymph nodes in the HIV-positive group with benign lymph nodes in the HIV-negative group (group 1 versus 3); and 4) the malignant lymph nodes in the HIV-positive group with malignant lymph nodes in the HIV-negative group (group 2 versus 4). For each group comparison, we used the mixed linear regression model (Proc MIXED; http://support.sas.com/documentation/cdl/en/statug/63033/HTML/default/viewer.htm#mixed_toc.htm) to take into consideration data clustering using the SAS 9.3 system (SAS Institute, Cary, North Carolina). Because each patient could contribute >1 lymph node, this approach allowed modeling of the variance-covariance matrix among multiple values recorded for each patient. Compound symmetry was specified for the covariance structure. To assess the potential clinical utility of texture features and nodal characteristics, we constructed receiver operating characteristic curves for repeat-measures designs to determine the performance and optimal cutoff point of each parameter in distinguishing the 2 node characterizations (for example, benign versus malignant lymph nodes in HIV-positive patients).³² The point on the receiver operating characteristic curve farthest from the 45-degree reference line with the best combination of sensitivity and specificity was considered the optimum cutoff point. The area under the receiver operating characteristic curve (AUC) was used to assess the predicted validity of each parameter. The closer the AUC value is to 1.0, the more predictive the features are with respect to malignant lymph nodes. Associations of demographic and clinical characteristics with HIV-positive and HIV-negative groups were tested with the Pearson χ^2 test or the Mann-Whitney U test. Due to the relatively small sample size and exploratory nature of this study, correction for multiple comparisons was not applied, and an uncorrected P value of .05 was regarded as the statistical threshold of significance for all analyses.

RESULTS

For HIV-positive patients, the median absolute CD4 counts were 473 cells/mm³ (range, 172–1809 cells/mm³), and 8 of 9 patients were receiving highly active antiretroviral therapy. In the HIV-positive group, 13 (59%) lymph nodes in 6 patients were confirmed as malignant (positive for metastases), and 9 (41%) lymph nodes in 5 patients were confirmed as benign (negative for metastases). Two patients in the HIV-positive group had both malignant and benign nodes. In the HIV-negative control group, 22 (36%) lymph nodes in 13 patients were confirmed as malignant (positive for metastases), and 39 (66%) lymph nodes in 20 pa-

Table 1: Patient demographics and tumor characteristics of patients with head and neck cancer^a

Characteristic	HIV-Positive Group (n = 9)	HIV-Negative Group (n = 26)	P Value
Age (yr)			.034 ^b
Median (range)	48 (29–62)	59 (30–86)	
Sex			.490
Male	7 (78)	17 (65)	
Female	2 (22)	9 (35)	
HPV status (protein 16)			.283
Positive	3	12	
Negative	1	14	
Unknown	5	0	
Primary site			.169
Oropharynx	3 (33)	10 (38)	
Hypopharynx	0 (0)	1 (4)	
Larynx	1 (11)	3 (12)	
Oral cavity	3 (33)	12 (46)	
Primary unknown	1 (11)	0 (0)	
Maxilla	1 (11)	0 (0)	
T-Stage			.444
T0	1 (11)	0 (0)	
T1	1 (11)	7 (27)	
T2	3 (33)	9 (35)	
T3	1 (11)	2 (8)	
T4	3 (33)	8 (30)	

Note:—HPV indicates human papillomavirus.

^a Data are presented as number of patients with percentages in parentheses unless otherwise noted.

^b Indicates a significant difference by the Pearson χ^2 or Mann-Whitney *U* test ($P < .05$).

tients were confirmed as benign (negative for metastases). Ten patients in the HIV-negative group had both malignant and benign nodes. Complete patient demographics and tumor characteristics are described in Table 1. The primary site and T-stage were not significantly different between the HIV-positive and HIV-negative groups.

Analysis between Lymph Node Characterization in HIV-Positive and HIV-Negative Patients with HNSCC

HIV-Positive Patient Group. The results of the [¹⁸F] FDG-PET/CT characteristics (SUVmax, node size, and node volume) and the 41 texture parameters differentiating lymph node characterization in HIV-positive patients with head and neck squamous cell carcinoma (group 1 versus 2) are shown in Table 2 (for selected parameters) and On-line Table 1 (for 41 parameters). There was a significant difference in the SUVmax (5.11 for benign nodes versus 8.56 for malignant nodes, $P = .042$), node size (1.40 cm for benign nodes versus 1.89 cm for malignant nodes, $P = .024$), and node volume (0.55 cm³ for benign nodes versus 2.54 cm³ for malignant nodes, $P = .007$) between malignant and benign nodes for the HIV-positive group. For the CT texture analysis in the HIV-positive group, there were 7 histogram features, including mean ($P = .017$), median ($P = .018$), second SD ($P = .017$), range ($P = .017$), geometric mean ($P = .032$), SD 5 ($P = .018$), and SD 9 ($P = .017$); 3 GLCM features, including contrast ($P = .009$), energy ($P = .025$), and homogeneity ($P = .020$); and 9 GLRL features, including short-run emphasis (SRE) ($P < .001$), long-run emphasis (LRE) ($P = .001$), gray-level nonuniformity (GLN) ($P = .001$), run-length nonuniformity (RLN) ($P = .002$), run percentage (RP) ($P = .033$), low gray-level run emphasis

(LGRE) ($P = .013$), high gray-level run emphasis (HGRE) ($P = .008$), short-run low gray-level emphasis (SRLGE) ($P = .021$), and long-run high gray-level emphasis (LRHGE) ($P = .035$) that demonstrated a significant difference in HIV-positive patients with either benign or malignant lymph nodes (On-line Table 1). No statistically significant differences were seen in the GLGM and Laws texture features. Among the imaging characteristics, the highest AUC to predict a malignant lymph node was 0.89, with a sensitivity of 92.3% and a specificity of 77.8% in node volume. Among the 41 texture features, the highest AUC was 0.97, with a sensitivity of 84.6% and a specificity of 100% in SRE, which is categorized as a GLRL feature (Table 2).

For the HIV-positive group, the optimal SUV cutoff was 5.50 for benign-versus-malignant nodes, and 3.98 for the HIV negative group (Tables 2 and 3). Among the 13 malignant nodes, 11 (84.6%) were correctly detected by both SUV and texture analysis (SRE); however, 2 (15.4%) false-negative findings were observed even using SUV and texture analysis (SRE). Among the 9 benign nodes, 2 (22.2%) were observed as false-positive findings on the SUV cutoff point (SUVmax = 8.1 and 7.4), whereas no false-positive findings were observed on texture analysis (SRE). Figure 2 shows a representative case of a false-positive finding on FDG-PET for benign nodes in an HIV-positive patient with HNSCC who had both benign and malignant nodes.

HIV-Negative Patient Subgroup as Controls. The results of the [¹⁸F] FDG-PET/CT characteristics (SUVmax, node size, and node volume) and the 41 texture parameters differentiating lymph node characterization in HIV-negative patients with head and neck squamous cell carcinoma (group 3 versus 4) are shown in Table 3 (for selected parameters) and On-line Table 2 (for 41 parameters). The node volume for the HIV-negative group (1.12 mL for benign nodes versus 3.47 mL for malignant nodes, $P = .001$) and the SUVmax for the HIV-negative group (3.23 for benign nodes versus 6.44 for malignant nodes, $P = .007$) showed significant differences. For the CT texture analysis, statistically significant differences among lymph node characterizations in patients with head and neck squamous cell carcinoma were seen in 5 histogram features, including mean ($P = .022$), geometric mean ($P = .020$), harmonic mean ($P = .020$), interquartile range ($P = .022$), and fourth moment ($P = .018$); 3 GLCM features, including contrast ($P = .015$), energy ($P = .034$), and homogeneity ($P = .029$); 5 GLRL features, including SRE ($P = .036$), RLN ($P = .034$), short-run high gray-level emphasis ($P = .016$), long-run low gray-level emphasis ($P = .006$), and LRHGE ($P = .003$); and 9 Laws features ($P = .024$ –.047), while there was no statistically significant difference in GLGM. The highest AUC among the 41 texture features to predict a malignant lymph node was 0.76 with the texture parameter of LRHGE (sensitivity of 54.6% and specificity of 84.6%), whereas the highest AUC among the imaging characteristics was SUVmax (AUC = 0.73, sensitivity = 63.6%, and specificity = 79.5%) (Table 3).

Analysis of Node Characterization among HIV Infections in Patients with HNSCC with Lymph Nodes

Benign Lymph Node (Negative for Metastases) Subgroup. The results of the texture parameters differentiating HIV infections in

Table 2: ¹⁸F FDG-PET/CT characteristics and selected texture parameters differentiating lymph node characterization in patients with HIV infection (group 1 vs 2)

Texture Parameter	Benign Nodes (n = 9)		Malignant Nodes (n = 13)		P Value ^a	Cutoff	AUC ^b (GLIMMROC)
	Mean	SD	Mean	SD			
Node characteristics							
Size (cm)	1.400	0.300	1.892	0.690	.024	<2.0	0.752
Volume (cm ³)	0.547	0.363	2.535	2.218	.007	>0.76	0.889
SUVmax	5.111	1.610	8.562	3.886	.042	>5.5	0.803
Histogram							
Mean	624.4	74.6	735.3	75.2	.017	>683.3	0.872
Median	774.0	217.9	1013.1	71.2	.018	>877.8	0.872
Second SD	93.76	28.70	59.85	19.19	.017	<76.3	0.872
Range	273.7	82.9	175.4	54.5	.017	<232.7	0.863
Geometric mean	199.6	44.7	272.8	63.8	.032	>237.3	0.829
SD 5	81.9	29.4	16.8	19.2	.018	<62.89	0.872
SD 9	99.7	49.3	19.5	17.3	.017	<63.16	0.889
GLCM							
Contrast	113.1	20.2	84.1	16.9	.009	<97.7	0.889
Energy	0.036	0.019	0.081	0.047	.025	>0.047	0.812
Homogeneity	0.451	0.065	0.542	0.069	.020	>0.498	0.821
GLRL							
SRE	0.177	0.007	0.157	0.009	<.001	<0.164	0.966 ^c
LRE	0.197	0.010	0.173	0.012	.001	<0.186	0.957
GLN	0.183	0.009	0.160	0.011	.001	<0.172	0.949
RLN	0.196	0.010	0.173	0.012	.002	<0.184	0.932
LRHGE	224.6	51.8	300.0	68.7	.035	>261.8	0.863

Note:—GLIMMROC indicates generalized linear mixed model receiver operating characteristic.

^aIndicates a significant difference by the mixed linear regression model (Proc MIXED) to adjust the variance-covariance matrix among multiple values recorded for each patient ($P < .05$).

^bUsing the generalized linear mixed model (GLIMMROC).

^cThe highest AUC among 41 texture features.

Table 3: ¹⁸F FDG-PET/CT characteristics and selected texture parameters differentiating lymph node characterization in patients with head and neck squamous cell carcinoma without HIV infection (group 3 vs 4)

Texture Parameter	Benign Nodes (n = 39)		Malignant Nodes (n = 22)		P Value ^a	Cutoff	AUC ^b (GLIMMROC)
	Mean	SD	Mean	SD			
Node characteristics							
Size (cm)	1.439	0.048	1.687	0.831	.079	DNC	0.643
Volume (cm ³)	1.122	0.147	3.468	4.718	.001 ^c	>2.599	0.702
SUVmax	3.228	0.315	6.438	4.811	.007 ^c	>3.980	0.731
Histogram							
Mean	670.6	68.4	751.8	137.3	.022 ^c	>738.1	0.705
Geometric mean	225.9	50.6	297.6	124.5	.020 ^c	>257.5	0.667
Harmonic mean	24.12	4.21	29.57	9.42	.020 ^c	>25.5	0.678
IQR	1064.3	63.9	865.0	360.2	.022 ^c	<1017.0	0.723
Fourth moment	8.71E+10	5.74E+09	9.41E+10	1.00E+10	.018 ^c	>9.38E+10	0.698
GLCM							
Contrast	102.5	18.2	81.8	28.3	.015 ^c	<75.7	0.754
Energy	0.041	0.022	0.072	0.055	.034 ^c	>0.058	0.712
Homogeneity	0.475	0.056	0.541	0.104	.029 ^c	>0.528	0.735
GLRL							
SRE	0.164	0.011	0.154	0.019	.036 ^c	<0.153	0.695
RLN	0.183	0.014	0.170	0.023	.034 ^c	<0.172	0.698
RHGE	254.2	77.2	367.0	193.6	.016 ^c	>305.4	0.739
LRLGE	322.6	91.4	469.8	231.9	.006 ^c	>397.1	0.759
LRHGE	246.2	60.5	352.7	168.8	.003 ^c	>340.9	0.760 ^d
Laws features							
LI	1,130,272.9	280,670.9	876,676.6	413,942.2	.024 ^c	<911,080.5	0.722

Note:—DNC indicates did not converge; IQR, interquartile range; GLIMMROC, generalized linear mixed model receiver operating characteristic.

^aIndicates a significant difference by the mixed linear regression model (Proc MIXED) to adjust the variance-covariance matrix among multiple values recorded for each patient ($P < .05$).

^bUsing the generalized linear mixed model (GLIMMROC).

^cSignificant.

^dThe highest AUC among 41 texture features.

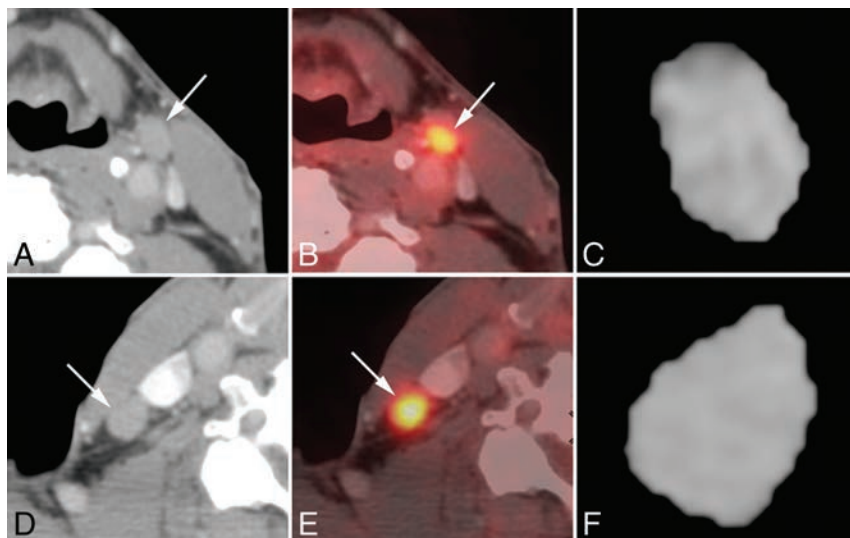


FIG 2. Representative case of false-positive findings on FDG-PET for benign nodes in a 74-year-old woman with unknown primary squamous cell carcinoma who had both benign and malignant nodes (HIV-positive; absolute CD4 = 473). Axial contrast-enhanced CT images (A and D), [^{18}F] FDG-PET/CT fusion images (B and E), and corresponding axial section ROI mask-segmented lymph nodes (C and F) for pathologically benign (A–C) and malignant (D–F) lymph nodes. [^{18}F] FDG-PET/CT shows abnormal uptake (cutoff = >5.5) for both lymph nodes with SUVmax = 8.1 (benign, B) and 9.5 (malignant, E). However, texture features with SRE (cutoff = <0.164) of both lymph nodes were correctly diagnosed as follows: 0.188 (benign, C) and 0.151 (malignant, F).

patients with head and neck squamous cell carcinoma with benign nodes (group 1 versus 3) are shown in On-line Table 3. For benign lymph nodes, the point estimate of the SUVmax of HIV-positive (5.11) was higher than that of HIV-negative (3.23); however, the difference among the SUVmax of HIV statuses was not statistically significant ($P = .111$). No statistically significant differences were seen in the node size (1.40 cm for HIV-positive versus 1.44 cm for HIV-negative, $P = .781$) and node volume (0.58 cm^3 for HIV-positive versus 1.12 cm^3 , $P = .137$) between the HIV-positive and HIV-negative groups. For the CT texture analysis in benign lymph nodes, there were 5 GLRL features, SRE ($P = .017$), LRE ($P = .027$), GLN ($P = .021$), LGRE ($P = .044$), and HGRE ($P = .012$), that demonstrated a significant difference with HIV-positive and HIV-negative patients. No statistically significant differences were seen in the histogram, GLCM, GLGM, and Laws texture features. Among the imaging characteristics and the 41 texture features, the highest AUC to predict HIV-infected lymph nodes was 0.87, with a sensitivity of 100% and a specificity of 84.6% in SUVmax.

Malignant Lymph Node (Positive for Metastases) Subgroup. The results of the texture parameters differentiating HIV infections in patients with head and neck squamous cell carcinoma with malignant nodes (group 2 versus 4) are shown in On-line Table 4. For malignant lymph nodes, there was no statistically significant differences in the SUVmax (8.56 for HIV-positive versus 6.46 for HIV-negative, $P = .192$), node size (1.89 cm for HIV-positive versus 1.69 cm for HIV-negative, $P = .186$), and node volume (2.54 cm^3 for HIV-positive versus 3.47 cm^3 , $P = .409$) between the HIV-positive and HIV-negative groups. Of the 41 CT texture analysis parameters in malignant lymph nodes, there were no statistically significant differences in the histogram, GLCM, GLGM, GLRL, and Laws texture features.

Subanalysis of Texture Features of Lymph Nodes without and with Exclusion of Necrotic Areas Differentiating Benign-versus-Malignant Lymph Nodes

The results of subanalysis of the lymph node characterization without and with exclusion of areas of obvious necrosis or cystic parts are shown in On-line Table 5 for patients with HIV (group 1 versus 2) and in On-line Table 6 for patients without HIV (group 3 versus 4). Even excluding the obvious necrotic parts, there was no major change in which a parameter was effective in distinguishing benign and malignant nodes. For the patients with HIV (group 1 versus 2), there were 6 histogram features ($P = .034$ – $.045$), 3 GLCM features ($P = .031$ – $.045$), and 4 GLRL features ($P = .011$ – $.048$) that demonstrated a significant difference in HIV-positive patients with either benign or malignant lymph nodes. For the patients without HIV (group 3 versus 4), there were 3 histogram features ($P = .032$ – $.043$), 2 GLCM features

($P = .037$ – $.047$), and 3 GLRL features ($P < .001$ – $.01$) that demonstrated a significant difference in HIV-positive patients with either benign or malignant lymph nodes. However, the AUC of the analysis, including the necrotic parts, was higher than that of the subanalysis excluding the necrotic parts for all texture parameters.

DISCUSSION

The results of our study demonstrated that the histogram, GLCM, and GLRL CT texture parameters of the lymph nodes showed a significant difference between metastatic lymph nodes and HIV-related lymphadenopathy in patients with head and neck squamous cell carcinoma with HIV infection. CT texture features, especially space-dependent features such as GLCM and GLRL, may provide important additional information to differentiate nodal metastases from disease-specific nodal reactivity in HIV-positive patients with head and neck squamous cell carcinoma.

In our study, none of the CT textural analysis features were found to have statistically significant differences between HIV-positive and HIV-negative patients with malignant lymph nodes. The lack of a significant difference suggests almost similar texture for HNSCC metastatic nodes regardless of HIV infection status. On the other hand, benign lymph nodes showed different textures in 5 GLRL features between HIV-positive and HIV-negative lymph nodes. HIV-positive patients often have lymph node enlargement consistent with AIDS-associated reactive adenopathy, and HIV viral loads may also be associated with viral infection, including human papillomavirus and Epstein-Barr virus, which are well-known etiologies of HNSCC.^{6,8} Therefore, the texture features may potentially reflect a different degree of uniformity due to inflammation or viral infection within the lymph nodes along both long and short matrix runs. Space-dependent texture

features such as GLRL on CT images could demonstrate significant differences in benign lymph nodes in HIV-positive patients with head and neck squamous cell carcinoma, which may have the potential to prove morphologic feature differences among disease-specific nodal reactivity in HIV-positive patients with head and neck squamous cell carcinoma.

CT texture analysis is a postprocessing technique and a new addition to the image-analysis armamentarium that extracts information native to image data that is not apparent on visual inspection of images. CT texture analysis has started to be investigated for its ability to predict lymph node metastasis in patients with lung cancer.^{21,33} In our study, for assessment of metastatic lymph nodes in HIV-negative patients, some histogram and GLRL texture features may be associated with nodal metastasis in patients with head and neck squamous cell carcinoma. However, the predictions of malignant nodes using texture analysis were almost similar to SUV values in HIV-negative patients. Further testing using a larger sample size is needed to validate the performance of the predictive model.

Immunosuppression predisposes HIV-infected patients to a number of opportunistic infections; therefore, special care must be taken in evaluating [¹⁸F] FDG-PET/CT. Benign hypermetabolic foci are common, especially in the context of high levels of HIV viremia (low CD4 counts) and can lead to false-positive interpretations of metastasis using only the SUV cutoff point.^{16,18,34} In past years, other quantitative approaches, including metabolic tumor volume and total lesion glycolysis for [¹⁸F] FDG-PET evaluations, have been investigated for differentiation of HIV-associated lymphoma from HIV-associated reactive adenopathy.^{35,36} CT texture features can also be obtained from the same [¹⁸F] FDG-PET/CT study. The combination model based on these quantitative PET metabolic metrics, CT texture parameters, and clinical parameters may need to be further evaluated in a future study for patients with head and neck squamous cell carcinoma.

There are several limitations associated with the small sample size in this study. This study included only a small number of HIV-infected patients with head and neck squamous cell carcinoma, and there were imbalances among the different groups. The statistical analysis was potentially limited in that the more reasonable analyses, including multiple-comparison correction, could not be conducted. The small sample size could also potentially mask the weak differences. In addition, for the HIV-positive group, there is a wide range of absolute CD4 cell counts, and a subset of patients were receiving highly active antiretroviral therapy. These distributions have significant implications for mounting an immune reaction and therefore potentially for the texture features of lymph nodes. Therefore, detailed analyses using stratification based on CD4 counts and administration of therapeutic regimens considering the influence of the status of HIV are desirable. These problems could be solved in future studies with larger sample sizes.

CONCLUSIONS

Histogram, GLCM, and GLRL CT texture parameters of the lymph nodes are associated with nodal metastasis in patients with head and neck squamous cell carcinoma with HIV infection. Although further testing using a larger sample size is needed to val-

idate the performance, CT texture analysis may be useful as a noninvasive method for obtaining additional quantitative information to differentiate nodal metastases from disease-specific nodal reactivity in HIV-positive patients with head and neck squamous cell carcinoma.

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REFERENCES

- Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *Lancet* 2008; 372:293–99 CrossRef Medline
- Bonnet F, Burty C, Lewden C, et al. Changes in cancer mortality among HIV-infected patients: the Mortalité 2005 Survey. *Clin Infect Dis* 2009;48:633–39 CrossRef Medline
- Coghill AE, Shiels MS, Suneja G, et al. Elevated cancer-specific mortality among HIV-infected patients in the United States. *J Clin Oncol* 2015;33:2376–83 CrossRef Medline
- Mourad WF, Hu KS, Shasha D, et al. Long-term outcome of seropositive HIV patients with head and neck squamous cell carcinoma treated with radiation therapy and chemotherapy. *Anticancer Res* 2013;33:5511–16 Medline
- Powles T, Robinson D, Stebbing J, et al. Highly active antiretroviral therapy and the incidence of non-AIDS-defining cancers in people with HIV infection. *J Clin Oncol* 2009;27:884–90 CrossRef Medline
- Beachler DC, Sugar EA, Margolick JB, et al. Risk factors for acquisition and clearance of oral human papillomavirus infection among HIV-infected and HIV-uninfected adults. *Am J Epidemiol* 2015;181:40–53 CrossRef Medline
- Frisch M, Biggar RJ, Engels EA, et al. Association of cancer with AIDS-related immunosuppression in adults. *JAMA* 2001;285:1736–45 CrossRef Medline
- McLemore MS, Haigentz M Jr, Smith RV, et al. Head and neck squamous cell carcinomas in HIV-positive patients: a preliminary investigation of viral associations. *Head Neck Pathol* 2010;4:97–105 CrossRef Medline
- Spano JP, Costagliola D, Katlama C, et al. AIDS-related malignancies: state of the art and therapeutic challenges. *J Clin Oncol* 2008;26:4834–42 CrossRef Medline
- D'Souza G, Carey TE, William WN Jr, et al. Epidemiology of head and neck squamous cell cancer among HIV-infected patients. *J Acquir Immune Defic Syndr* 2014;65:603–10 CrossRef Medline
- Olsen WL, Jeffrey RB Jr, Sooy CD, et al. Lesions of the head and neck in patients with AIDS: CT and MR findings. *AJR Am J Roentgenol* 1988;151:785–90 CrossRef Medline
- Holliday RA, Cohen WA, Schinella RA, et al. Benign lymphoepithelial parotid cysts and hyperplastic cervical adenopathy in AIDS-risk patients: a new CT appearance. *Radiology* 1988;168:439–41 CrossRef Medline
- Quon A, Fischbein NJ, McDougall IR, et al. Clinical role of ¹⁸F-FDG PET/CT in the management of squamous cell carcinoma of the head and neck and thyroid carcinoma. *J Nucl Med* 2007;48(Suppl 1):58S–67S Medline
- Kyzas PA, Evangelou E, Denaxa-Kyza D, et al. ¹⁸F-fluorodeoxyglucose positron emission tomography to evaluate cervical node metastases in patients with head and neck squamous cell carcinoma: a meta-analysis. *J Natl Cancer Inst* 2008;100:712–20 CrossRef Medline
- Gupta T, Master Z, Kannan S, et al. Diagnostic performance of post-treatment FDG PET or FDG PET/CT imaging in head and neck cancer: a systematic review and meta-analysis. *Eur J Nucl Med Mol Imaging* 2011;38:2083–95 CrossRef Medline
- Davison JM, Subramaniam RM, Surasi DS, et al. FDG PET/CT in patients with HIV. *AJR Am J Roentgenol* 2011;197:284–94 CrossRef Medline

17. Sathekge M, Maes A, Kgomo M, et al. **Fluorodeoxyglucose uptake by lymph nodes of HIV patients is inversely related to CD4 cell count.** *Nucl Med Commun* 2010;31:137–40 [CrossRef Medline](#)
18. Sathekge M, Maes A, Van de Wiele C. **FDG-PET imaging in HIV infection and tuberculosis.** *Semin Nucl Med* 2013;43:349–66 [CrossRef Medline](#)
19. Frankel SS, Tenner-Racz K, Racz P, et al. **Active replication of HIV-1 at the lymphoepithelial surface of the tonsil.** *Am J Pathol* 1997;151:89–96 [Medline](#)
20. Goldenberg D, Sciubba J, Koch WM. **Cystic metastasis from head and neck squamous cell cancer: a distinct disease variant?** *Head Neck* 2006;28:633–38 [CrossRef Medline](#)
21. Bayanati H, Thornhill RE, Souza CA, et al. **Quantitative CT texture and shape analysis: can it differentiate benign and malignant mediastinal lymph nodes in patients with primary lung cancer?** *Eur Radiol* 2015;25:480–87 [CrossRef Medline](#)
22. Huang YQ, Liang CH, He L, et al. **Development and validation of a radiomics nomogram for preoperative prediction of lymph node metastasis in colorectal cancer.** *J Clin Oncol* 2016;34:2157–64 [CrossRef Medline](#)
23. Knogler T, El-Rabadi K, Weber M, et al. **Three-dimensional texture analysis of contrast enhanced CT images for treatment response assessment in Hodgkin lymphoma: comparison with F-18-FDG PET.** *Med Phys* 2014;41:121904 [CrossRef Medline](#)
24. Buch K, Fujita A, Li B, et al. **Using texture analysis to determine human papillomavirus status of oropharyngeal squamous cell carcinomas on CT.** *AJNR Am J Neuroradiol* 2015;36:1343–48 [CrossRef Medline](#)
25. Fujita A, Buch K, Li B, et al. **Difference between HPV-positive and HPV-negative non-oropharyngeal head and neck cancer: texture analysis features on CT.** *J Comput Assist Tomogr* 2016;40:43–47 [CrossRef Medline](#)
26. Haralick RM, Shanmugam K, Dinstein IH. **Textural features for image classification.** *IEEE Transactions on Systems, Man and Cybernetics* 1973;SMC-3:610–21 [CrossRef Medline](#)
27. Laws KI. *Textured Image Segmentation* [dissertation and thesis]. Los Angeles: University of Southern California; 1980
28. Tang X. **Texture information in run-length matrices.** *IEEE Trans Image Process* 1998;7:1602–09 [CrossRef Medline](#)
29. Castellano G, Bonilha L, Li LM, et al. **Texture analysis of medical images.** *Clin Radiol* 2004;59:1061–69 [CrossRef Medline](#)
30. Yu H, Buch K, Li B, et al. **Utility of texture analysis for quantifying hepatic fibrosis on proton density MRI.** *J Magn Reson Imaging* 2015;42:1259–65 [CrossRef Medline](#)
31. Li B, Jara H, Yu H, et al. **Enhanced Laws textures: a potential MRI surrogate marker of hepatic fibrosis in a murine model.** *Magn Reson Imaging* 2017;37:33–40 [CrossRef Medline](#)
32. Liu H, Wu T. **Estimating the area under a receiver operating characteristic (ROC) curve for repeated measures design.** *Journal of Statistical Software* 2003;8:1–18 [CrossRef](#)
33. Pham TD, Watanabe Y, Higuchi M, et al. **Texture analysis and synthesis of malignant and benign mediastinal lymph nodes in patients with lung cancer on computed tomography.** *Sci Rep* 2017;7:43209 [CrossRef Medline](#)
34. Brust D, Polis M, Davey R, et al. **Fluorodeoxyglucose imaging in healthy subjects with HIV infection: impact of disease stage and therapy on pattern of nodal activation.** *AIDS* 2006;20:985–93 [CrossRef Medline](#)
35. Mhlanga JC, Durand D, Tsai HL, et al. **Differentiation of HIV-associated lymphoma from HIV-associated reactive adenopathy using quantitative FDG PET and symmetry.** *Eur J Nucl Med Mol Imaging* 2014;41:596–604 [CrossRef Medline](#)
36. Lawal IO, Nyakale NE, Harry LM, et al. **The role of F-18 FDG PET/CT in evaluating the impact of HIV infection on tumor burden and therapy outcome in patients with Hodgkin lymphoma.** *Eur J Nucl Med Mol Imaging* 2017;44:2025–33 [CrossRef Medline](#)

Etiology-Specific Mineralization Patterns in Patients with Labyrinthitis Ossificans

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ABSTRACT

BACKGROUND AND PURPOSE: Our aim was to identify whether specific patterns of ossification in labyrinthitis ossificans are associated with the known risk factors. Labyrinthitis ossificans has been described as sequela of prior temporal bone trauma, prior infection, and other disorders including sickle cell disease. Specific patterns of mineralization in the membranous labyrinth associated with these risk factors has not been previously described.

MATERIALS AND METHODS: This was a retrospective study evaluating temporal bone CT scans at our institution from November 2005 to May 2018 in patients with labyrinthitis ossificans. Membranous labyrinthine structures evaluated for ossification included the following: basal, middle, and apical cochlear turns; lateral, posterior, and superior semicircular canals; and the vestibule for both ears in all patients. These structures were assigned a severity score, 0–4, based on degree of mineralization. Clinical records were reviewed for potential labyrinthitis ossificans risk factors. Basic descriptive statistics and a mixed model were used to correlate the degree and patterns of ossification with clinical history.

RESULTS: Forty-four patients (58 ears) with labyrinthitis ossificans were identified and evaluated. The most common risk factors were chronic otomastoiditis ($n = 18$), temporal bone surgery ($n = 9$), temporal bone trauma ($n = 6$), sickle cell disease ($n = 5$), and meningitis ($n = 4$). For all etiologies, the semicircular canals were most severely affected, and the vestibule was the least. In patients with prior temporal bone surgery, significantly greater mineralization was seen in the basal turn of the cochlea ($P = .027$), the vestibule ($P = .001$), and semicircular canals ($P < .001$ – $.008$). No significant pattern was identified in patients with meningitis, sickle cell disease, or trauma.

CONCLUSIONS: Significant patterns of mineralization in labyrinthitis ossificans were observed in patients with prior temporal bone surgery. For all etiologies, the semicircular canals were most severely affected. No significant mineralization pattern was observed in patients with chronic otomastoiditis, meningitis, sickle cell disease, or prior temporal bone trauma.

ABBREVIATIONS: AAO-HNS = American Academy of Otolaryngology–Head and Neck Surgery; LO = labyrinthitis ossificans

Labyrinthitis ossificans (LO) is a pathologic process involving the ossification of structures within the membranous labyrinth of the inner ear, leading to sensorineural hearing loss.^{1–8} There are typically 3 described phases of LO, including an acute, fibrotic, and ossifying phase.⁹ Ossification has been described on histopathology as starting in the perilymph of the basal turn of the cochlea and then spreading to involve the entire inner ear.⁹ LO is

an uncommon entity with a reported incidence of approximately 2%¹⁰; however, it is one of the more common etiologies in patients presenting for cochlear implantation, involving 13% of these patients.¹¹

A multitude of etiologies have been described as potential causes of LO, including otologic infection, infectious meningitis, inflammatory/autoimmune diseases, traumatic injury, iatrogenic injury related to a prior operation, and hematologic causes such as sickle cell disease.^{1–6,11–14} Prior publications on LO comprise mostly case reports, with few studies reporting findings of observational/cross-sectional studies.

High-resolution CT and MR imaging are common modalities for the evaluation of the temporal bone, particularly as a preoperative assessment for cochlear implant placement.¹⁵ While MR imaging evaluation affords some advantage over high-resolution CT in that it may better assess the intracochlear compartments for obstruction and may better identify the fibrous stages of LO, high-

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resolution CT remains commonly used for the detection of LO.^{15,16} The early identification of LO is important for hearing preservation, early intervention with possible cochlear implant placement, and alerting surgical colleagues to carefully evaluate obstruction during cochlear implant placement.¹⁷ Significant challenges related to the ability to place the cochlear implant arise with progression of LO and the extent of ossification throughout the membranous labyrinth, which may ultimately lead to alternative cochlear implant insertion techniques.^{18–20} Furthermore, early identification is important because a prior study has suggested a role for treatment with steroids to prevent the progression of LO, particularly for patients with a history of meningitis.²¹

The purpose of this study was to identify potential etiology-specific ossification patterns in patients with LO using CT.

METHODS AND MATERIALS

Patients

This was a retrospective, institutional review board–approved study performed at Boston Medical Center. Inclusion criteria were patients with hearing loss referred from the otolaryngology clinic who underwent temporal bone CT between November 2005 and May 2018. Patients with LO were identified retrospectively through the radiologic information system using keywords “labyrinthitis ossificans,” and CT examinations were retrospectively reviewed. Exclusion criteria were patients with motion-limited CT examinations, which precluded a diagnostic assessment of the temporal bones, and patients with incomplete medical records.

Electronic medical records were reviewed by first-year and fourth-year radiology residents for each of the patients who met the inclusion criteria. Medical record information collected included patient age at the time of the CT scan, sex, and suspected cause of hearing loss, including a history of meningitis, chronic otomastoiditis, sickle cell disease, temporal bone trauma, and prior resection of a temporal bone mass lesion, including vestibular schwannomas or temporal bone cholesteatomas.

A total of 45 patients met the inclusion criteria for this study. One patient was excluded secondary to severe motion artifacts that precluded a diagnostic assessment of the temporal bones, leading to a cohort of 44 patients.

CT Imaging Techniques

CT studies were performed by 64–detector row multidetector CT (LightSpeed VCT; GE Healthcare, Milwaukee, Wisconsin) ($n = 42$), 16–detector row multidetector row CT (BrightSpeed VCT; GE Healthcare) ($n = 1$), or an Mx8000 CT scanner (Philips Healthcare, Best, the Netherlands) ($n = 1$). All CT images were helically acquired through the temporal bones; 0.625-mm-thick images with a 0.3-mm ($n = 33$) or 0.625-mm ($n = 10$) interval reconstruction, or 0.6-mm-thick images with a 0.3-mm-interval reconstruction ($n = 1$), using both bone and soft-tissue reconstruction algorithms.

Image Evaluation

All images are viewed at an independent workstation (Advantage Windows Workstation; GE Healthcare) with multiplanar reconstructions.

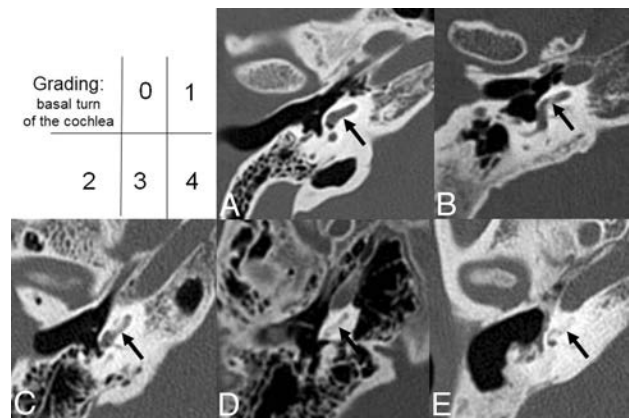


FIG 1. Example of LO mineralization grades (0–4) within the basal turn of the cochlea. Axial, noncontrast temporal bone images through the basal turn of the cochlea demonstrate various grades of mineralization/ossification. A, Grade 0, no evidence of mineralization/ossification. B, Grade 1, mineralization/ossification between 0% and 25%. C, Grade 2, mineralization/ossification between 25% and 50%. D, Grade 3, mineralization/ossification between 50% and 75%. E, Grade 4, Mineralization/ossification of >75%.

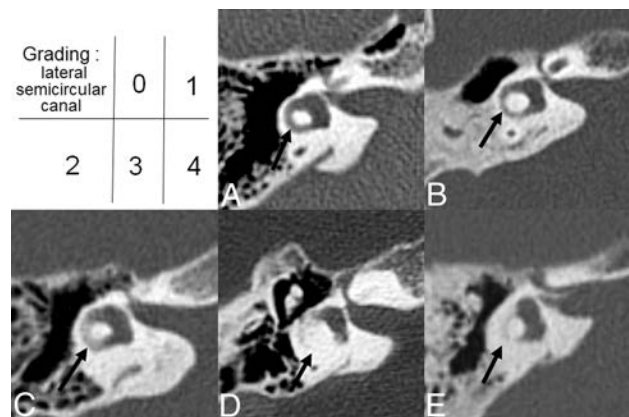


FIG 2. Example of LO mineralization grades (0–4) within the lateral semicircular canal. Axial, noncontrast temporal bone images through the lateral semicircular canals demonstrate various grades of mineralization/ossification. A, Grade 0, no evidence of mineralization/ossification. B, Grade 1, mineralization/ossification between 0% and 25%. C, Grade 2, mineralization/ossification between 25% and 50%. D, Grade 3, mineralization/ossification between 50% and 75%. E, Grade 4, mineralization/ossification of >75%.

Image evaluation was performed independently by 2 neuroradiologists with >10 and 15 years of head and neck imaging experience, blinded to the clinical data, to evaluate the degree of mineralization/ossification. Any discrepancies were resolved by consensus.

Structures of both the right and left membranous labyrinth in all patients were evaluated for the degree of mineralization/ossification. A severity score was assigned to the degree of mineralization/ossification, ranging from 0 to 4 (0 = no mineralization/ossification, 1 = up to 25% mineralization/ossification, 2 = 25%–50% mineralization/ossification, 3 = 50%–75% mineralization/ossification, 4 = >75% mineralization/ossification), as illustrated in Figs 1 and 2. Each structure of the membranous labyrinth was assigned its own mineralization/ossification score. Structures per ear evaluated included the following: the basal turn of the cochlea, middle turn of the cochlea, apical turn of the cochlea, vestibule, lateral

semicircular canal, posterior semicircular canal, and superior semicircular canal.

Audiology Evaluation

Clinical records were reviewed for audiogram results on all patients included in our cohort. Hearing was stratified by the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) classification.²² Correlations between the degree of mineralization within the labyrinth and audiogram results were performed.

Statistical Analysis

Basic descriptive statistics, including mean and median ossificans grades, were calculated for the patient cohort. For comparison of the mean LO grade by anatomic location, we used paired *t* tests. A mixed linear regression model was used to correlate the severity of mineralization within the membranous labyrinth and specific clinical risk factors to potentially identify location-specific patterns of mineralization/ossification. Because each patient could contribute >1 ear to the analysis, this approach allows modeling of the variance-covariance matrix among multiple values recorded for each patient. Compound symmetry was specified for the covariance structure. A *P* value < .05 was considered statistically significant. No adjustments for multiple comparisons in determining significance were made. Statistical computations were performed using SAS 9.1.3 software (SAS Institute, Cary, North Carolina).

RESULTS

Study Population

The patient cohort comprised 28 women and 16 men, ranging from 3 to 75 years of age (mean age, 39.5 ± 17.6 years). Distribution of LO involvement included 18 patients with LO affecting only the right ear, 12 patients with LO affecting only the left ear, and 14 patients with bilateral LO.

Distribution of LO Risk Factors

Etiologies predisposing patients to LO based on a search of the clinical medical records led to 35 patients with at least 1 risk factor for LO, including the following: 18 patients (23 ears) with chronic otomastoiditis, 4 patients (6 ears) with meningitis, 5 patients (7 ears) with sickle cell anemia, and 6 patients (8 ears) with temporal bone trauma (5 patients had no violation of the otic capsule; 1 patient had violation of the otic capsule). There were 9 patients (11 ears) with prior temporal bone surgery, including surgery related to resection of a cholesterol cyst (*n* = 1 ear, canal wall down mastoidectomy), cholesteatoma (*n* = 5 ears, 4 ears with canal wall down mastoidectomy, and 1 ear with a canal wall up mastoidectomy and a history of autoatticotomy), and vestibular schwannoma, (*n* = 3 ears, 2 retrosigmoid approaches and 1 translabyrinthine approach). The remaining 2 ears had temporal bone surgery related to tympanoplasty.

Seven of these 35 patients had >1 risk factor for LO, including 4 patients with chronic otomastoiditis and a prior operation for treatment of a cholesteatoma, 2 additional patients with a history of sickle cell anemia and prior otomastoiditis, and 1 patient with chronic otomastoiditis and meningitis. Nine patients had no

Table 1: Distribution of labyrinthitis ossificans grade by membranous labyrinthine structures^a

	No.	Mean	SD
Overall			
Apical turn of cochlea	57	0.81	1.51
Middle turn of cochlea	57	0.86	1.46
Basal turn of cochlea	57	1.04	1.48
Vestibule	58	0.55	1.14
Lateral semicircular canal	58	1.81	1.37
Posterior semicircular canal	58	1.31	1.56
Superior semicircular canal	58	1.02	1.54
Right side			
Apical turn of cochlea	31	0.90	1.60
Middle turn of cochlea	31	0.94	1.48
Basal turn of cochlea	31	1.26	1.57
Vestibule	32	0.66	1.18
Lateral semicircular canal	32	2.03	1.40
Posterior semicircular canal	32	1.50	1.59
Superior semicircular canal	32	1.25	1.63
Left side			
Apical turn of cochlea	26	0.69	1.41
Middle turn of cochlea	26	0.77	1.45
Basal turn of cochlea	26	0.77	1.34
Vestibule	26	0.42	1.10
Lateral semicircular canal	26	1.54	1.30
Posterior semicircular canal	26	1.08	1.52
Superior semicircular canal	26	0.73	1.40

Note:—No. indicates the total number of patients.

^a LO grades stratified by each structure in the membranous labyrinth and stratified for the left-versus-right ear.

readily identifiable predisposing risk factors for LO based on a search of the electronic medical records.

Bilateral LO Involvement

A total of 14 patients had LO involving both ears. Four patients had a history of chronic, bilateral otomastoiditis only; 1 patient had a history of chronic otomastoiditis and sickle cell anemia; 1 patient had sickle cell anemia only; 2 patients had a history of meningitis; 2 patients had a history of bilateral temporal bone trauma; 2 patients had a history of temporal bone surgery (1 for a retrosigmoid resection of a right-sided vestibular schwannoma; and 1 patient with a translabyrinthine resection of a cholesterol granuloma); and 2 patients had no identifiable risk factor documented in the electronic medical records.

Distribution of Mineralization in LO

Overall, the semicircular canals were more severely affected compared with the cochlea and vestibules, irrespective of the side, as shown in Tables 1 and 2.

The lateral semicircular canal was more severely affected than the posterior and superior semicircular canals, as well as the apical, middle, and basal turns of the cochlea and the vestibule (Tables 1 and 2). On both sides, the vestibule was the least severely affected.

Mineralization by Risk Factor

The 18 patients with chronic otomastoiditis demonstrated the greatest degree of mineralization within the lateral, posterior, and superior semicircular canals; however, these findings were not statistically significant (Table 3).

The 4 patients with a history of meningitis demonstrated no

Table 2: Comparing mean labyrinthitis ossificans grade by anatomic location

	Apical Turn of Cochlea	Middle Turn of Cochlea	Basal Turn of Cochlea	Vestibule	Lateral Semicircular Canal	Posterior Semicircular Canal	Superior Semicircular Canal
Apical turn of cochlea	—	0.839	.377	.371	.001	.071	.423
Middle turn of cochlea		—	.490	.256	.001	.109	.539
Basal turn of cochlea			—	.061	.011	.342	.966
Vestibule				—	<.001	.004	.069
Lateral semicircular canal					—	.060	.004
Posterior semicircular canal						—	.308
Superior semicircular canal							—

Note:—indicates analysis is based on 57 ears; data are *P* values.

Table 3: Comparing mean labyrinthitis ossificans grade by chronic otomastoiditis^a

	Mean (SE)		<i>P</i> Value
	No Chronic Otomastoiditis (n = 35)	Chronic Otomastoiditis (n = 23)	
Apical turn of cochlea ^b	0.79 (0.29)	0.82 (0.35)	.947
Middle turn of cochlea ^b	0.80 (0.28)	0.96 (0.34)	.720
Basal turn of cochlea ^b	0.98 (0.29)	1.23 (0.35)	.578
Vestibule	0.44 (0.22)	0.76 (0.27)	.347
Lateral semicircular canal	1.81 (0.23)	1.74 (0.28)	.853
Posterior semicircular canal	1.13 (0.26)	1.54 (0.33)	.328
Superior semicircular canal	0.75 (0.26)	1.39 (0.32)	.136

Note:—*n* indicates the number of ears; SE, standard error.

^a LO grade for each structure within the membranous labyrinth is reported stratified by risk factor. *P* value is from a mixed-effects model.

^b Analysis based on 57 ears (34 with no chronic otomastoiditis and 23 with chronic otomastoiditis).

Table 4: Comparing mean labyrinthitis ossificans grade by meningitis^a

	Mean (SE)		<i>P</i> Value
	No Meningitis (n = 52)	Meningitis (n = 6)	
Apical turn of cochlea ^b	0.84 (0.23)	0.50 (0.71)	.657
Middle turn of cochlea ^b	0.88 (0.23)	0.72 (0.70)	.829
Basal turn of cochlea ^b	1.11 (0.24)	0.81 (0.73)	.697
Vestibule	0.63 (0.18)	0.04 (0.55)	.317
Lateral semicircular canal	1.77 (0.19)	1.91 (0.56)	.806
Posterior semicircular canal	1.22 (0.22)	1.96 (0.65)	.296
Superior semicircular canal	1.0 (0.22)	0.94 (0.64)	.925

^a LO grade for each structure within the membranous labyrinth is reported stratified by risk factor. *P* value is from a mixed-effects model.

^b Analysis is based on 57 ears (51 without meningitis and 6 with meningitis).

statistically significant difference in the degree of mineralization within any structure within the membranous labyrinth compared with the 40 patients without a history of meningitis (Table 4).

In the 5 patients with a history of sickle cell disease, no statistically significant difference was noted in the degree of mineralization within any structure within the membranous labyrinth compared with the 39 patients without a history of sickle cell disease (Table 5).

In the 6 patients with a history of temporal bone trauma, no statistically significant difference was noted in the degree of mineralization within any structure of the membranous labyrinth (Table 6). The basal turn of the cochlea, followed by the lateral semicircular canal, was affected the most. The vestibule had the

Table 5: Comparing mean labyrinthitis ossificans grade by sickle cell disease^a

	Mean (SE)		<i>P</i> Value
	No Sickle Cell Disease (n = 51)	Sickle Cell Disease (n = 7)	
Apical turn of cochlea ^b	0.79 (0.24)	0.91 (0.65)	.858
Middle turn of cochlea ^b	0.89 (0.23)	0.67 (0.63)	.738
Basal turn of cochlea ^b	1.15 (0.24)	0.50 (0.65)	.349
Vestibule	0.63 (0.18)	0.09 (0.50)	.316
Lateral semicircular canal	1.84 (0.19)	1.40 (0.51)	.422
Posterior semicircular canal	1.32 (0.22)	1.11 (0.60)	.747
Superior semicircular canal	1.09 (0.22)	0.37 (0.60)	.261

^a LO grade for each structure within the membranous labyrinth is reported stratified by risk factor. *P* value is from a mixed-effects model.

^b Analysis is based on 57 ears (50 with no sickle cell disease and 7 with sickle cell disease).

Table 6: Comparing mean labyrinthitis ossificans grade by trauma^a

	Mean (SE)		<i>P</i> Value
	No Trauma (n = 50)	Trauma (n = 8)	
Apical turn of cochlea ^b	0.75 (0.24)	1.15 (0.60)	.535
Middle turn of cochlea ^b	0.80 (0.23)	1.25 (0.58)	.477
Basal turn of cochlea ^b	1.0 (0.24)	1.58 (0.60)	.372
Vestibule	0.59 (0.18)	0.44 (0.46)	.763
Lateral semicircular canal	1.82 (0.19)	1.55 (0.48)	.605
Posterior semicircular canal	1.36 (0.21)	0.50 (0.52)	.130
Superior semicircular canal	1.03 (0.22)	0.66 (0.54)	.528

^a LO grade for each structure within the membranous labyrinth is reported stratified by risk factor. *P* value is from a mixed-effects model.

^b Analysis is based on 57 ears (49 with no trauma and 8 with trauma).

lowest grade of mineralization. These findings were not statistically significant compared with the 38 patients without a documented history of trauma.

In the 9 patients (11 ears) with a history of prior temporal bone surgery for resection of a mass lesion, a significantly higher degree of mineralization was seen in the basal turn of the cochlea, the vestibule, and the semicircular canals compared with the remaining patients with LO who had not had prior temporal bone surgery (Table 7).

Mineralization by Any Etiology

For the patients with an identifiable risk factor (35 patients), compared with those without an identifiable risk factor (9 patients), no statistically significant differences were seen in mineralization grades within the structures of the membranous labyrinth (Table 8).

Table 7: Comparing mean labyrinthitis ossificans grade by surgery^a

	Mean (SE)		P Value
	No Surgery (n = 47)	Surgery (n = 11)	
Apical turn of cochlea ^b	0.74 (0.24)	1.07 (0.51)	.553
Middle turn of cochlea ^b	0.74 (0.23)	1.41 (0.49)	.223
Basal turn of cochlea ^b	0.84 (0.23)	2.07 (0.48)	.027
Vestibule	0.30 (0.16)	1.67 (0.33)	.001
Lateral semicircular canal	1.49 (0.15)	3.04 (0.32)	<.001
Posterior semicircular canal	0.99 (0.20)	2.44 (0.43)	.004
Superior semicircular canal	0.75 (0.22)	2.13 (0.45)	.008

^a LO grade for each structure within the membranous labyrinth is reported stratified by risk factor. *P* value is from a mixed-effects model.

^b Analysis is based on 57 ears (47 with no prior temporal bone surgery and 10 with prior temporal bone surgery).

Table 8: Comparing mean labyrinthitis ossificans grade by any condition^a

	Mean (SE)		P Value
	No Risk Factor (n = 11)	Any Risk Factor (n = 47)	
Apical turn of cochlea ^b	0.33 (0.49)	0.92 (0.24)	.280
Middle turn of cochlea ^b	0.22 (0.47)	1.03 (0.24)	.132
Basal turn of cochlea ^b	0.35 (0.48)	1.26 (0.24)	.095
Vestibule	0.01 (0.37)	0.71 (0.19)	.097
Lateral semicircular canal	1.29 (0.40)	1.90 (0.19)	.181
Posterior semicircular canal	0.65 (0.46)	1.44 (0.23)	.136
Superior semicircular canal	0.45 (0.47)	1.15 (0.23)	.190

^a LO grade is reported per membranous labyrinth structure based on patients with an identified LO risk factor compared with those without a risk factor. *P* value is from a mixed-effects model.

^b Analysis is based on 57 ears (11 with no condition and 46 with a condition).

Correlation with Audiogram Results

Audiogram results were available in 37 of the 44 patients, with 7 ears categorized as AAO-HNS class A, 2 ears categorized as AAO-HNS class B, 4 ears categorized as AAO-HNS class C, and 34 ears categorized as AAO-HNS class D. In 6/7 ears categorized as AAO-HNS class A, the cochlea had no perceptible mineralization and the semicircular canals were the only structures involved. In the remaining 1/7 AAO-HNS class A ears, both the semicircular canals and all segments of the cochlea were involved. In 1 of the 2 AAO-HNS class B ears, all 3 turns of the cochlea were involved (mineralization score, 2–3). The other AAO-HNS class B ear had mineralization only in the lateral semicircular canal. Three of the 4 AAO-HNS class C ears had a history of a temporal bone mass lesion. All 4 AAO-HNS class C ears had mineralization only in the semicircular canals (mineralization score = 1, in all cases). Marked variation in known LO risk factors, involvement of labyrinthine structures, and mineralization scores was seen in the 34 AAO-HNS class D ears.

DISCUSSION

A cohort of 44 patients with radiographically proved LO were analyzed. The severity and distribution of mineralization at specific locations within the membranous labyrinth were analyzed and correlated with suspected risk factors for the LO. The results of this study demonstrate a higher grade of mineralization within the labyrinth in patients with a history of temporal bone surgery. For all structures within the membranous labyrinth, the lateral

semicircular canal was most severely affected and the vestibule was the least severely affected. In several instances, subtle trends suggestive of etiology-specific patterns of mineralization were observed in this study, including greater mineralization within the lateral semicircular canal in patients with chronic otomastoiditis, a greater degree of mineralization within the basal turn of the cochlea in patients with prior meningitis, a greater degree of mineralization within the cochlea in patients with a history of temporal bone trauma, and significantly greater mineralization within the vestibule in patients with prior temporal bone surgery.

Multiple prior studies have investigated potential etiologies related to LO and the mechanism of cochlear damage. Two studies performed by Kaya et al^{23,24} evaluating 23 temporal bone specimens with cochlear damage related to serous labyrinthitis, suppurative labyrinthitis, and LO found damage specifically to the spiral ganglion, hair cells, stria vascularis, and spiral ligament with endolymphatic hydrops.

Within the radiology literature, prior publications on LO have focused on case reports and case series describing the occurrence of LO in the setting of infectious etiologies, traumatic etiologies, sickle cell disease, and inflammatory/autoimmune disorders.^{1–3,8,11,13–14,25} This study attempts to fill in gaps in knowledge examining a large cohort of cases of LO related to a variety of underlying suspected etiologies. The patterns of mineralization within the labyrinth based on the suspected underlying etiologies were investigated in an attempt to uncover specific patterns of ossification based on the underlying etiology. One finding noted in this study that has not been previously reported in the literature is a statistically significant increase in mineralization within the vestibule of patients with a history of temporal bone surgery. This finding was unique to patients with prior surgery and was not encountered in patients with other LO risk factors. This may potentially be related to the induction of a local inflammatory process or potentially related to aberrations in fluid dynamics within the labyrinth.

MR imaging may have increased sensitivity for the detection of LO in patients with a fibrous stage of LO and for the evaluation of subtle and isolated involvement of LO along the scala vestibuli in the proximal basal turn of the cochlea.^{16,20,26} Despite these advantages, high-resolution CT remains a common technique for the evaluation of LO and includes a shorter scan time than MR imaging, which may be easier to tolerate in certain patients.

Recognition and detection of mineralization involving specific components of the membranous labyrinth may have significant impact in the clinical management of these patients, and the use of a mineralization scoring system to grade the severity and location of mineralization within the membranous labyrinth may be important to convey to otologists evaluating patients for cochlear implantation. Specifically, the location of mineralization within the labyrinth and the mineralization score may be helpful for electrode-device selection (based on an inference of the number of viable cells in the spiral ganglion), cochlear electrode implantation technique (apical cochleostomy with retrograde insertion of cochlear implant electrode array), and additional procedural changes, including selection for a circummodiolar drill-out procedure.^{18,21,27} Additionally, the outcome of cochlear implantation may be different depending on the location and degree of ossification/calcification within the labyrinth; for example, elec-

trical conduction may be different in patients with higher mineralization scores, who may experience more facial nerve stimulation.²⁸ These findings may ultimately affect electrode choice and cochlear implant manufacture selection. Therefore, the knowledge of the location and degree of ossification/calcification is important for preoperative patient counseling and postoperative patient training.

There are limitations to this study. First, a small number of patients were included in this analysis. LO is a relatively uncommon entity, and the cohort described reflects the total population of patients with LO who underwent diagnostic CT imaging at our institution. Patients were identified for inclusion into this study on the basis of a review of their imaging findings. We realize that this may introduce a study-selection bias because only patients with LO detected on CT were included in this study. This study describes imaging findings related to LO assessed only by CT. CT remains one of the most common imaging modalities of LO; however, some institutions may also use MR imaging for preoperative evaluation of hearing loss before cochlear implant placement.²⁶ CT may be less sensitive for the detection of isolated LO involvement within certain structures, including the scala tympani of the proximal basal turn.²⁰ Therefore, patients with involvement of such structures and a fibrous stage of LO may not have been identified.

We had relatively few patients with a history of meningitis compared with a history of chronic otomastoiditis. The distribution of reported LO risk factors in our patient population may not be reflective of a more generalized population, and specific patterns of mineralization should not necessarily be assigned to a specific contributing LO risk factor. The inclusion criteria for this study were based on CT imaging findings of LO; therefore, there is potential bias in this patient cohort and patients with a fibrous stage of LO and very subtle mineralization might not have been included. We are unable to correlate the imaging findings with surgical outcomes because most patients in this cohort did not end up undergoing cochlear implantation, at least not at our institution. Last, this study was performed as an exploratory evaluation; thus, we did not make any adjustment for multiple comparisons in our statistical analysis, and our results should be interpreted with caution.

CONCLUSIONS

Trends in mineralization patterns within the membranous labyrinth are suggested in this large cohort of patients with LO, with the most severe mineralization observed in the lateral semicircular canals and the least severe mineralization within the vestibule. Overall, the most severe patterns of mineralization were seen in patients with prior temporal bone surgery, with subtle trends in mineralization noted in patients with history of meningitis, chronic otomastoiditis, and temporal bone trauma. Knowledge of these patterns of mineralization may be helpful for practicing neuroradiologists. Additionally, these findings may be helpful for the preoperative assessment before cochlear implantation as discussed; however, additional investigations in this area and on a larger patient cohort are needed.

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REFERENCES

- Hoffman RA, Brookler KH, Bergeron RT. **Radiologic diagnosis of labyrinthitis ossificans.** *Ann Otol Rhinol Laryngol* 1979;88:253–57 CrossRef Medline
- Swartz JD, Mandell DM, Faerber EN, et al. **Labyrinthine ossification: etiologies and CT findings.** *Radiology* 1985;157:395–98 CrossRef Medline
- Liu BP, Saito N, Wang JJ, et al. **Labyrinthitis ossificans in a child with sickle cell disease: CT and MRI findings.** *Pediatr Radiol* 2009;39:999–1001 CrossRef Medline
- Saito N, Nadgir RN, Flower EN, et al. **Clinical and radiologic manifestations of sickle cell disease in the head and neck.** *Radiographics* 2010;30:1021–34 CrossRef Medline
- Xu HX, Joglekar SS, Paparella MM. **Labyrinthitis ossificans.** *Otol Neurotol* 2009;30:579–80 CrossRef Medline
- deSouza C, Paparella MM, Schachern P, et al. **Pathology of labyrinthine ossification.** *J Laryngol Otol* 1991;105:621–24 CrossRef Medline
- Saito N, Watanabe M, Liao J, et al. **Clinical and radiologic findings of inner ear involvement in sickle cell disease.** *AJNR Am J Neuroradiol* 2011;32:2160–64 CrossRef Medline
- Paparella MM, Sugiura S. **The pathology of suppurative labyrinthitis.** *Ann Otol Rhinol Laryngol* 1967;76:554–86 CrossRef Medline
- Lin HY, Fan YK, Wu KC, et al. **The incidence of tympanogenic labyrinthitis ossificans.** *J Laryngol Otol* 2014;128:618–20 CrossRef Medline
- Nair SB, Abou-Elhamd KA, Hawthorne M. **A retrospective analysis of high resolution computed tomography in the assessment of cochlear implant patients.** *Clin Otolaryngol Allied Sci* 2000;25:55–61 CrossRef Medline
- Khoo JN, Tan TY. **Progression of autoimmune inner ear disease to labyrinthitis ossificans: clinical and radiologic correlation.** *Ear Nose Throat J* 2015;94:108–10 Medline Medline
- Ashfield T, Pai I, Wilson K, et al. **Cochlear implantation in children with sickle cell disease.** *Pediatr Int* 2015;57:174–76 CrossRef Medline
- Dhanjal H, Rainsbury J, Irving RM. **Bilateral sensorineural hearing loss and labyrinthitis ossificans secondary to neurosarcoidosis.** *Cochlear Implants Int* 2014;15:337–40 CrossRef Medline
- Aralaşmak A, Dinçer E, Arslan G, et al. **Posttraumatic labyrinthitis ossificans with perilymphatic fistulization.** *Diagn Interv Radiol* 2009;15:239–41 CrossRef Medline
- Lee TC, Aviv RI, Chen JM, et al. **CT grading of otosclerosis.** *AJNR Am J Neuroradiol* 2009;30:1435–39 CrossRef Medline
- Booth TN, Roland P, Kutz JW Jr, et al. **High-resolution 3-D T2-weighted imaging in the diagnosis of labyrinthitis ossificans: emphasis on subtle cochlear involvement.** *Pediatr Radiol* 2013;43:1584–90 CrossRef Medline
- Trimble K, Blaser S, James AL, et al. **Computed tomography and/or magnetic resonance imaging before pediatric cochlear implantation? Developing an investigative strategy.** *Otol Neurotol* 2007;28:317–24 CrossRef Medline
- El-Kashlan, Ashbaugh C, Zwolan T, et al. **Cochlear implantation in prelingually deaf children with ossified cochleae.** *Otol Neurotol* 2003;24:596–600 CrossRef Medline
- Philippon D, Bergeron F, Ferron P, et al. **Cochlear implantation in post-meningitic deafness.** *Otol Neurotol* 2010;31:83–87 CrossRef Medline
- Isaacson B, Booth T, Kutz JW Jr, et al. **Labyrinthitis ossificans: how accurate is MRI in predicting cochlear obstruction?** *Otolaryngol Head Neck Surg* 2009;140:692–96 CrossRef Medline
- Hartnick CJ, Kim HH, Chute PM, et al. **Preventing labyrinthitis ossificans: the role of steroids.** *Arch Otolaryngol Head Neck Surg* 2001;127:180–83 CrossRef Medline
- Committee on Hearing and Equilibrium guidelines for the evaluation of hearing preservation in acoustic neuroma (vestibular schwannoma): American Academy of Otolaryngology-Head and Neck Surgery Foundation INC. *Otolaryngol Head Neck Surg* 1995;113:179–80 CrossRef Medline

23. Kaya S, Paparella MM, Cureoglu S. **Pathologic findings of the cochlea in labyrinthitis ossificans associated with the round window membrane.** *Otolaryngol Head Neck Surg* 2016;155:635–40 [CrossRef Medline](#)
24. Kaya S, Schachern PA, Tsuprun V, et al. **Deterioration of vestibular cells in labyrinthitis.** *Ann Otol Rhinol Laryngol* 2017;126:89–95 [CrossRef Medline](#)
25. Chan CC, Saunders DE, Chong WK, et al. **Advancement in post-meningitic lateral semicircular canal labyrinthitis ossificans.** *J Laryngol Otol* 2007;121:105–09 [Medline](#)
26. Digge P, Solanki RN, Shah DC, et al. **Imaging modality of choice for pre-operative cochlear imaging: HRCT vs. MRI temporal bone.** *J Clin Diagn Res* 2016;10:TC01–04 [CrossRef Medline](#)
27. Angeli SI, Goncalves S. **Predicting depth of electrode insertion by cochlear measurements on computed tomography scans.** *Laryngoscope* 2016;126:1656–61 [CrossRef Medline](#)
28. Nassiri AM, Yawn RJ, Dedmon MM, et al. **Facial nerve stimulation patterns associated with cochlear implantation in labyrinthitis ossificans.** *Otol Neurotol* 2018;39:e992–95 [CrossRef Medline](#)

Diagnostic Utility of Optic Nerve Measurements with MRI in Patients with Optic Nerve Atrophy

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ABSTRACT

BACKGROUND AND PURPOSE: No MR imaging measurement criteria are available for the diagnosis of optic nerve atrophy. We determined a threshold optic nerve area on MR imaging that predicts a clinical diagnosis of optic nerve atrophy and assessed the relationship between optic nerve area and retinal nerve fiber layer thickness measured by optical coherence tomography, an ancillary test used to evaluate optic nerve disorders.

MATERIALS AND METHODS: We evaluated 26 patients with suspected optic nerve atrophy (8 with unilateral, 13 with bilateral and 5 with suspected but not demonstrable optic nerve atrophy) who had both orbital MR imaging and optical coherence tomography examinations. Forty-five patients without optic nerve atrophy served as controls. Coronal inversion recovery images were used to measure optic nerve area on MR imaging. Retinal nerve fiber layer thickness was determined by optical coherence tomography. Individual eyes were treated separately; however, bootstrapping was used to account for clustering when appropriate. Correlation coefficients were used to evaluate relationships; receiver operating characteristic curves, to investigate predictive accuracy.

RESULTS: There was a significant difference in optic nerve area between patients' affected eyes with optic nerve atrophy (mean, $3.09 \pm 1.09 \text{ mm}^2$), patients' unaffected eyes (mean, $5.27 \pm 1.39 \text{ mm}^2$; $P = .008$), and control eyes (mean, $6.27 \pm 2.64 \text{ mm}^2$; $P < .001$). Optic nerve area $\leq 4.0 \text{ mm}^2$ had a sensitivity of 0.85 and a specificity of 0.83 in predicting the diagnosis of optic nerve atrophy. A significant relationship was found between optic nerve area and retinal nerve fiber layer thickness ($r = 0.68$, $P < .001$).

CONCLUSIONS: MR imaging–measured optic nerve area $\leq 4.0 \text{ mm}^2$ has moderately high sensitivity and specificity for predicting optic nerve atrophy, making it a potential diagnostic tool for radiologists.

ABBREVIATIONS: OCT = optical coherence tomography; ONA = optic nerve atrophy; ON_{area} = optic nerve area; RNFL = retinal nerve fiber layer; ROC = receiver operating characteristic

Optic nerve atrophy (ONA) occurs when there is injury to the retinal ganglion cells or their axons and, at present, is primarily diagnosed on a clinical basis.^{1,2} Careful assessment, taking into account the history and demographic profile of the patient and the clinical examination (including visual acuity, color vision, pupils, and the fundus), combined with specific ancillary testing such as computerized visual fields, is necessary to establish the diagnosis and etiology. However, it has been previously shown that the clinical diagnosis of ONA may not be reliable in the hands of clinical practitioners without specialized training in neuro-

ophthalmology.³ Because specialists with such training are usually limited to tertiary care centers, a final diagnosis may require additional referrals to these centers.

The classic clinical presentation of ONA includes decreased visual acuity, visual fields, and color vision.^{1,4} It is our experience that patients with such vision-related symptoms are often referred for orbital MR imaging examinations before they are seen by a neuro-ophthalmologist. This procedure puts radiologists in a unique frontline position of assessing the optic nerves before a final diagnosis of ONA is made. While the diagnosis of ONA can usually be suggested on MR imaging by observing the decreased size of the intraorbital optic nerve, there are no definite measurement criteria currently available to the radiologist. We believe that for MR imaging–based optic nerve measurements to be clinically useful, such measurements need to be validated, with the final diagnosis of ONA made by a neuro-ophthalmologist based on clinical examination and retinal nerve fiber layer (RNFL) thickness measured on optical coherence tomography (OCT), which

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correlates with axonal loss and is routinely used in ophthalmologic practice in the initial and follow-up assessment of various optic nerve disorders.

Based on this background information, our purpose was the following: 1) to determine a threshold optic nerve area (ON_{area}) on MR imaging that predicts the clinical diagnosis of ONA in the adult population made by a neuro-ophthalmologist, and 2) to assess the relationship between MR imaging-measured ON_{area} and RNFL thickness measured by OCT.

MATERIALS AND METHODS

Patients

Institutional review board approval was obtained for this Health Insurance Portability and Accountability Act–compliant retrospective study with a waiver of informed consent. Patients diagnosed with optic nerve atrophy by a neuro-ophthalmologist at a single institution between June 2009 and December 2016 were identified. Twenty-six adult patients who had both clinical and OCT examinations and an orbital MR imaging within 1 month of each other were included. The diagnostic criteria used for optic nerve atrophy were the following: 1) clinical examination unequivocally consistent with optic nerve atrophy, and 2) RNFL thickness $<85 \mu m$. Among these 52 patient eyes, a total of 34 “affected” eyes with an unequivocal clinical diagnosis of ONA and 18 “unaffected” eyes were used for analysis. The patient population consisted of 14 women and 12 men. The mean age was 58.2 ± 14.9 years (range, 32–89 years).

Controls

The controls were collected in the following manner: 1) 18 unaffected eyes of the patients, and 2) 90 “healthy” eyes from 35 consecutive patients undergoing imaging for seizures, which included coronal inversion recovery images that provided details of optic nerves, and 10 patients evaluated for suspected orbital abnormalities but had no findings suggestive of ONA on neuro-ophthalmologic examination. The healthy eye population consisted of 20 women and 25 men. The mean age was 55.2 ± 11.9 years (range, 27–77 years).

MR Imaging

MR imaging examinations were performed on 1 of two 1.5T Signa HDx MR imaging scanners (GE Healthcare Milwaukee, Wisconsin). The MR imaging parameters for patients and controls with visual symptoms not related to ONA were the following: TR = 6600 ms, TE = 85 ms, TI = 50 ms, slice thickness = 3 mm, FOV = 18, matrix = 320×320 . The MR imaging parameters for controls belonging in the seizure cohort were the following: TR = 6000 ms, TE = 80 ms, TI = 50 ms, slice thickness = 2.5 mm, FOV = 22, matrix = 320×320 .

For both patients and controls, images from a coronal inversion recovery sequence were used to measure ON_{area} (excluding the optic nerve sheath) at an image slice along the intraorbital portion of the optic nerve. The image was chosen on the basis of where the optic nerves appeared most round and most perpendicular to the coronal plane based on visual inspection, approximately halfway between the optic nerve–globe junction and the orbital apex. Measurements were obtained from the same image

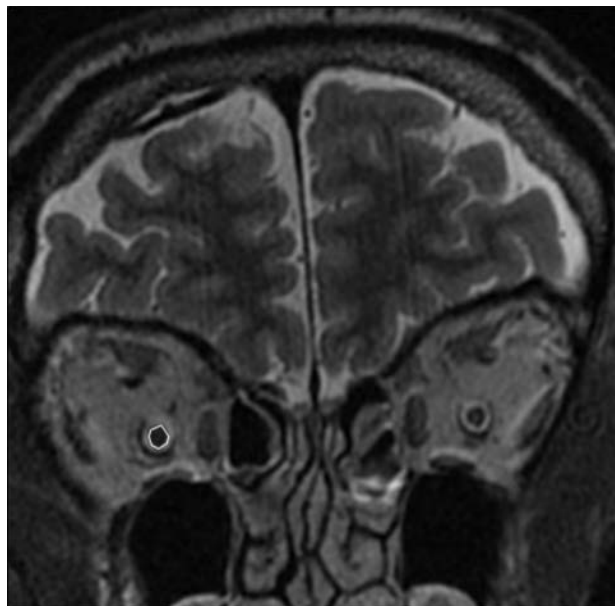


FIG 1. MR imaging measurements of the optic nerve area. Coronal inversion recovery image through the orbits approximately midway between the orbital apex and globes. The measurement of the cross-sectional area of the right optic nerve (excluding the optic nerve sheath) is shown using a freeform ROI measurement tool on the PACS. The left optic nerve is not outlined for comparison.

slice by 2 of the coauthors (radiology residents who received training in ON_{area} measurements from the senior author with >25 years' experience) independently and blinded to whether the study belonged to a patient or a control.

A freeform ROI measurement tool on the PACS was used to outline and measure the cross-sectional optic nerve areas (Fig 1). The optic nerve area measurement process involved zooming in on each nerve separately to facilitate precise and accurate outlining of the nerve contours.

OCT

RNFL thickness was determined on a Spectralis SD OCT machine (Heidelberg Engineering, Heidelberg, Germany), and an average RNFL thickness was calculated for each eye. RNFL thickness measurements were available for the entire patient population of 26 individuals for both diseased and nondiseased eyes. The control population did not have any RNFL thickness measurements because they did not have clinical concerns to warrant OCT.

Statistical Analyses

Individual eyes were treated separately; however, bootstrapping was used to account for clustering when appropriate. The average of ON_{area} measurements between the 2 readers was used for all analyses and comparisons, except for the discussion of interreader variability. Correlation coefficients were used to evaluate relationships; ANOVA with a Tukey post hoc procedure or *t* test, to compare measurements; a χ^2 test, to compare sex distribution; and a receiver operating characteristic (ROC) curve, to investigate predictive accuracy. Calculations were performed using Matlab 9.3 (MathWorks, Natick, Massachusetts). *P* values $\leq .05$ were used to determine statistical significance.

Comparison of MRI-measured optic nerve area between patients' affected and unaffected eyes and healthy eyes of controls and comparison of RNFL thickness between patients' affected and unaffected eyes^a

	Optic Nerves		
	Patients' Affected (n = 34)	Patients' Unaffected (n = 18)	Healthy (n = 90)
RNFL (μm)	67.12 ± 13.55	94.00 ± 8.66	NA
Optic nerve area (mm ²)	3.09 ± 1.09	$P_p < .001$	6.27 ± 2.64
		5.27 ± 1.39	
		$P_p = .008$	
		$P_{uc} = .21$	

Note:—NA indicates not applicable; P_c , comparison between patients' affected optic nerves and control optic nerves; P_p , comparison between patients' affected and unaffected optic nerves; P_{uc} , comparison between patients' unaffected optic nerves and control optic nerves.

^aData are mean ± SD unless otherwise indicated. No OCT data were available for the 90 healthy eyes in the control population because these individuals did not have clinical symptoms to warrant OCT measurement.

RESULTS

There was no statistically significant difference in sex ($P = .44$) or age ($P = .35$) between the patient and control groups. No statistically significant relationship was found between ON_{area} and age in the adult population of this study ($r = -0.1$, $P = .23$). There was a high correlation ($r = 0.87$) between the 2 readers in measuring the ON_{area}. The mean difference in ON_{area} between the 2 observers was 0.93 mm² with a within-subject SD of 1.2 mm².

The Table summarizes the ON_{area} and RNFL thickness in patients' affected and unaffected eyes and ON_{area} measurements in healthy eyes. There was a statistically significant difference in RNFL thickness between the patients' affected and unaffected eyes ($P < .001$).

There was a statistically significant difference in ON_{area} among patients' eyes with ONA (mean, 3.09 ± 1.09 mm²), patients' unaffected eyes (mean, 5.27 ± 1.39 mm²; $P = .008$), and control eyes (mean, 6.27 ± 2.64 mm²; $P < .001$). No significant difference in ON_{area} was observed between patients' unaffected eyes and control eyes ($P = .21$).

An ROC curve was created to test the ability of ON_{area} to predict the diagnosis of optic nerve atrophy, namely its ability to separate 34 affected eyes from 90 healthy eyes (Fig 2). The area under the curve was 0.91. Selecting a threshold MR imaging-measured ON_{area} ≤ 4.0 mm² yielded a sensitivity of 0.85 and a specificity of 0.83 in predicting the presence of ONA by clinical diagnosis.

A statistically significant positive relationship was found (Fig 3) between MR imaging-measured ON_{area} and RNFL thickness measured by OCT ($r = 0.68$, $P < .001$).

DISCUSSION

In our investigation of optic nerve area measured by MR imaging, a considerable variability between patients and controls and between eyes in the same individual was observed, as reported previously.² Nonetheless, a statistically significant difference in ON_{area} was observed between patients' diseased eyes, patients' unaffected eyes, and healthy eyes. Our analysis also showed that measurement of ON_{area} by MR imaging can be used clinically with very good diagnostic accuracy.⁵ We also observed a statistically significant relationship between MR imaging-measured

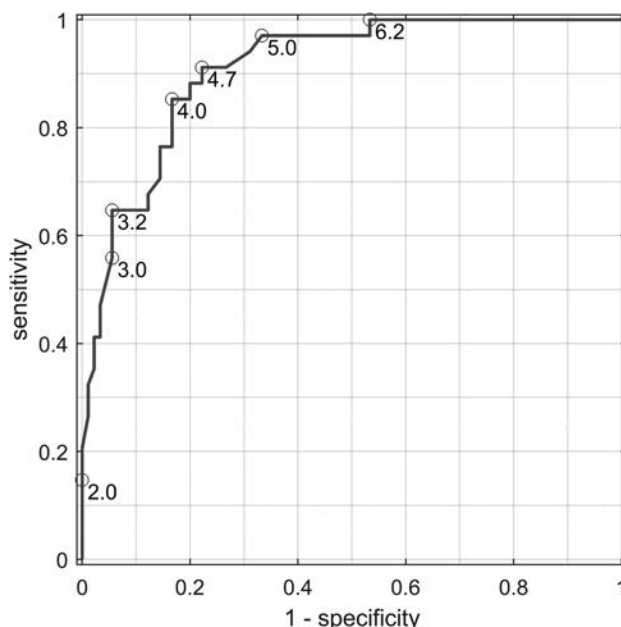


FIG 2. ROC curve showing the ability of ON_{area} to predict the diagnosis of optic nerve atrophy. The ROC curve shows the ability to distinguish 34 affected eyes from 90 healthy eyes on the basis of the ON_{area}. Using a threshold MR imaging-measured ON_{area} ≤ 4.0 mm² yields a sensitivity of 0.85, specificity of 0.83, and an AUC of 0.91.

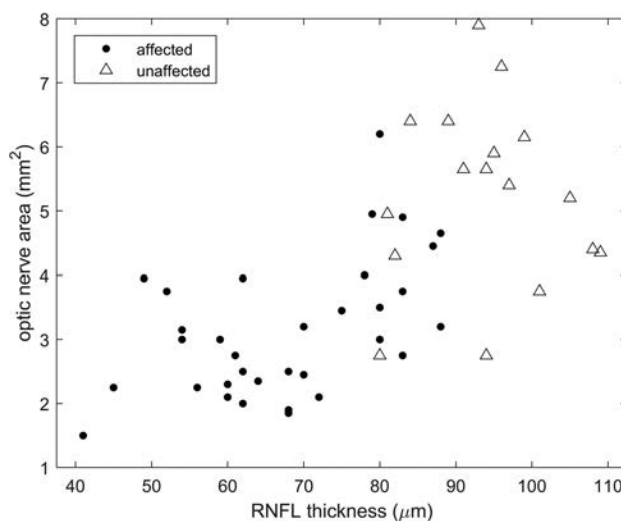


FIG 3. The relationship between MR imaging-measured optic nerve area and OCT-measured RNFL thickness. The scatterplot demonstrates a positive correlation between MR imaging-measured optic nerve area and OCT-measured RNFL thickness in patients with optic nerve atrophy. Circle data points denote those eyes with a clinical diagnosis of optic nerve atrophy. Triangle data points denote the unaffected eyes in the patient population (correlation coefficient $r = 0.68$; 95% CI, 0.50–0.80; $P < .001$).

ON_{area} and RNFL thickness measured by OCT. This is consistent with the understanding of the pathophysiology of optic nerve atrophy—that is, the damage to retinal ganglion cells can cause anterograde (Wallerian) degeneration of the optic nerve or direct damage to the optic nerve can cause retrograde degeneration of the retinal ganglion cells.^{2,4,6,7}

The optic nerve comprises the coalesced, myelinated axons of retinal ganglion cells. These axons are unmyelinated as they tra-

verse within the retina toward the optic disc, comprising the retinal nerve fiber layer.⁸ Optic nerve atrophy occurs when there is injury to these ganglion cells or their axons. This process can result from various underlying etiologies, which include optic neuritis commonly associated with multiple sclerosis and various other optic neuropathies, such as ischemic (hypertension, diabetes, giant-cell arteritis); compressive (orbital or intracranial mass); and inflammatory, toxic, traumatic, or hereditary (mitochondrial disease) causes.^{1,4} Irrespective of the mechanism, loss of retinal ganglion cells or their axons results in irreversible atrophy, which manifests clinically in the form of vision impairment.² The degree of optic atrophy depends entirely on the extent of damage to the optic nerve and is independent of the underlying etiology.

As previously mentioned, optic nerve atrophy remains primarily a clinical diagnosis. Specific vision testing and RNFL measurements via OCT have been used as adjunctive tools to establish the diagnosis and monitor disease progression.^{4,7,9-11} The results of this study suggest that optic nerve area measurements made on orbital MR imaging can also play a role in detecting and potentially diagnosing optic nerve atrophy and provide radiologists a role in identifying these patients and referring their care to an appropriate specialist.

The measurement of optic nerve area is a manual process, which raises concerns for interobserver variability. One element of variability depends on where the optic nerve is measured along its intraorbital segment. It has previously been demonstrated that optic nerve size significantly decreases from the globe to the orbital apex.¹² To minimize this feature, we measured the optic nerve area at the same intraorbital location (approximately halfway between the optic nerve–globe junction and the orbital apex) in both patients and controls. The difference between the measurements of the 2 independent observers was noteworthy with a mean difference of 0.93 mm² and a within-subject SD of 1.2 mm². However, it can be reasonably expected that interobserver variability can be minimized by adhering to basic guidelines for the measurement technique. Furthermore, we also believe that increasing the resolution of images from 1 mm² used in this study can also improve detection of optic nerve margins.

Optic nerve area (excluding the optic nerve sheath) was chosen as the main metric of measurement, as opposed to optic nerve diameter. During the measurement process, it was observed that many optic nerves and in particular those carrying a clinical diagnosis of optic nerve atrophy were not circular when viewed in cross-section. Many were ellipsoid, thus allowing varying diameter measurements. Thus, it was thought that measuring the total cross-sectional area would more accurately represent actual optic nerve size.

Optical coherence tomography is an established tool in ophthalmology and neurology and is used as an ancillary test to aid in the diagnosis of many ophthalmic diseases, including ONA.¹⁰

OCT uses measurement of the TE delay of backscattered infrared light via an interferometer and a low-coherence light source and quantifies RNFL thickness.^{2,9} The association between measurable thinning of the RNFL in patients with optic nerve atrophy has been previously observed.¹¹

The moderately strong positive correlation found between MR imaging–measured ON_{area} and OCT-measured RNFL thickness is consistent with intuitive expectations, because they represent different regions of the same underlying cellular structures.⁸ This finding also corroborates the conclusions from prior investigations into this relationship² and further establishes orbital MR imaging as a method of assessing for optic nerve pathology relating to atrophy.

CONCLUSIONS

Our data suggest that an MR imaging–measured optic nerve area of ≤ 4.0 mm² has both strong sensitivity and high specificity for predicting the presence of optic nerve atrophy, making it a potential diagnostic tool for radiologists.

REFERENCES

1. Biousse V, Newman NJ. **Diagnosis and clinical features of common optic neuropathies.** *Lancet Neurol* 2016;15:1355–67 CrossRef Medline
2. Trip SA, Schlottmann PG, Jones SJ, et al. **Optic nerve atrophy and retinal nerve fibre layer thinning following optic neuritis: evidence that axonal loss is a substrate of MRI-detected atrophy.** *Neuroimage* 2006;31:286–93 CrossRef Medline
3. Mackay DD, Garza PS, Bruce BB, et al. **The demise of direct ophthalmoscopy: a modern clinical challenge.** *Neurol Clin Pract* 2015;5:150–57 CrossRef Medline
4. Behbehani R. **Clinical approach to optic neuropathies.** *Clin Ophthalmol* 2007;1:233–46 Medline
5. Šimundić AM. **Measures of diagnostic accuracy: basic definitions.** *EJIFCC* 2009;19:203–11 Medline
6. Hobom M, Storch MK, Weissert R, et al. **Mechanisms and time course of neuronal degeneration in experimental autoimmune encephalomyelitis.** *Brain Pathol* 2004;14:148–57 CrossRef Medline
7. Mead B, Tomarev S. **Evaluating retinal ganglion cell loss and dysfunction.** *Exp Eye Res* 2016;151:96–106 CrossRef Medline
8. Barrett K, Barman SM, Brooks S, et al. *Ganong's Review of Medical Physiology.* New York: McGraw Hill; 2010
9. Hee MR, Izatt JA, Swanson EA, et al. **Optical coherence tomography of the human retina.** *Arch Ophthalmol* 1995;113:325–32 CrossRef Medline
10. Maldonado RS, Mettu P, El-Dairi M, et al. **The application of optical coherence tomography in neurologic diseases.** *Neurol Clin Pract* 2015;5:460–69 CrossRef Medline
11. Wang XL, Yu T, Xia DZ, et al. **Measurement of retinal nerve fiber layer thickness in optic atrophy eyes of patients with optic neuritis using optical coherence tomography.** *Graefes Arch Clin Exp Ophthalmol* 2010;248:1013–18 CrossRef Medline
12. Karim S, Clark RA, Poukens V, et al. **Demonstration of systematic variation in human intraorbital optic nerve size by quantitative magnetic resonance imaging and histology.** *Invest Ophthalmol Vis Sci* 2004;45:1047–51 CrossRef Medline

Infant Midnasal Stenosis: Reliability of Nasal Metrics

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ABSTRACT

BACKGROUND AND PURPOSE: Midnasal stenosis is a poorly defined entity that may be a component of other conditions of nasal obstruction contributing to respiratory distress in infants. We sought to establish whether midnasal vault narrowing is a component of well-defined syndromes of nasal narrowing, such as bilateral choanal atresia and pyriform aperture stenosis, and to characterize the nasal anatomy of patients with syndromic craniosynostosis.

MATERIALS AND METHODS: A convenience sample of patients with pyriform aperture stenosis, bilateral choanal atresia, and Apert and Crouzon syndromes with maxillofacial CT scans was identified. Patients with Pierre Robin Sequence were used as controls. Nasal measurements were performed at the pyriform aperture, choana, and defined midnasal points on axial and coronal CT scans. Intra- and interrater reliability was quantified with the intraclass correlation coefficient. *T* tests with Bonferroni adjustment were used to assess differences from controls.

RESULTS: The study included 50 patients: Eleven had pyriform aperture stenosis, 10 had Apert and Crouzon syndromes, 9 had choanal atresia, and 20 were controls. Measurements in patients with pyriform aperture stenosis and Apert and Crouzon syndromes were narrower than those of controls at all measured points ($P < .001$). Measurements in patients with choanal atresia were only narrow in the posterior half of the nose ($P < .001$). The intra- and interrater reliability of midnasal and pyriform measurements was very good to excellent (intraclass correlation coefficient > 0.87). The choanal measurement was good (intraclass correlation coefficient = $0.76-0.77$).

CONCLUSIONS: Pyriform aperture stenosis, Apert and Crouzon patients were narrower at all measured points compared to controls. Bilateral choanal atresia patients were only narrower in the posterior half of the nose. More research is needed to evaluate the clinical implications of these radiographic findings.

ABBREVIATIONS: BCA = bilateral choanal atresia; ICC = intraclass correlation coefficient; LD = lacrimal duct; LM = last molar; PAS = pyriform aperture stenosis; PRS = Pierre Robin Sequence; SC = syndromic craniosynostosis (includes Apert and Crouzon syndromes)

Neonates are obligate nasal breathers. Stenosis at the pyriform aperture (pyriform aperture stenosis [PAS]) or the choana (bilateral choanal atresia [BCA]) may lead to severe nasal obstruction, necessitating intubation and/or surgical intervention in infants. Each condition is relatively rare, with an incidence of pyri-

form aperture stenosis of 1 in 25,000 live births¹ and choanal atresia overall occurring in 1 in 5000–8000 live births, most commonly unilateral.² Children with syndromic craniosynostosis (SC), such as Apert and Crouzon syndromes, likewise often require management of nasal obstruction as a part of their multidisciplinary care. In one series examining the airway manifestations in Apert syndrome, 60% of patients were found to have CT evidence of nasal abnormalities, including BCA, bilateral or unilateral bony nasal stenosis, and septal deviation.³

When PAS or BCA causes anatomic obstruction, the clinical and radiographic diagnosis is relatively straightforward and measurements at these specific sites have been previously described.^{4,5} Reeves et al⁶ characterized the dimensions of the bony pyriform aperture and the more posterior nasal cavity in the imaging of patients with PAS and found that there was associated posterior narrowing. In most other studies, the remainder of the nasal cavity was not discussed in evaluating patients with BCA and

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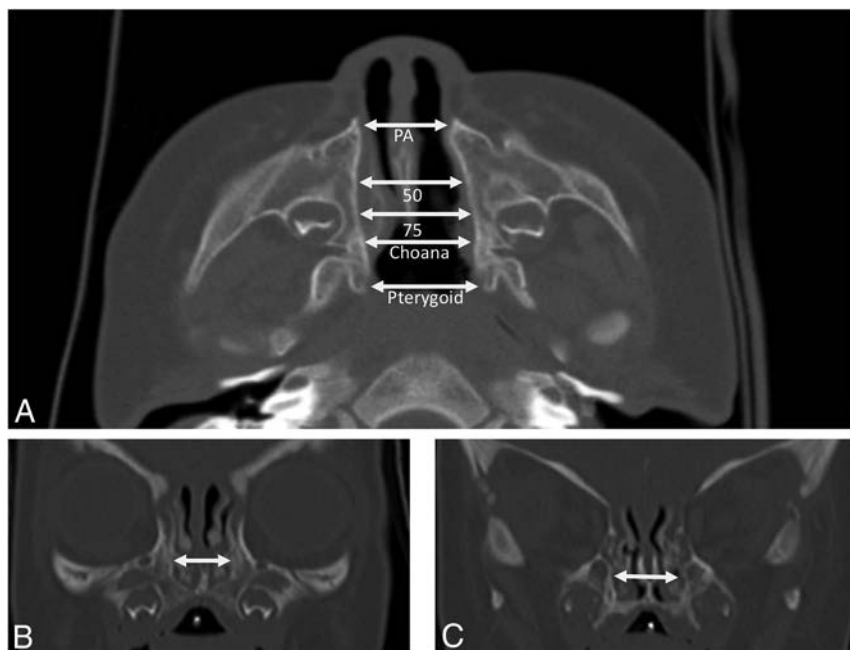


FIG 1. Measurement landmarks. Axial scans (A) were measured from bony lateral nasal wall to bony lateral nasal wall at the level of the pyriform aperture (PA), the choana, and at points 50% and 75% posteriorly between these two landmarks. An additional measurement on axial scan was obtained between the medial pterygoid plates. On coronal views, measurements were obtained from bony lateral nasal wall to bony lateral nasal wall at the pyriform aperture (not shown), just posterior to the lacrimal duct (B), and at the last molar (C).

PAS.^{1,2,4} Previous work on Crouzon syndrome identified the nasal cavity as the narrowest portion of the airway by fluid dynamics and 3D modeling but did not quantify nasal dimensions on CT, which is more easily used in clinical practice.⁷ We are not aware of any studies quantifying the nasal caliber in SC in this way.

Providing comparisons of nasal metrics across nasal-obstruction disorders and controls is the first step in improving our understanding of the nasal airway beyond complete or near-complete obstruction at the pyriform aperture and choana. Given the ability to measure the nasal airway at many different points and in different planes on imaging, the reliability of measurements may also help decide which measurements would be the most useful moving forward. Although abnormalities are suspected from previous work, the degree of midnasal narrowing, if present, is not definitively known in patients with BCA and PAS.^{2,6} While it is also suspected that SC may be associated with midnasal or transnasal stenosis, this association has not been established or quantified.

We sought to determine the area or areas of stenosis in patients with SC, the degree of stenosis, and the caliber of the remainder of the nasal cavity in PAS/BCA in comparison with a control group of patients. Additionally, we sought to test the reliability of our measurements to define nasal stenosis from both the axial and coronal planes of the CT scan.

MATERIALS AND METHODS

Population

A retrospective convenience sample of patients with CT scans of the maxillofacial skeleton meeting 1 of the 4 categories of diagnoses was used. Diagnoses included PAS, BCA, Apert or Crouzon

syndrome, or Pierre Robin Sequence ([PRS] used as the control group), confirmed by chart review. Inclusion criteria required an available maxillofacial CT scan before 3 months of age with coronal and axial slices through the nasal floor. Patients with Apert and Crouzon syndromes were grouped together as having “syndromic craniosynostosis” because these groups were each small and have a similar etiology and facial morphology. PRS was used as a control group because these children are not known to have associated nasal narrowing and represent a uniform population of infants with a maxillofacial CT scan in early infancy.

Radiographic Measurements

CT measurements were performed in the axial view for each patient as has been described in the literature previously,^{6,8} with the caliper tool in standard imaging software (Impax; Agfa-Gevaert, Mortsel, Belgium). Axial measurements were performed using the following landmarks: pyriform aperture, choana, and points 50% and 75% between these 2 landmarks, and between the medial pterygoid plates (millimeters) (Fig 1A). Raters scrolled through the images to find the identified landmarks independent of one another in each patient.

In the coronal view, 3 landmarks were used. The pyriform aperture width was measured from the first frame in which it was fully visible, slightly above the floor of the nasal cavity, immediately below the head of the inferior turbinate. The nasal width posterior to the lacrimal duct (measurement [LD]) was determined by taking a measurement on the scan directly posterior to the last frame in which the lacrimal duct could be identified (Fig 1B). The width of the posterior nasal cavity was measured in a similar manner at the level of the last molar (measurement [LM]) (Fig 1C).

Distances were independently measured at the above points by 2 raters (J.R.S., K.M.L.). Each rater performed all measurements a second time 1 week after first data collection. The raters were not formally blinded to the diagnosis because, in most cases, anomalies could be easily diagnosed on reviewing the imaging before performing measurements.

Statistical Analysis

The groups were compared for differences in age at scanning, which could contribute to differences in measurements across groups. The discriminant validity of the metric tested the ability to detect a difference among groups of nasal disorders.⁹ The nasal dimensions of each condition were compared with those of the control group using a *T* test. The Bonferroni correction for multiple comparisons was used when defining statistical significance. With 32

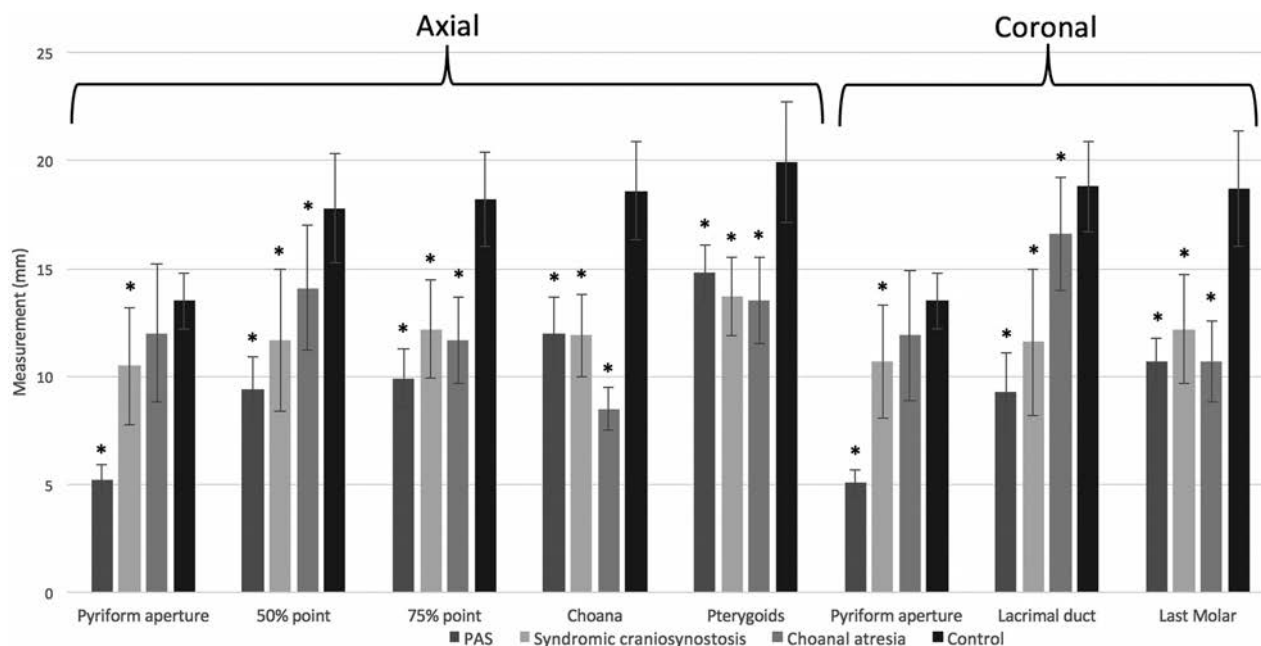


FIG 2. Mean nasal measurements. Measurements are given in millimeters. Asterisks indicate statistical significance ($P < .001$).

individual tests, the threshold for statistical significance was $P < 0.002$.

Intrater reliability used the intraclass correlation coefficient (ICC) with a 95% confidence interval to calculate the reproducibility of repeat measurements in the same rater. Interrater reliability was similarly calculated for the reproducibility of repeat measurements in different raters. In a modification of the Altman thresholds for reliability,¹⁰ values from 0.41 to 0.60 were considered “moderate”; those from 0.61 to 0.80, “good”; those from 0.81 to 0.90, “very good”; and those of >0.90 , “excellent” reliability. Additionally, the difference between the 2 raters’ mean measurements at each site was provided in millimeters.

All analyses were performed with STATA/SE 10.1 (StataCorp, College Station, Texas).

RESULTS

Patient Demographics

Fifty patients were identified and categorized as having congenital PAS ($n = 11$), SC ($n = 9$), and BCA ($n = 10$) or were controls (PRS) ($n = 20$). Patients were, on average, 0.7 months of age at the time of their scan. Mean ages by diagnostic group were as follows: patients with PAS, 0.50 ± 0.5 months; patients with SC, 0.55 ± 1.6 months; patients with BCA, 0.33 ± 0.5 months; and controls, 0.81 ± 1.1 months. There was no statistically significant difference in age at scanning between any group and the control group ($P \geq .2$ on all tests).

Pyriform Aperture

The mean pyriform aperture measurement on axial slices for patients with PAS was 5.2 ± 0.7 mm (Fig 2). Patients with SC had a mean pyriform aperture width of 10.5 ± 2.7 mm. Patients with BCA had a mean pyriform aperture width of 12.0 ± 3.2 mm. Controls had a mean pyriform width of 13.6 ± 1.3 mm. The coronal measurements were similar.

Pyriform aperture measurements in patients with both PAS

and SC were narrower than those in controls ($P < .001$). In comparing patients with BCA with controls, the difference in pyriform aperture dimension was not statistically significant when measured in the coronal ($P = .02$) or axial ($P = .07$) plane.

Midnasal Passage

Midnasal width was measured at 2 sites in both the axial and coronal views (LD and LM on coronal, 50% and 75% on axial). Infants with PAS had mean LD and LM measurements of 9.3 ± 1.8 mm and 10.7 ± 1.1 mm, respectively. These were narrower than those in controls (PRS) (LD and LM measurements, 18.8 ± 2.1 mm and 18.7 ± 2.7 mm, respectively; $P < .001$). PAS mean axial measurements were similar to these. Measurements of patients with syndromic craniosynostosis were 11.6 ± 3.4 mm (LD) and 12.2 ± 2.5 mm (LM), with similar findings on axial measurements, also narrower than those in controls ($P < .001$).

In our BCA group, mean coronal measurements were 16.6 ± 2.6 mm (LD), which were not considered different from those in the controls (18.8 mm) after adjusting for multiple testing ($P = .03$). The means for the LM measurement (11.7 ± 3.3 mm), 50% measurement (14.1 ± 2.9 mm), and 75% measurement (11.7 ± 2.0 mm) were all narrower than those in controls ($P < .001$).

Choana

The mean choanal measurements were 12.0 ± 1.7 mm (PAS), 11.9 ± 1.9 mm (SC), and 8.5 ± 1.0 mm (BCA). The control mean choanal measurement was 18.6 ± 2.3 mm. For all 3 conditions, the narrower choanal measurement was statistically significant ($P < .001$).

Pterygoid

Patients with PAS, SC, and BCA had mean measurements of 14.8 ± 1.3 mm, 13.7 ± 1.8 mm, and 13.5 ± 2.0 mm, respectively, at the level of the pterygoid on axial CT, with the control PRS

Inter- and intrater reliability

	Intrater Reliability				Interrater Reliability			
	ICC	SE	95% CI		ICC	SE	95% CI	
Coronal								
PA	0.97	0.01	0.96	0.99	0.97	0.01	0.95	0.99
LD	0.94	0.02	0.89	0.98	0.94	0.02	0.90	0.98
LM	0.88	0.04	0.79	0.96	0.95	0.02	0.92	0.98
Axial								
PA	0.97	0.01	0.95	0.99	0.96	0.01	0.94	0.99
50%	0.90	0.04	0.83	0.97	0.93	0.03	0.88	0.99
75%	0.87	0.05	0.78	0.96	0.93	0.03	0.86	0.99
CA	0.76	0.08	0.60	0.91	0.77	0.09	0.59	0.96
Pty	0.86	0.05	0.76	0.95	0.45	0.21	0.04	0.86

Note:—SE indicates standard error; CA, choana; Pty, pterygoid plate; PA, pyriform aperture.

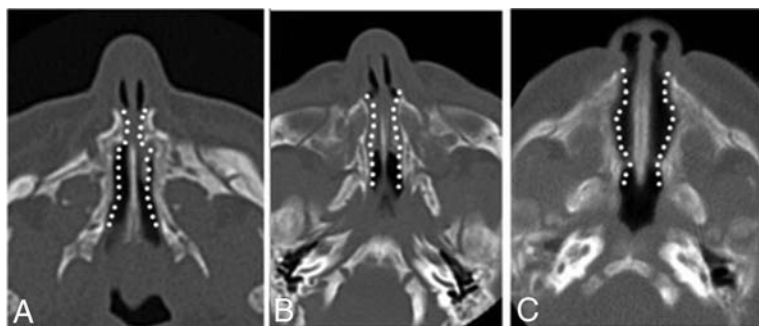


FIG 3. Trends seen in the nasal cavity of pyriform aperture stenosis (A), syndromic craniosynostosis (B), and bilateral choanal atresia (C). Note the more global narrowing in patients with PAS and SC versus a more posterior narrowing in patients with BCA. Although the pyriform aperture in patients with BCA appears narrower than that in controls (Fig 1A) visually, this difference is not statistically significant.



FIG 4. 3D reconstructions of maxillofacial CT scans highlighting the pyriform aperture, in particular in patients with PAS (A), Apert syndrome (B), and PRS (C).

population having a mean pterygoid measurement of 19.9 ± 2.8 mm. The mean pterygoid measurement of each group was significantly narrower than that of controls ($P < .001$).

Intra- and Interrater Reliability

Intrater reliability was found to be very good to excellent for all measurements except the choana on axial views (ICC = 0.77, good). Interrater reliability for the medial pterygoid plate was moderate (ICC = 0.45). The remainder of the nasal metrics were excellent, except for the choana (ICC = 0.77, good), the only other measurement < 0.9. (Table). The measured difference in millimeters varied by ICC. Those measurements with ICC values of >0.93 had a <1-mm difference in measurements between raters (differences: coronal pyriform aperture = 0.1 mm, LD = 0.8 mm, LM = 0.2 mm, axial pyriform aperture = 0.6 mm). Those with an ICC $\leq$ 0.93 had an average of a 2.2-mm difference between raters (differences: axial 50% = 2.6 mm, axial 75% = 2.7 mm, axial choana = 1.4 mm, axial pterygoid = 2.2 mm).

DISCUSSION

Neonates are obligate nasal breathers, and understanding infant nasal anatomy is therefore very important.¹¹ Nevertheless, measurements have not been standardized, and in many conditions, only 1 anatomic site is measured. Reeves et al⁶ described a method of measuring the posterior nasal cavity using the choana and pyriform aperture as initial landmarks on axial CT as well as points 50% and 75% between the two. We adapted this technique with the addition of several other points and coronal landmarks. The 8 sites we present have interrater and intrater reliability that is, at minimum, rated as good, with most being excellent. An exception is in the use of the medial pterygoid plate. It is possible that due to the superoinferior flaring of the plates, the axial plane is not ideal for measurement of this landmark. We suspect that this landmark might have differences among our patient groups as an important buttress of the midface and that narrowing in this location may represent narrowing of the entire maxilla, but the clinical significance of this difference is unclear because it is outside the nasal cavity.

Using our measurement technique, we found that the shape of the nasal passage may be different in the groups with nasal airway obstruction. We found that patients with syndromic craniosynostosis have global narrowing, as seen in the previous fluid dynamic study and in keeping with the symptoms noted in case series.^{3,7} Most interesting, patients

with PAS and BCA also appear to have more than an isolated narrowing. Figure 3 illustrates the shape of the nasal cavity on axial scans in each condition. It appears that the nasal cavity of patients with PAS and SC are globally narrow. Patients with BCA also have a narrower nasal passage than controls, but this is only statistically significant in the more posterior nasal cavity, from the 50% point posterior on axial scans and from the last molar posterior on the coronal cuts. The difference in the pyriform aperture is further illustrated in 3D reconstructions generated from maxillofacial CTs (Fig 4).

Reeves et al⁶ examined CT scans in patients with PAS and found that the anterior 75% of the nasal cavity was narrower than that in controls. Their patients with PAS ($n = 7$) had narrower choanae than controls ($n = 13$), but this finding was not statistically significant. In our slightly larger case series of patients with PAS ($n = 11$) and controls ($n = 20$), we found that the nasal cavity was globally narrower, including the choana, and this was statistically significant throughout. Aslan et al² similarly performed

detailed analysis of the nasal caliber in patients with BCA. Their measurement sites were different from ours, making comparison difficult, and they did not include a midnasal bony measurement. In contrast to our study, the authors did find a statistically significant difference at the bony pyriform aperture between patients with BCA and controls. Our study used the Bonferroni correction for multiple testing, which might make it less likely that the null hypothesis would be refuted by chance. More studies with a larger sample size and with limited numbers of statistical tests looking more specifically at this site in patients with BCA may reveal whether there is a true global narrowing in patients with BCA as well.

There are few studies of management of the nasal airway in Apert and Crouzon syndromes. A case series in airway management in Apert syndrome indicated that those patients with bony nasal stenosis required an average of 3–5 dilations per patient.³ Further defining the problem of narrowing throughout the nasal passage on preoperative imaging may help optimize future treatments for nasal airway obstruction in infants with syndromic craniosynostosis.

The most important clinical implication of our results may be in predicting the likelihood of surgical success. A globally narrow nose as seen in SC and PAS is unlikely to respond to an anatomically directed single-site drilling, and even those patients with BCA have narrowing not limited to the choana. Revision rates in choanal atresia are estimated to be between 6% and 36%.^{12,13} Because the incidence of PAS is low, there are limited data regarding revision surgery rates. A systematic review and case series from 1 institution included a total of 73 patients undergoing surgical management for PAS, with a 15% revision rate.¹⁴ It is possible that surgical failures in these conditions may be due to concomitant stenosis elsewhere that is neither recognized nor managed, but this requires more study.

Our control group (patients with PRS) could be considered a limitation. It is not common for an infant with no known congenital anomalies or syndromes to undergo a maxillofacial CT. Patients with Pierre Robin Sequence commonly undergo CT for surgical planning for mandibular distraction and therefore provide a pool of similarly aged patients, presumably without nasal abnormalities. It is possible, though not described, that they have a wider or narrower nasal passage than nonsyndromic infants, over- or underestimating the difference in nasal dimensions. We did not identify other similarly aged groups undergoing scans; those presenting with peritonsillar or other deep space neck abscesses tended to be older than 5 years of age, and those undergoing CT for cochlear implantation typically are older than 6 months of age.¹⁵

An additional limitation may be a selection bias in those patients undergoing CT. Patients with milder nasal obstruction, particularly those with pyriform aperture stenosis or choanal atresia may not undergo imaging, and our measurement data might be biased toward patients with narrower nasal cavities. While this bias may be present, it would only limit the generalizability of these results to those patients with less severe nasal obstruction (those who are less likely to be surgical candidates). Nasal metrics in these patients would be unlikely to change management. This limitation is likely not significant in those patients with craniosynostosis who are being imaged for their cranial vault

issues rather than nasal obstruction, and we would expect many patients in this group to be included. Some patients with SC had only a head CT, which did not capture the maxillofacial skeleton, limiting our sample size. In patients with SC with Apert syndrome, an additional concern is the potential for orbital asymmetry.¹⁶ This did not affect the interrater reliability of the LD measurement (0.97; 95% CI, 0.93–1.0) but may mean that this measurement represents a different portion of the nose in patients with SC. Future studies of the position of the lacrimal system in these patients may be helpful.

Future directions include analysis of the clinical implications of midnasal narrowing with the goal of defining the best location for evaluating midnasal stenosis and creating a cutoff value for significant stenosis under which poorer outcomes or increased revision rates are more likely. Measuring more control patients would also better define a metric of typical nasal diameter to be used for comparison in future work.

CONCLUSIONS

There is global narrowing of the nasal airway in patients with PAS and Apert and Crouzon syndromes and narrowing of the mid-to-posterior nasal cavity in patients with BCA. This finding highlights the need to evaluate the entire nasal airway in surgical planning and may have implications for the likelihood of surgical success. The anatomic sites we have proposed to evaluate the nasal caliber have good-to-excellent inter- and intrarater reliability and may be extended to use in other studies.

REFERENCES

1. Wormald R, Hinton-Bayre A, Bumbak P, et al. **Congenital nasal pyriform aperture stenosis 5.7 mm or less is associated with surgical intervention: a pooled case series.** *Int J Pediatr Otorhinolaryngol* 2015;79:1802–05 [CrossRef Medline](#)
2. Aslan S, Yilmazer C, Yildirim T, et al. **Comparison of nasal region dimensions in bilateral choanal atresia patients and normal controls: a computed tomographic analysis with clinical implications.** *Int J Pediatr Otorhinolaryngol* 2009;73:329–35 [CrossRef Medline](#)
3. Xie C, De S, Selby A. **Management of the airway in Apert syndrome.** *J Craniofac Surg* 2016;27:137–41 [CrossRef Medline](#)
4. Moreddu E, Le Treut-Gay C, Triglia JM, et al. **Congenital nasal pyriform aperture stenosis: elaboration of a management algorithm from 25 years of experience.** *Int J Pediatr Otorhinolaryngol* 2016;83:7–11 [CrossRef Medline](#)
5. Wine TM, Dedhia K, Chi DH. **Congenital nasal pyriform aperture stenosis: is there a role for nasal dilation?** *JAMA Otolaryngol Head Neck Surg* 2014;140:352–56 [CrossRef Medline](#)
6. Reeves TD, Discolo CM, White DR. **Nasal cavity dimensions in congenital pyriform aperture stenosis.** *Int J Pediatr Otorhinolaryngol* 2013;77:1830–32 [CrossRef Medline](#)
7. Wang T, Mu X, Deng J, et al. **Investigation on the structure of nasal cavity and its airflow field in Crouzon syndrome.** *J Craniofac Surg* 2011;22:166–72 [CrossRef Medline](#)
8. Belden CJ, Mancuso AA, Schmalfuss IM. **CT features of congenital nasal pyriform aperture stenosis: initial experience.** *Radiology* 1999;213:495–501 [CrossRef Medline](#)
9. Westen D, Rosenthal R. **Quantifying construct validity: two simple measures.** *J Pers Soc Psychol* 2003;84:608–18 [CrossRef Medline](#)
10. Altman DG. *Practical Statistics for Medical Research.* London: Chapman and Hall; 1991
11. Miller MJ, Martin RJ, Carlo WA, et al. **Oral breathing in newborn infants.** *J Pediatr* 1985;107:465–69 [CrossRef Medline](#)
12. Tatar EC, Öcal B, Doğan E, et al. **Stentless endoscopic repair of con-**

- genital choanal atresia: is it enough for maintaining choanal patency?** *Eur Arch Otorhinolaryngol* 2017;274:3673–78 [CrossRef Medline](#)
13. Brihaye P, Delpierre I, De Villé A, et al. **Comprehensive management of congenital choanal atresia.** *Int J Pediatr Otorhinolaryngol* 2017;98: 9–18 [CrossRef Medline](#)
 14. Gonik NJ, Cheng J, Lesser M, et al. **Patient selection in congenital pyriform aperture stenosis repair: 14 year experience and systematic review of literature.** *Int J Pediatr Otorhinolaryngol* 2015;79: 235–39 [CrossRef Medline](#)
 15. Novis SJ, Pritchett CV, Thorne MC, et al. **Pediatric deep space neck infections in U.S. children, 2000–2009.** *Int J Pediatr Otorhinolaryngol* 2014;78:832–36 [CrossRef Medline](#)
 16. Kreiborg S, Cohen MM Jr. **Ocular manifestations of Apert and Crouzon syndromes: qualitative and quantitative findings.** *J Craniofac Surg* 2010;21:1354–57 [CrossRef Medline](#)

Evaluation of the Implementation of the Response Assessment in Neuro-Oncology Criteria in the HERBY Trial of Pediatric Patients with Newly Diagnosed High-Grade Gliomas

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ABSTRACT

BACKGROUND AND PURPOSE: HERBY was a Phase II multicenter trial setup to establish the efficacy and safety of adding bevacizumab to radiation therapy and temozolomide in pediatric patients with newly diagnosed non–brain stem high-grade gliomas. This study evaluates the implementation of the radiologic aspects of HERBY.

MATERIALS AND METHODS: We analyzed multimodal imaging compliance rates and scan quality for participating sites, adjudication rates and reading times for the central review process, the influence of different Response Assessment in Neuro-Oncology criteria in the final response, the incidence of pseudoprogression, and the benefit of incorporating multimodal imaging into the decision process.

RESULTS: Multimodal imaging compliance rates were the following: diffusion, 82%; perfusion, 60%; and spectroscopy, 48%. Neuroradiologists' responses differed for 50% of scans, requiring adjudication, with a total average reading time per patient of approximately 3 hours. Pseudoprogression occurred in 10/116 (9%) cases, 8 in the radiation therapy/temozolomide arm and 2 in the bevacizumab arm ($P < .01$). Increased target enhancing lesion diameter was a reason for progression in 8/86 cases (9.3%) but never the only radiologic or clinical reason. Event-free survival was predicted earlier in 5/86 (5.8%) patients by multimodal imaging (diffusion, $n = 4$; perfusion, $n = 1$).

CONCLUSIONS: The addition of multimodal imaging to the response criteria modified the assessment in a small number of cases, determining progression earlier than structural imaging alone. Increased target lesion diameter, accounting for a large proportion of reading time, was never the only reason to designate disease progression.

ABBREVIATIONS: BEV = bevacizumab; CRRC = Centralized Radiologic Review Committee; EFS = event-free survival; HGG = high-grade glioma; MM = multimodal; RANO = Response Assessment in Neuro-Oncology; RT = radiotherapy; TMZ = temozolomide

The recent Avastin in Glioblastoma (AVAglio) clinical trial investigated the use of bevacizumab (BEV) plus radiation therapy

(RT) and temozolomide (TMZ) compared with a placebo plus RT–TMZ in adult patients with newly diagnosed glioblastoma.¹ This was subsequently investigated in a pediatric patient population. The Study of Bevacizumab (Avastin) in Combination with Temozolomide and Radiotherapy in Paediatric and Adolescent Participants with High-Grade Glioma (HERBY) (BO25041; clinicaltrials.gov NCT01390948) was a Phase II, open-label, randomized, multicenter, comparator study set up to establish the efficacy and safety of the addition of BEV to RT and TMZ in patients between 3 and 18 years of age with newly diagnosed non–brain stem high-grade glioma (HGG).²

The radiologic aspects of the HERBY trial were expanded compared with AVAglio in a number of aspects. In HERBY, the

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 Indicates article with supplemental on-line tables.

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Table 1: HERBY trial imaging schedule

Neuroimaging Visits	Descriptions
Preoperative	Preferably MRI (CT accepted) performed according to the site standard of care
Baseline (postoperative)	From 24–48 hr after the operation and no later than 72 hr after initial operation
First assessment	Prior to day 1 of cycle 1
During adjuvant temozolomide treatment period	Within 7 days prior to first treatment administration and every 3 mo (in cycles 1, 4, 7, and 10)
Follow-up period	Every 3 mo (± 21 days) until 3 years after randomization
End of study/unscheduled/ withdrawn consent	Performed when an event-free survival event suspected (confirmed or unconfirmed) or consent withdrawn, if possible

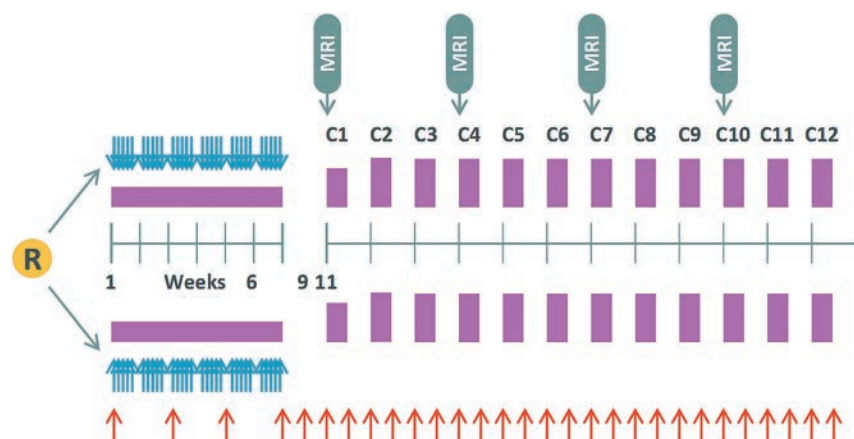


FIG 1. Treatment and imaging schedule for HERBY. Four weeks after the operation, patients are randomized (R) and chemoradiotherapy commences for 6 weeks followed by a 4-week break. Multiple cycles of adjuvant treatment are then initiated, indicated by C1 through C12, with 4 weeks per cycle. Blue arrows indicate radiation therapy; purple blocks, temozolomide, and red arrows, bevacizumab treatment.

determination of progression, recurrence, or response was mandated on the basis of meeting predefined clinical and radiographic criteria, as defined by the Response Assessment in Neuro-Oncology (RANO) criteria,^{3,4} assessed by a central site-independent radiology review. In addition, changes in the tumor on MR diffusion and perfusion imaging were evaluated and correlated with the structural imaging review.

In addition to the conventional MR imaging (T1WI, contrast-enhanced T1WI, and T2WI/FLAIR sequences) required for RANO, the optional acquisition of MR diffusion imaging, perfusion imaging, and proton spectroscopy was requested, to allow analysis of potential additional impact on the efficacy outcome measures of the trial.

To implement the radiologic assessment for HERBY, the trial steering group instigated the following:

Central Radiologic Review Committee

A Centralized Radiologic Review Committee (CRRC) was formed to oversee and advise on the MR imaging acquisition and analysis aspects of the HERBY trial. It consisted of a number of international expert pediatric neuroradiologists, an imaging physicist, and sponsor representatives.

MR Imaging Acquisition

MR imaging was requested following a standardized protocol (which can be accessed in the Supplementary Materials Section of Jaspan et al⁵). Images were provided by the sites to the contract research organization of the trial, ICON Medical Imaging, and all

radiologic reviews were conducted using their MIRA platform (ICON Medical Imaging, Dublin, Ireland).

For each patient, a baseline postoperative MR imaging scan was acquired no later than 72 hours following the operation, in addition to a first scan before the start of treatment and then subsequent scans every 3 months for 3 years after randomization or the unscheduled end of study due to an event-free survival (EFS) event. The imaging schedule is further detailed in Table 1 and Fig 1. Where available, preoperative imaging was requested.

Each participating imaging center was issued with both structural and multimodal (MM) imaging manuals to instruct them in protocol-specific image acquisition requirements, necessary documentation and data transfer instructions, data

archiving and shipping, and the query resolution process for any clerical discrepancies and/or noncompliant data.

Central Radiology Reviews

Three image-review processes were implemented, performed by a selection of the 5 expert pediatric neuroradiologists on the CRRC: these were eligibility reviews, early progression reviews, and retrospective central efficacy radiology reviews. Consensus training was undertaken by the neuroradiologists in advance.

Eligibility Review. This optional review could be requested by the local site, for 1 of the neuroradiologists on the CRRC to assess whether the postoperative MR imaging showed findings consistent with newly diagnosed localized HGG but excluding gliomatosis cerebri (or multifocal HGG). The postoperative scans must not have shown evidence of substantial surgically related intracranial bleeding. Patients may have had either measurable or assessable-but-nonmeasurable disease and would still qualify for enrollment.

Early Progression Review. To aid the local site in its assessment of early tumor-related enhancement on the first postcontrast MR imaging following commencement of treatment, a pathway to seek advice from 1 of the neuroradiologists on the CRRC was implemented, to advise on identification of early tumor progression compared with early treatment effects (pseudoprogression). This optional review could be sought for any neuroimaging acquired between (and including) the first postoperative scan and

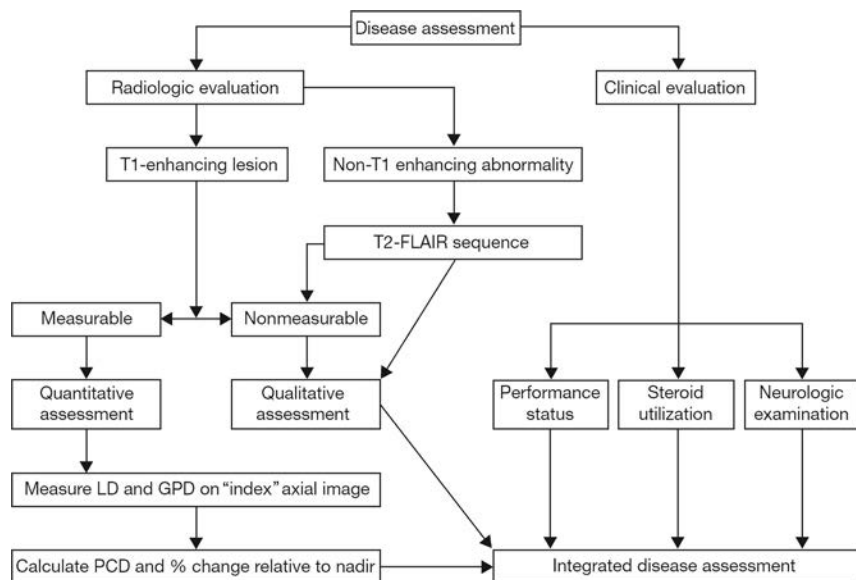


FIG 2. Integrated disease assessment using radiologic and clinical decision criteria (RANO). LD is the longest in-plane lesion diameter; GPD, the greatest perpendicular diameter; PCD, the product of cross-sectional enhancing diameters.³⁻⁵

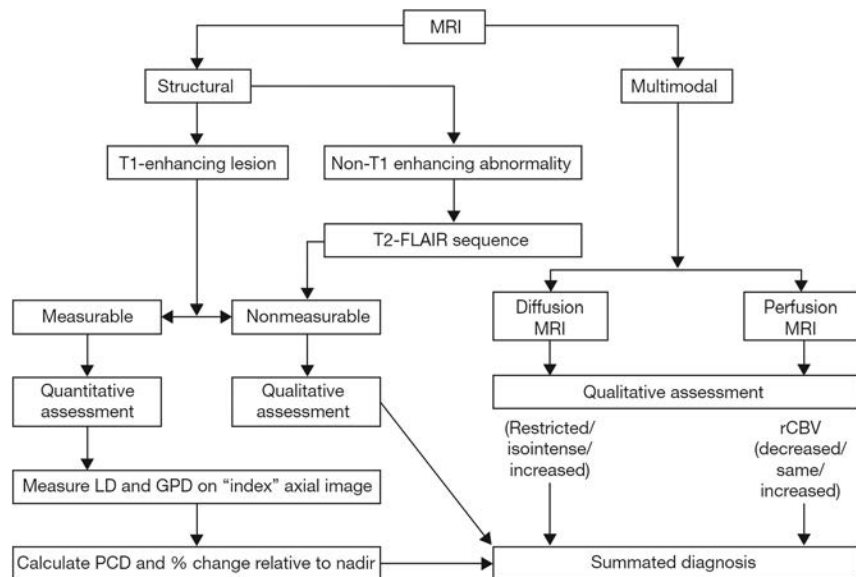


FIG 3. Flowchart combining structural and multimodal imaging used in the central efficacy radiology review. LD is the longest in-plane lesion diameter; GPD, the greatest perpendicular diameter; PCD, the product of cross-sectional enhancing diameters; rCBV, relative CBV.⁵

those acquired up to the end of the 12-week period following completion of the first cycle of treatment (ie, up to 23 weeks after commencing treatment) (Fig 1). The opinion was provided within 2 weeks of receiving the request and was nonbinding; the site investigator determined whether treatment should continue if the local opinion differed from the advice given.

Central Efficacy Radiology Review. Pairs of the expert pediatric neuroradiologists on the CRRC were randomly assigned to cases to assess the structural MR imaging, in parallel but separately, according to the RANO criteria (Fig 2). When there were discrepant radiologic findings, a third pediatric neuroradiologist from the CRRC adjudicated. Following image review, an independent pediatric oncologist reviewed supportive clinical data

and corticosteroid dosage and provided the final status for that time point. The structural MR imaging review produced a definitive response level per time point for each patient and determined the earliest occurrence of tumor progression or recurrence in support of the primary end point of the trial of event-free survival. On completing the structural MR imaging review, the same central reviewers performed an additional evaluation combining diffusion and perfusion MR imaging findings (when available) with the structural assessment to determine whether they would alter the structural MR imaging review response. The incorporation of the multimodal imaging into the RANO assessment followed that proposed previously, both with respect to the evaluation of the multimodal data (Supplementary Material in Jaspán et al, 2016,⁵) and its incorporation into the overall response decision (Fig 3).

This article evaluates the implementation of the radiologic aspects of HERBY, summarized above. To assess these, the aims of this work were as follows:

- 1) To evaluate the implementation of the RANO criteria in a Phase II trial of pediatric patients with HGG
- 2) To assess the feasibility of obtaining multimodal imaging of adequate quality from multiple sites
- 3) To assess the effect of including diffusion and perfusion imaging into the response criteria.⁵

MATERIALS AND METHODS

The aims of this work were addressed by evaluating the following:

Compliance Rates and Data Quality

A pretrial assessment indicated the type of data expected from each participating site because multimodal MR imaging was not available at all sites. This was then compared with the actual collected data available for central review to determine compliance rates. Data quality was evaluated by the CRRC, with scans labeled as optimal, readable but not optimal, or not readable.

Early Progression Review

The number of requests for early progression reviews by a neuro-radiologist from the CRRC was assessed, as an indication of the value of this process. In addition, of these requests, the proportion

in which the opinion of the central read was adopted by the local site was ascertained.

Adjudication Rates

In cases in which there were discrepancies between reviewers 1 and 2 undertaking a structural MR imaging review, an additional neuroradiologist (reviewer 3, blinded to reviewer identities) adjudicated by selecting the preferred opinion, establishing the final CRRC decision for that patient. Adjudication rates for this trial were defined as the percentage of cases in which the date of progression or recurrence differed between reviewers 1 and 2.

Reading Times

Average reading times per scan were estimated post-trial by the neuroradiologists involved and were multiplied by the number of scans per patient and the number of reviewers.

Breakdown of RANO Decision Components

The proportion of cases in which enhancing or nonenhancing tumor (ie, measurable or nonmeasurable) was the factor that determined progression was calculated to determine which imaging sequence was most influential in the RANO criteria and how it compared with clinical findings.

RANO and Multimodal Imaging

The number of times that radiologic evaluation of perfusion or diffusion data changed the EFS time point (ie, the EFS incorporating diffusion and/or perfusion) was calculated to determine the potential influence of adding these imaging findings to the RANO criteria. In addition, a subjective score of the multimodal imaging influence in each case was recorded by each reader on a scale of 1 to 5, with the highest score indicating the most influence in the decision.

Central Radiology Review Committee versus Local Investigator

Discrepancies in the EFS determined by the CRRC and local investigators were calculated.

Pseudoresponse and Pseudoprogession

Within the first 12 weeks after completion of radiation therapy, evidence of progression was designated as "pseudoprogession." This was later revised after assessment of the subsequent scan by the CRRC according to the criteria of Chinot et al⁴ (On-line Table 1). The CRRC would then assign patient status as stable disease, confirmed pseudoprogession, or true progressive disease.

Statistical Analysis

EFS distributions were compared with the related-samples Wilcoxon signed rank test, using SPSS Statistics for Windows, Version 23 (IBM, Armonk, New York). A χ^2 test of independence was performed to examine the relation between the treatment arm and both adjudication rates and pseudoprogession. Values of $P < .01$ were considered statistically significant.

RESULTS

Between October 2011 and February 2015, one hundred seventy-four patients were screened, and 121 were randomized to receive treatment (RT/TMZ, $n = 59$; BEV + RT/TMZ, $n = 62$). Of these

174, three were children younger than 3 years of age with recurrent HGGs who were recruited at the request of the European Medicines Agency but were not included in this analysis. One patient was excluded following identification of metastatic disease in the spine, with a second exclusion due to gliomatosis. All 121 patients underwent an operation (total/near-total resection, $n = 60$; other resection, $n = 39$; biopsy, $n = 22$). Five randomized patients did not receive treatment (RT/TMZ: withdrew consent, $n = 3$; BEV + RT/TMZ: failed to meet eligibility criteria, $n = 1$; withdrew consent, $n = 1$). Overall, 116 patients (RT/TMZ, $n = 56$; BEV + RT/TMZ, $n = 60$) received study treatment at 50 sites. For a more detailed description of the trial see Grill et al.²

Preoperative imaging, though not part of the initial HERBY protocol and performed according to the site standard of care, was available in 91/116 (78%) patients (MR imaging, $n = 89$; CT, $n = 2$). Postoperatively, there were 623 centrally reviewed MR imaging scans, with an average of 4.9 scan time points acquired per patient during the trial (range, 1–15).

Compliance Rates and Data Quality

From the 76 sites that responded to the initial survey, 20 (26%) offered structural imaging only, while 56 (74%) sites offered multimodal imaging in addition: diffusion, $n = 50$ (66%); perfusion, $n = 49$ (65%); spectroscopy, $n = 53$ (70%); and all 3 MM imaging sequences, $n = 44$ (48%).

A total of 50/85 sites (59%) successfully recruited patients and acquired imaging data (5 sites withdrew and 4 sites subsequently joined the study after the survey). The compliance rates for structural and MM imaging for these sites can be seen in On-line Table 2. All 30 sites that had committed to return diffusion imaging did return it at least once for each patient (100%); of 28 that had committed to return perfusion imaging 23 did (82%), and of 31 that had committed to return spectroscopy 22 did (71%). For all sites in the trial that offered to provide MM imaging, the percentage of scans actually acquired was 82% for diffusion, 60% for perfusion, and 48% for spectroscopy.

In terms of data quality, from the structural data available for central review, there were 10/623 (1.6%) cases for which both reviewers thought they could not provide a response on the basis of the quality of data available (unreadable scans). From the MM imaging data available for central review, there were 95 (22.5%) time points at which there were nonevaluable scans (55 diffusion and 89 perfusion). There were 20/116 cases in which scanners with different magnetic field strengths were used to scan the same patient. Of these, the change occurred in 5 cases between pre- and postoperative scans (4%), in 7 cases when the patient did not progress during the trial (6%), and in 8 cases (7%) when the scanner change occurred between the time points immediately before and at progression.

Early Progression Review

In 19 patients (23 scans), advice was sought from the CRRC regarding imaging performed either at week 10 (52%) or at the end of cycle 3 (48%). There were 5/11 patients who had an imaging event suggestive of progression documented on the week 10 scan, but for whom the local investigator decided to continue with treatment. Following cycle 3 scan reviews, treatment for 8/11 pa-

Table 2: Breakdown of elements of the RANO Criteria in assessing progression

	Reason for Progression (No.) (%)	Unique Reason for Progression (No.) (%)
Clinical	41 (47.7)	3 (3.5)
Radiologic	78 (90.7)	40 (46.5)
Target SPD increase	8 (9.3)	0 (0.0)
New lesions ^a	54 (62.8)	15 (17.4)
Nontarget lesions ^b	33 (38.4)	4 (4.7)
Total	86	62

Note:—SPD indicates sum of products of diameters.

^a New lesions may be enhancing or nonenhancing (T2WI/FLAIR). New enhancing lesions do not need to meet the size criteria for being considered measurable but must, in the best judgment of the reviewer, be true tumor lesions rather than benign or incidental findings.

^b At baseline, any radiologic evidence of disease beyond the designated target lesion may be identified as nontarget lesions. These include enhancing T1WI nonmeasurable and nonenhancing lesions on FLAIR/T2WI.

tients was discontinued, including in all those for whom an imaging event had been documented at week 10.

Adjudication Rates

On an individual scan basis, of 613 structural imaging assessments, 304 (49.6%) were not adjudicated, while 309 (50.4%) required adjudication due to a divergent response of a neuroradiologist. On a per-patient basis, adjudication corresponding to the primary trial end point (ie, the number of all cases that were adjudicated for the date of progression or recurrence) was undertaken in 17/116 patients (14.7%).

Reading Times

The average time to read a scan was estimated at 15 minutes. With 2 reviewers and an adjudication rate of 50% and an average of 4.9 scans per patient in the trial, the average RANO reading time per patient was just >3 hours.

Breakdown of RANO Decision Components

Of a total of 86 cases of progression or recurrence, clinical reasons were reported in 41 cases (47.7%), and radiologic reasons, in 78 (90.7%). A breakdown of the different reasons for progression can be seen in Table 2.

The increase in diameter of the target-enhancing lesion was a reason for progression in 8 of 86 cases (9.3%). In these 8 cases, there were always other coexisting reasons for progression at the same visit, either clinical (neurologic deterioration with stable or increased corticosteroid use, $n = 4$) or radiologic (unequivocal nontarget progression, $n = 3$; new lesions, $n = 7$).

RANO and Multimodal Imaging

The addition of diffusion/perfusion data changed the structural imaging EFS, with 1/89 (1.2%) patients for whom it occurred later and 5/89 (5.8%) for whom it occurred earlier. These differences in EFS were not significantly different according to a Wilcoxon signed rank test: structural imaging EFS median = 300 days, diffusion/perfusion EFS median = 288 days; $Z = 21.0$, $P = .28$. These 5 patients would have been classified as having an event, on average, 95 days earlier on the basis of inclusion of MM imaging, which mostly corresponded to the previous scan visit, though for 2 patients, it was evident from even earlier scans. Of these 5 pa-

Table 3: Readers' subjective scores of the influence of diffusion and perfusion scans on their assessment

Influence Score	Diffusion		Perfusion	
	No.	%	No.	%
5 (Higher influence)	14	2.7	4	1.8
4	43	8.2	15	6.6
3	110	21.0	58	25.7
2	177	33.8	101	44.7
1 (Lower influence)	180	34.3	48	21.2
Total	524		226	

tients, there was only 1 case in which an earlier EFS would have been called on the basis of perfusion imaging alone. In the remaining cases, either an event was also apparent on diffusion images ($n = 4$) and/or there was no perfusion imaging available ($n = 2$).

The subjective influence of multimodal imaging is reported in Table 3. As perceived by the readers, for most time points that included multimodal scans (>65%), this additional evaluation had little-or-no influence on the reader's decision.

RANO Central Read versus Local Investigator

There were 34 patients of 86 (39.5%) for whom the EFS determined by local investigators was later than according to the EFS determined by the CRRC and 4 patients (4.7%) for whom it was earlier. A Wilcoxon signed rank test indicated that EFS determined by local investigators (median = 322 days) was statistically significantly different from EFS determined by the CRRC (median = 288 days, $Z = 943.0$, $P < .01$).

Pseudoprogression

Initially, 33 cases (28.4%) were designated pseudoprogression at the week 10 scan. Of those, 19 were deemed at a later visit to have progressed or recurred and thus were retrospectively assigned as progressive/recurrent disease, while 14/116 (12.1%) were deemed to have been stable disease and therefore assigned as true pseudoprogression. A post hoc analysis indicated that leptomeningeal spread and evolution of distant lesions would further bring down the number of true pseudoprogression cases to 10/116 (8.6%). No confirmed cases of pseudoresponse were identified in this study cohort.

DISCUSSION

The HERBY study is one of the largest Phase II, open-label, randomized, international pediatric high-grade glioma trials that has been undertaken. The primary end point was to evaluate whether the addition of BEV to RT/TMZ would significantly increase the event-free survival (as determined by radiologic evaluation of the imaging by a panel of 5 experienced pediatric neuroradiologists who formed the CRRC) in children with newly diagnosed non-brain stem high-grade gliomas. Structural imaging was analyzed by the CRRC using the now-established adult-based RANO criteria³ and subsequently re-evaluated alongside multimodal imaging⁵ with the prespecified aim to evaluate these criteria in the pediatric age group. While the quality of the structural imaging was generally high, the number of cases with consistently acquired multimodal imaging was relatively low and of variable quality, reflecting the reality of clinical practice in a wide range of centers

investigating and managing children with these tumors. The number of cases with evaluable MR spectroscopy was too low to allow valid inclusion in this process. In addition, the European Medicines Agency only required that diffusion-weighted imaging and perfusion imaging be used for this study. The poor compliance rates for the multimodal imaging arm of the study reflected the overestimation of local site capability/commitment for acquiring these sequences (particularly the case for MR spectroscopy).

Lack of preoperative imaging availability largely related to cases in which children were initially investigated in a nonspecialist hospital and subsequently transferred to the local primary treatment center without electronic transfer of the imaging to the clinical research organization of the study. The pretreatment imaging characteristics of the tumor provide important correlative information for the pathologic and, increasingly, molecular evaluation of the tumor type and in the future may help in individualizing treatment. Thus, inclusion of preoperative imaging should be considered a prerequisite for any future such studies.

Lack of adherence to the study imaging protocol was a concern for this trial, as has been the case for previous multicenter studies. Adoption, at a national level, of standardized imaging protocols that have been proposed in both North America⁶ and Europe⁷ and electronic dissemination of trial-specific scanner protocols using these agreed sequences offer the potential for ensuring consistent high-quality imaging, reducing the variability of response assessment and improving the validity and comparability of research in this field.

The logistics of undertaking independent analysis of imaging within a large treatment trial must be taken into consideration in the study design. After an initial training period, all 5 CRRC neuroradiologists undertook the study reads, working independently with a trial monitor. Each read required, on average, 15 minutes per time point. In the HERBY study, this involved a range of read times from 0.5 to 3.8 hours per patient, with an average of 1.3 hours per radiologist per patient. Read times for trials involving more imaging time points could be significantly higher. The early progression review was instituted to support local investigators who may value advice on imaging features. This was found to be a useful resource in 19 of 121 cases (16%) and could be considered in future study designs.

The EFS was assigned earlier by the CRRC than by local investigators on average by 1 month. This is shorter but similar to findings in adult trials (2–3 months).^{8,9}

Measured lesion diameters were never the unique reason for determining a radiologic event on their own and were always accompanied by unequivocal progression of either a nontarget lesion or the appearance of a new lesion. There were some cases (7%) in which the same patient was scanned with a different magnetic strength scanner near the point of progression. Although this could subtly affect the enhancement pattern, we believe the variability of these effects would be far less than the interobserver variability associated with drawing postoperative ROIs around poorly defined lesions and the related diameter measurements. In addition, even if there were subtle differences in radiologic interpretation due to changes in scanner magnetic field strength, because we found that change in lesion diameter was never the unique reason for assigning progression, the field strength change

would not influence the assignment of progression. Lesion diameter measurements account for a large proportion of the reading time; however, we found that they did not influence the final response-assessment decision in this trial. Volumetric evaluation of tumor size was not part of the initial trial methodology but will be evaluated in subsequent imaging analysis of the HERBY cohort.

The addition of MM imaging to the response criteria only modified the assessment in a small number of cases, and in most of these cases, progression was determined earlier than by the assessment of structural imaging alone. The acquired rates of MM imaging were lower than indicated by the initial site survey responses. Diffusion was the most commonly acquired technique, which was also the technique that most influenced the modified response assessment. Unfortunately, due to the inconstant provision of diffusion and perfusion data, we cannot validate the pathway used in HERBY for incorporating diffusion and perfusion assessment into the final radiologic response.⁵ However, the relatively low acquisition of diffusion and perfusion in practice across the contributing sites is, in itself, an important finding. In addition, in the cases in which multimodal imaging was provided, the observation that it modified the radiologic response of that imaging time point in only a small number of cases is also of note.

Imaging assessment of postsurgical and subsequent treatment surveillance in pediatric high-grade gliomas is challenging in view of the heterogeneous and poorly enhancing imaging characteristics of these tumors. This challenge can be further confounded by pseudoprogression (a local inflammatory reaction after RT and TMZ, resulting in increased enhancement in the early post-radiation therapy imaging, followed by radiologic improvement without therapy modification) and pseudoresponse. Interobserver variability in determining the date of progression can be as high as 40%–50%,¹ and a similar figure was observed in this study. No confirmed cases of pseudoresponse were identified in the HERBY study. Potential pseudoprogression, occurring within 12 weeks of initiation of treatment, was present in 33/116 cases. Of these 33 cases, 23 showed imaging features of continued tumor growth or development of distant lesions and were therefore subsequently re-assigned as progressive/recurrent disease. In the remaining 10/116 (8.6%) cases, follow-up imaging showed that the tumor had stabilized or regressed; therefore, the previous time point was maintained as pseudoprogression. This differs from the proportion of pseudoprogression generally reported in adult HGG studies: 31%¹⁰ and 48%,¹¹ though the AVAglio study reported only 6%.⁹ The greater biologic variation of these tumors in children, with a higher proportion of centrally located thalamic tumors and a higher proportion of poorly or nonenhancing tumors, may, in part, explain this contrast with adult HGG cases.

The protocol for HERBY was approved in 2011 and incorporated contemporary radiologic evaluation to assess the response, as reported here. Since then, a number of groups have suggested modifications and improvements to the RANO criteria^{12–15} and its implementation in clinical trials. Reardon et al¹⁶ provided guidance on incorporating imaging criteria into glioblastoma clinical trials and identifying a number of the issues also found in the HERBY trial, as well as highlighting the need to pay attention to early progression and early response, as implemented in

HERBY. Ellingson et al¹⁷ proposed modifications to the imaging protocol used for RANO, especially focusing on 3D MR imaging acquisitions and the volumetric parameters that can be calculated from them, as well as the promise of using subtractions maps of post- and precontrast imaging to increase lesion conspicuity. These are incorporated into more detailed proposed response assessments. While this article focuses on reporting results from the HERBY trial as performed, the newer proposed assessments can also be applied retrospectively to the HERBY imaging data, which may better characterize the imaging assessment. In addition to these modified and more quantitative metrics derivable from structural MR imaging, other quantitative metrics can be extracted from the multimodal imaging,^{12,18–23} building on the qualitative radiologic assessment performed here,⁵ to inform on their value in pediatric response assessment. This will form the basis for ongoing evaluation of data from the HERBY study.

CONCLUSIONS

This work evaluated the practical implementation of the use of RANO and RANO plus multimodal imaging to inform the end point of a large multinational trial of high-grade brain tumors in a pediatric cohort. Thus, the results reported provide an indication for future studies on practical issues. These include the following:

- Appropriate radiologic resources needed to implement RANO (1.3 hours per radiologist per patient).
- The expected compliance to the MR imaging protocol, which could be improved by incorporating radiology-specific site initiation to include evidence of imaging compliance in advance of opening the site.
- Adjudication rates (of approximately 50%).
- The variability of the RANO criteria when comparing retrospective central assessment with that performed locally (earlier event identification by an average of 1 month).

Of note, the finding that no assessment of progression or recurrence was dependent on the evaluation of the lesion diameters alone has implications in the use of this particular quantitative metric. In addition, the effect of implementing a new proposed pathway for incorporating multimodal imaging assessment into the structural RANO⁵ criteria was assessed and was found to indicate earlier progression or recurrence (by an average of 95 days) in only 5/86 cases. These findings will inform the development of future radiology-focused response-assessment criteria in pediatric high-grade gliomas, in particular that the measurement of tumor diameters and compliance of diffusion or perfusion are not of primary importance, because we found that simple metrics derived from these made little difference in the determination of the time point of radiology-defined progression.

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REFERENCES

1. Provenzale JM, Ison C, DeLong D. **Bidimensional measurements in brain tumors: assessment of interobserver variability.** *Am J Roentgenol.* 2009;193:W515–22 [CrossRef Medline](#)
2. Grill J, Massimino M, Bouffet E, et al. **Phase II, open-label, randomized, multicenter trial (HERBY) of bevacizumab in pediatric patients with newly diagnosed high-grade glioma.** *J Clin Oncol* 2018; 36:951–58 [CrossRef Medline](#)
3. Wen PY, Macdonald DD, Reardon DA, et al. **Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group.** *J Clin Oncol* 2010;28:1963–72 [CrossRef Medline](#)
4. Chinot OL, Macdonald DR, Abrey LE, et al. **Response assessment criteria for glioblastoma: practical adaptation and implementation in clinical trials of antiangiogenic therapy.** *Curr Neurol Neurosci Rep* 2013;13:347 [CrossRef Medline](#)
5. Jaspan T, Morgan PS, Warmuth-Metz M, et al. **Response assessment in pediatric neuro-oncology: implementation and expansion of the RANO criteria in a randomized Phase II trial of pediatric patients with newly diagnosed high-grade gliomas.** *AJNR Am J Neuroradiol* 2016;37:1581–87 [CrossRef Medline](#)
6. Ellingson BM, Bendszus M, Boxerman J, et al; Jumpstarting Brain Tumor Drug Development Coalition Imaging Standardization Steering Committee. **Consensus recommendations for a standardized brain tumor imaging protocol in clinical trials.** *Neuro Oncol* 2015; 17:1188–98 [CrossRef Medline](#)
7. Manias KA, Gill SK, Macpherson L, et al. **Magnetic resonance imaging based functional imaging in paediatric oncology.** *Eur J Cancer* 2017;72:251–65 [CrossRef Medline](#)
8. Stupp R, Hegi ME, Gorlia T, et al; European Organisation for Research and Treatment of Cancer (EORTC), Canadian Brain Tumor Consortium, CENTRIC study team. **Cilengitide combined with standard treatment for patients with newly diagnosed glioblastoma**

- with methylated MGMT promoter (CENTRIC EORTC 26071-22072 study): a multicentre, randomised, open-label, Phase 3 trial. *Lancet Oncol* 2014;15:1100–08 [CrossRef Medline](#)
9. Chinot OL, Wick W, Mason W, et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. *N Engl J Med*. 2014; 370:709–22 [CrossRef Medline](#)
 10. Brandes AA, Franceschi E, Tosoni A, et al. MGMT promoter methylation status can predict the incidence and outcome of pseudoprogression after concomitant radiochemotherapy in newly diagnosed glioblastoma patients. *J Clin Oncol* 2008;26:2192–97 [CrossRef Medline](#)
 11. Nasseri M, Gahramanov S, Netto JP, et al. Evaluation of pseudoprogression in patients with glioblastoma multiforme using dynamic magnetic resonance imaging with ferumoxytol calls RANO criteria into question. *Neuro Oncol* 2014;16:1146–54 [CrossRef Medline](#)
 12. Barajas RF Jr, Butowski NA, Phillips JJ, et al. The development of reduced diffusion following bevacizumab therapy identifies regions of recurrent disease in patients with high-grade glioma. *Acad Radiol* 2016;23:1073–82 [CrossRef Medline](#)
 13. Hyare H, Thust S, Rees J. Advanced MRI techniques in the monitoring of treatment of gliomas. *Curr Treat Options Neurol* 2017;19:11 [CrossRef Medline](#)
 14. Huang RY, Neagu MR, Reardon DA, et al. Pitfalls in the neuroimaging of glioblastoma in the era of antiangiogenic and immuno/targeted therapy: detecting illusive disease, defining response. *Front Neurol* 2015;6:33 [CrossRef Medline](#)
 15. Aquino D, Gioppo A, Finocchiaro G, et al. MRI in glioma immunotherapy: evidence, pitfalls, and perspectives. *J Immunol Res* 2017;2017:5813951 [CrossRef Medline](#)
 16. Reardon DA, Ballman KV, Buckner JC, et al. Impact of imaging measurements on response assessment in glioblastoma clinical trials. *Neuro Oncol* 2014;16:vii24–35 [CrossRef Medline](#)
 17. Ellingson BM, Wen PY, Cloughesy TF. Modified criteria for radiographic response assessment in glioblastoma clinical trials. *Neurotherapeutics* 2017;14:307–20 [CrossRef Medline](#)
 18. Boulton JR, Box G, Vinci M, et al. Evaluation of the response of intracranial xenografts to VEGF signaling inhibition using multiparametric MRI. *Neoplasia* 2017;19:684–94 [CrossRef Medline](#)
 19. Schmainda KM, Zhang Z, Prah M, et al. Dynamic susceptibility contrast MRI measures of relative cerebral blood volume as a prognostic marker for overall survival in recurrent glioblastoma: results from the ACRIN 6677/RTOG 0625 multicenter trial. *Neuro Oncol* 2015;17:1148–56 [CrossRef Medline](#)
 20. Ellingson BM, Kim E, Woodworth DC, et al. Diffusion MRI quality control and functional diffusion map results in ACRIN 6677/RTOG 0625: a multicenter, randomized, Phase II trial of bevacizumab and chemotherapy in recurrent glioblastoma. *Int J Oncol* 2015;46: 1883–92 [CrossRef Medline](#)
 21. Tensaouti F, Khalifa J, Lusque A, et al. Response Assessment in Neuro-Oncology criteria, contrast enhancement and perfusion MRI for assessing progression in glioblastoma. *Neuroradiology* 2017;59:1013–20 [CrossRef Medline](#)
 22. Singh R, Kesavabhotla K, Kishore SA, et al. Dynamic susceptibility contrast-enhanced MR perfusion imaging in assessing recurrent glioblastoma response to superselective intra-arterial bevacizumab therapy. *AJNR Am J Neuroradiol* 2016;37:1838–43 [CrossRef Medline](#)
 23. Nelson SJ. Assessment of therapeutic response and treatment planning for brain tumors using metabolic and physiological MRI. *NMR Biomed* 2011;24:734–49 [CrossRef Medline](#)

Underdevelopment of the Human Hippocampus in Callosal Agenesis: An In Vivo Fetal MRI Study

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ABSTRACT

BACKGROUND AND PURPOSE: In subjects with agenesis of the corpus callosum, a variety of structural brain alterations is already present during prenatal life. Quantification of these alterations in fetuses with associated brain or body malformations (corpus callosum agenesis and other related anomalies) and so-called isolated cases may help to optimize the challenging prognostic prenatal assessment of fetuses with corpus callosum agenesis. This fetal MR imaging study aimed to identify differences in the size of the prenatal hippocampus between subjects with isolated corpus callosum agenesis, corpus callosum agenesis and other related anomalies, and healthy controls.

MATERIALS AND METHODS: Eighty-five in utero fetal brain MR imaging scans, (20–35 gestational weeks) were postprocessed using a high-resolution algorithm. On the basis of multiplanar T2-TSE sequences, 3D isovoxel datasets were generated, and both hippocampi and the intracranial volume were segmented.

RESULTS: Hippocampal volumes increased linearly with gestational weeks in all 3 groups. One-way ANOVA demonstrated differences in hippocampal volumes between control and pathologic groups (isolated corpus callosum agenesis: left, $P = .02$; right, $P = .04$; corpus callosum agenesis and other related anomalies: $P < .001$). Differences among the pathologic groups were also present for both sides. Intracranial volume and right and left hippocampal volume ratios were different between corpus callosum agenesis cases and controls ($P < .001$). When we corrected for intracranial volume, no differences were found between corpus callosum agenesis and other associated anomalies and isolated corpus callosum agenesis (left, $P = .77$; right, $P = .84$). Hippocampal size differences were more pronounced at a later gestational age.

CONCLUSIONS: Callosal agenesis apparently interferes with the normal process of hippocampal formation and growth, resulting in underdevelopment, which could account for certain learning and memory deficits in individuals with agenesis of the corpus callosum in later life.

ABBREVIATIONS: aACC = corpus callosum agenesis and other associated anomalies; ACC = agenesis of the corpus callosum; GW = gestational weeks; HF = hippocampal formation; iACC = isolated agenesis of the corpus callosum; ICV = intracranial volume

As the largest of the human forebrain commissures, containing >190 million axons, the corpus callosum begins to develop

between 13 and 14 gestational weeks (GW) in the region of the ventral lamina reuniens and becomes fully mature at around 10 years of age.^{1,2} Many complex biologic processes are involved in its formation, such as birth and migration of commissural neurons, growth and elongation of their axons, crossing of the midline structures, synaptogenesis, and retraction of exuberant axons. Consequently, numerous human genetic disorders result in either complete or partial agenesis of the corpus callosum (ACC), which currently is the most common brain malformation and occurs in 1:4000 individuals.³ ACC is a very heterogeneous group of congenital malformations that can be found as isolated agenesis

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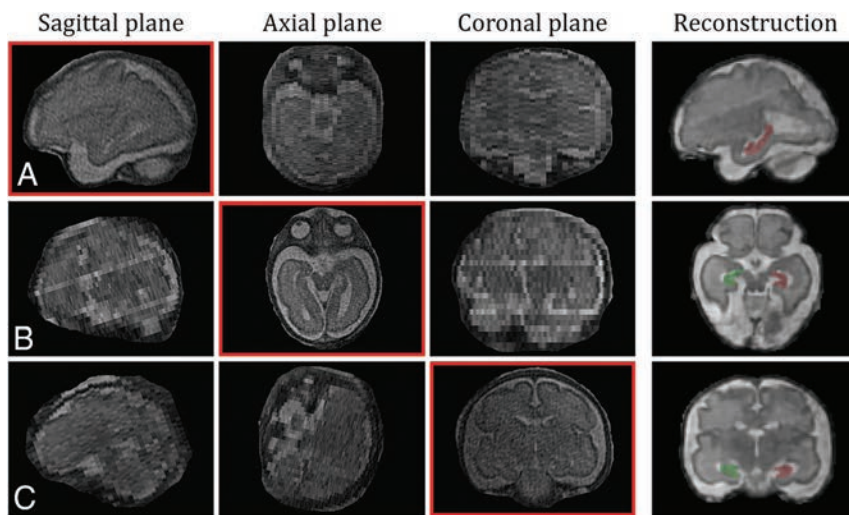


FIG 1. In vivo T2-weighted images of a control fetal brain, at 30 GW. An example of 3D-reconstructed MR imaging and segmentation borders for the left (red) and right (green) hippocampus in sagittal (A), axial (B), and coronal (C) views.

of the corpus callosum (iACC) or can be associated with other brain and body malformations (aACC). When associated with other comorbid features, ACC is part of a wide range of genetic and chromosomal anomalies, toxic syndromes, or metabolic diseases and, therefore, has a severe clinical presentation.⁴ On the contrary, individuals with iACC have a more favorable prognosis, with a normal range of intellectual functioning. They display a typical pattern of neuropsychological and psychosocial deficits, which include impaired verbal learning and memory.^{4,5} Several studies have indicated that the absence of callosal fibers during development might influence the maturational processes of other brain regions; this influence can lead, for example, to a reduction in cortical thickness in some brain regions.^{6,7}

Because the appearance and growth of callosal fibers coincide with the development of the human hippocampus, we hypothesized that ACC could, consequently, affect the proper formation of this structure, which is crucial for learning and memory functions.^{8–10} Therefore, in this retrospective MR imaging study, we aimed to determine the relationship between ACC and the development of the human hippocampal formation.

MATERIALS AND METHODS

Fetuses and MR Imaging

We retrospectively selected 85 fetal MR imaging datasets obtained from singleton pregnant women who underwent 1.5T fetal MR imaging examinations between January 2010 and March 2017, after a clinical indication for referral to the Department of Radiology, Medical University of Vienna. These women gave written, informed consent for a prenatal MR imaging study before the examination. The local ethics committee approved the study protocol (registration No. EK Nr. 2174/2016), and the research was conducted according to the principles expressed in the Declaration of Helsinki. All image data were pseudonymized before further analysis.

All MR imaging scans were re-reviewed by a pediatric neuro-radiologist (G.K.) with extensive experience in fetal MR imaging. Inclusion criteria for the entire cohort were the following: available multiplanar T2-TSE sequences, acquired on a 1.5T MR

imaging scanner (cardiac or body coil; Philips, Best, the Netherlands) in the left decubitus or supine position without sedation (orthogonal axial, coronal, and sagittal views; Fig 1) (TE = 140 ms, FOV = 200–250 mm, slice thickness = 3–4.4 mm, 0.7-mm in-plane resolution), and gestational age between 20 and 35 GW.

The inclusion criteria for the healthy reference cases were the following: normal central nervous system findings at screening sonography and MR imaging examinations, no known genetic or chromosomal diseases, and normal fetal growth (On-line Table 1). The inclusion criteria for the iACC group were the following: complete or partial absence of the corpus callosum, no known genetic abnormality (as detected by a chromosomal microarray), and no additional

body or brain malformation (as seen by screening sonography and/or fetal MR imaging) (On-line Table 2). The inclusion criteria for aACC were the following: complete or partial absence of the corpus callosum and additional body and/or brain malformation as detected by prenatal sonography and/or MR imaging (On-line Table 3). Cases with motion-degraded T2WI were excluded from further analysis (On-line Figure). Fetal age was calculated from the first day of the woman's last menstrual cycle (gestational weeks) and determined with reference to a previous sonographic examination.

Overall, 85 fetuses were retrospectively selected. The control group consisted of 39 fetuses with normal brain development, with gestational ages ranging between 20 and 35 GW (mean age, 28 ± 3.8 GW). Two groups with ACC comprised 31 cases with iACC, with a gestational age ranging between 22 and 34 GW (mean age, 28 ± 3.5 GW) and 15 cases with aACC, with a gestational age ranging between 21 and 32 GW (mean age, 26 ± 3.7 GW).

MR Imaging Postprocessing

Fiducials placed manually at the distal ends of the lateral ventricles served as the initialization for an atlas-based brain-masking procedure on each anisotropic scan. The side of the scan was determined on the basis of the location of the stomach.

Three anisotropic scans in approximately orthogonal views were merged using a slice-wise motion-correction procedure and were used to reconstruct a high-resolution isotropic representation of the fetal brain (Fig 1).¹¹ Automatic brain extraction was performed by nonlinear registration of a publicly available spatiotemporal atlas of fetal brain development¹² to the reconstructed isotropic volume.

Volume Measurement

One reader (V.K.) manually performed the segmentation of the hippocampal formation (HF) using ITK-SNAP, Version 3.6, software (www.itksnap.org).¹³ For this study, we defined the HF as a structure that includes the dentate gyrus, the cornu ammonis, the

subiculum, the fimbria, and the alveus (Fig 2). The anatomic borders used for segmentation of the fetal HF were based on prior studies^{14,15} and were traced from the anterior head to the posterior tail. The left HF was always segmented before the right. The segmentation protocol would start in the sagittal plane, followed by the axial, and then was confirmed in the coronal plane (Fig 1). Note that although the HF in this study comprised the dentate gyrus, the cornu ammonis, the fimbria, the alveus, and the subiculum, these structures were indistinguishable (or partly distinguishable) on fetal MR imaging and, thus, were roughly sampled as a whole complex.¹⁴ A few brains had recording artifacts on some sections where borders of the HF were difficult to recognize. In these cases, it was necessary to navigate and compare several sections, forward and backward, to identify the shape and position of the structures where the borders were clear.

We obtained intracranial volume (ICV) from labeling the tissue types in the fetal brain using an atlas-based approach, using successive rigid and nonrigid registrations to a publicly available spatiotemporal atlas of fetal brain development.¹² Available tissue segmentations in the atlas space were projected onto the individual case and served as frame for a graph-based segmentation procedure.¹⁶ ICV was then computed as the sum of the volumes of the gray matter, white matter, thalamus, germinal matrix, brain stem, cerebellum, ventricles, and CSF.

Statistical Analysis

Statistical analysis was preformed using SPSS Statistics for Windows, Version 24.0 (IBM, Armonk, New York). Absolute volumes

(hippocampal volumes and ICV) are presented in cubic millimeters. Relative hippocampal volumes are ratios of the absolute hippocampal volume and ICV. Metric data are presented as mean $\pm$ SD and counts, and percentages were used for nominal data. To determine differences between the ACC and iACC groups, as well as among age groups, we used a 2-way ANOVA. Paired *t* tests were assessed to analyze the differences between the left and right hippocampal volumes. An intraclass correlation coefficient from repeated measurements of 18 randomly selected fetal brains, obtained 8 months later, was calculated as a measure of rater segmentation consistency. The level of significance was set at $\alpha = .05$.

RESULTS

Segmentation Reliability

An intraclass correlation coefficient was calculated from 18 repeated measurements (21.2%). The intraclass correlation coefficient for the left hippocampus was 0.953, and for the right, 0.906.

Volume Analysis

As shown in Fig 3, absolute volumes of the left and right hippocampus demonstrated an almost linear increase in the control group, the iACC group, and the aACC group. No significant differences between the left and right hippocampal volumes were present in the control group and the aACC group (Table). However, the iACC group showed a significant difference between the left and the right hippocampal volumes, with the right hippocampus having higher values (Table). One-way ANOVA analysis revealed significant differences between the absolute hippocampal volumes of the control and the pathologic groups. When we compared the means of the left and right hippocampal volumes between the control group and the iACC group, the *P* values were .02 and .04, and for the aACC group, the *P* value was <.001. Differences between the pathologic groups were also present for both sides (left, *P* = .005; right, *P* = .01). When comparing absolute ICV, there was no difference between the control group and the pathologic groups (iACC, *P* = .08; aACC *P* = .19). However, when we included the ratios of absolute left and right hippocam-

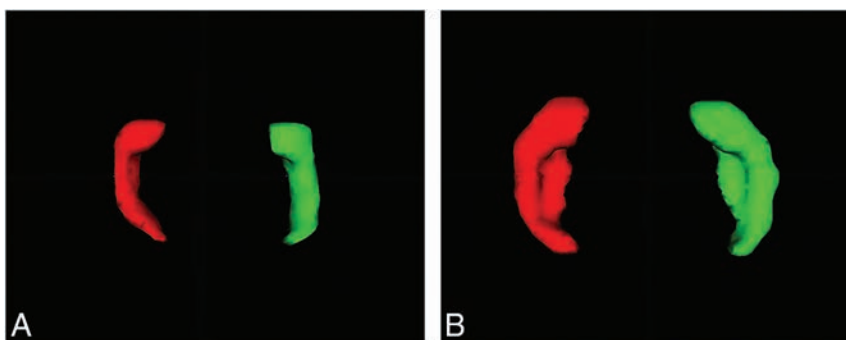


FIG 2. Axial view of a 3D surface model of the left (red) and right (green) hippocampus at 23 GW (A) and 30 GW (B).

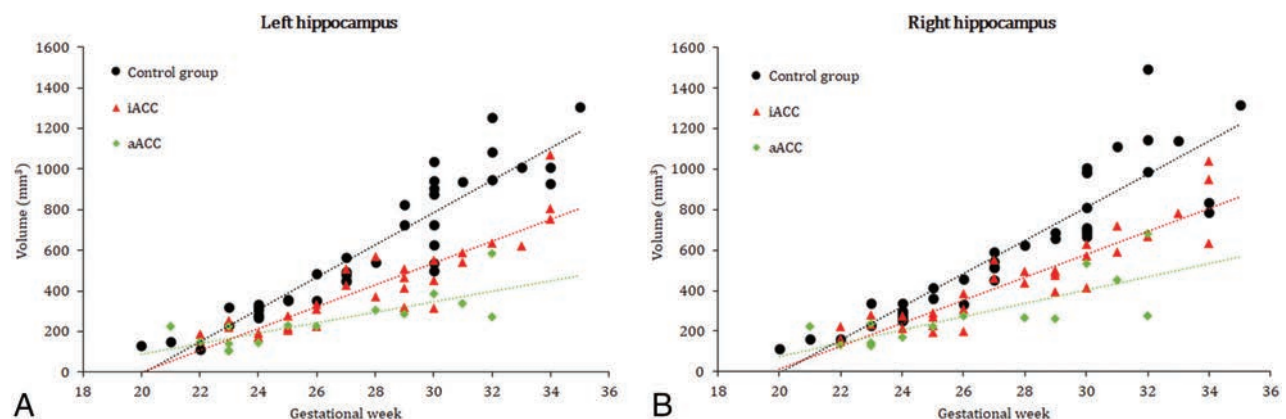


FIG 3. Scatterplots present absolute hippocampal volumes of controls, iACC, and aACC for the left (A) and right (B) hippocampus.

pal volumes and their ICVs in the analysis, we found a great difference between the control group and the pathologic groups ($P < .001$), while a comparison of the ratios of iACC and aACC did not show any differences (left, $P = .77$; right, $P = .84$).

To gain an even better insight into the extent of differences among our groups, we divided our data into 3 different time intervals: 20–25 GW, 26–30 GW, and 31–35 GW. Change of volume was significant, indicating that the difference among the 3 groups is not the same for different age groups. As can be seen

from Fig 4, the differences among groups increased with advancing age (Fig 4).

DISCUSSION

This quantitative prenatal neuroimaging study aimed to assess hippocampal development in human fetuses with complete and/or partial callosal agenesis. Compared with age-matched controls, there were reduced hippocampal volumes in both the iACC and aACC groups during the early second and third trimesters of pregnancy, suggesting the distinct impact of callosal formation on early hippocampal development.

Correlation of the Development of the Corpus Callosum and the Hippocampal Formation

The corpus callosum begins to develop between 13 and 14 GW in the region of the ventral lamina reunions and becomes fully mature at around 10 years of age.^{1,2} The first callosal fibers originate

Mean volumes of hippocampi and P values of left-right difference

Groups	Left Volume (mm ³)	SD	Right Volume (mm ³)	SD	P Value
	601.21	328.40	621.51	347.10	.180
iACC	416.23	216.20	454.58	223.80	.003
aACC	248.07	125.20	276.27	160.90	.070

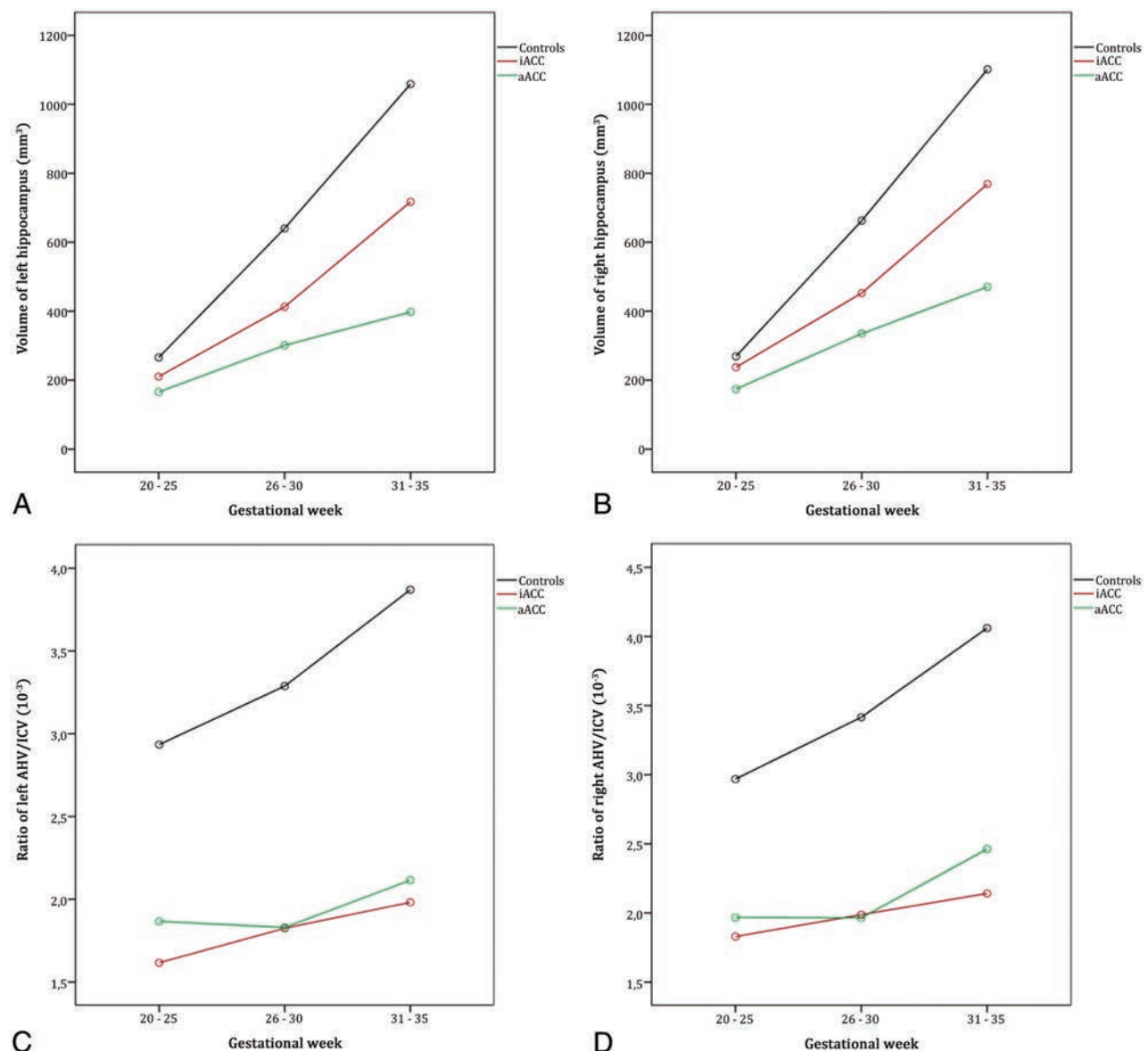


FIG 4. Moderation effects of age groups on volume group differences were found for the left (A) and right (B) hippocampal volumes but not for the ratios of absolute hippocampal volume and ICV (C and D).

from neurons located in the cingulate cortex, then cross the midline through the transient zone, known as the massa commissuralis, and grow toward the contralateral hemisphere, guided by many molecular factors and elaborate intercellular interactions.¹⁷⁻²³ These initial growing pioneer axons serve as “guideposts” for later-arriving axons, which have to decide at several decision points to travel in the proper direction.¹⁹ All parts of the adult corpus callosum (rostrum, splenium, truncus, and genu) are visible around 20 GW. Moreover, after 20 GW, the corpus callosum continues with active growth, as well as with intense reorganizational processes, until 31 GW, characterized by the retraction of an abundant portion of the callosal fibers.²⁴

The HF emerges around 10 GW in the dorsomedial region of the cerebral hemisphere in the dorsal part of the lamina reuniens.^{8,9} Between 10 and 14 GW, before the formation of the corpus callosum, the HF occupies most of the medial hemispheric wall.²⁵ However, around 14 GW, coincident with the emergence of the formation of the future corpus callosum, the supracallosal portion of the HF starts to display regressive changes.¹⁰ In adult vertebrates that lack a corpus callosum, the HF occupies a large portion of the medial surface, and the human HF manifests the same features until the outgrowth of the first callosal fibers. Between 14 and 15 GW, the HF starts to rotate as a result of the growth of surrounding brain structures, particularly the expansion of the corpus callosum. As an archicortical structure, the HF grows more rapidly than the surrounding neocortical regions.²⁶ Between 18 and 20 GW, the rotation of the HF is nearly complete, and by this time, the hippocampal morphology begins to resemble that in the adult. After this period, the HF grows more slowly than other neocortical regions.

Is reduced hippocampal volume directly caused by the ACC or is it a completely independent event? The absence of callosal fibers during development is frequently associated with various limbic system malformations²⁷ and an abnormal vertical orientation of the HF, and an arrest of the normal process of its inversion has been reported.^{28,29} In addition to its abnormal orientation, the HF appears to be hypoplastic in human patients lacking a corpus callosum.²⁹⁻³² According to animal studies, the axonal collaterals of developing hippocampal neurons serve as guideposts for callosal axons while crossing the midline structures on their way to the contralateral hemisphere.^{19,33} Hence, abnormal hippocampal development may indirectly influence the proper growth and elongation of callosal fibers.

The formation of the corpus callosum is a very complex process, and disruption of any of the multiple steps involved in its development, such as the generation and migration of callosal neurons, axon elongation, glial patterning at the midline, or synaptogenesis, could lead to partial or complete absence of this commissure. It may therefore be assumed that the different genes responsible for guiding all these processes overlap significantly with those that are important for hippocampal development. One of the genes known to be crucial for both hippocampal and corpus callosum development is *doublecortin*, a gene required for normal neural migration. In both knockout *doublecortin* mice and *doublecortin*-mutated human patients, severe abnormalities of both of these structures were found, indicating a potentially conserved role for *doublecortin* in hippocampal and callosal development.³⁴

Our data from control cases are in accordance with those in previous studies on fetal hippocampal development that demonstrate a linear increase in total hippocampal volume between 20 and 31 GW.^{14,15} It is known that the HF is the fastest growing brain structure until 20 GW, but after 30 GW, its development lags behind neocortical regions.¹⁰ Because we found an arrest of hippocampal growth in the second phase of this period in subjects with ACC, the question is whether this decrease of hippocampal volume found in subjects with ACC is a result of slowing of normal growth in this period, or is it possibly a consequence of accelerated regressive changes? Thus, it is particularly difficult to decide whether the poorly formed hippocampus results from hypoplasia or from atrophy. Hypoplasia is defined as underdevelopment of an organ or tissue. Extending postnatal observations,²⁹⁻³² we were able to demonstrate that the fetal hippocampus in cases of callosal agenesis mostly does not reach an age-appropriate size, even during prenatal life. Thus, the term “underdevelopment” or “hypoplasia” was used to describe the reduction in volume of this archicortical brain structure. Decreased size and connectivity of the cingulum have also been reported in ACC.³⁵ Thus, as previously assumed,³⁰ size differences and positional changes of the hippocampus in ACC may be a consequence of changes in the paralimbic cortices.

To our knowledge, there are no dedicated histologic analyses of the HF in fetal ACC. To ultimately clarify this point, histologic studies on postmortem human brain tissue have to be performed in the future, which will be able to precisely demonstrate possible changes in cellular and extracellular components in the HF in cases of ACC.

Finally, a certain limitation of this study is lack of postnatal or postmortem confirmation of prenatal findings in most of the ACC cases and healthy controls.

CONCLUSIONS

Our study suggests a relationship between abnormal commissural development and development of the human HF at prenatal stages of human life. In fetuses with ACC, the HF follows an abnormal anatomic developmental trajectory compared with healthy subjects, which ultimately results in an underdeveloped and smaller brain structure. The clinical impact of hippocampal underdevelopment on postnatal cognitive function in learning and memory-processing domains must be assessed by future postnatal follow-up studies.

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REFERENCES

1. Rakic P, Yakovlev PI. Development of the corpus callosum and caudum septi in man. *J Comp Neurol* 1968;132:45–72 CrossRef Medline
2. Giedd JN, Blumenthal J, Jeffries NO, et al. Development of the human corpus callosum during childhood and adolescence: a longitudinal MRI study. *Prog Neuropsychopharmacol Biol Psychiatry* 1999; 23:571–88 CrossRef Medline
3. Paul LK, Brown WS, Adolphs R, et al. Agenesis of the corpus

- callosum: genetic, developmental and functional aspects of connectivity.** *Nat Rev Neurosci* 2007;8:287–99 [CrossRef Medline](#)
4. Paul LK, Erickson RL, Hartman J, et al. **Learning and memory in individuals with agenesis of the corpus callosum.** *Neuropsychologia* 2016;86:183–92 [CrossRef Medline](#)
 5. Erickson RL, Paul LK, Brown WS. **Verbal learning and memory in agenesis of the corpus callosum.** *Neuropsychologia* 2014;60:121–30 [CrossRef Medline](#)
 6. Abreu-Villaça Y, Silva WC, Manhães AC, et al. **The effect of corpus callosum agenesis on neocortical thickness and neuronal density of BALB/cCF mice.** *Brain Res Bull* 2002;58:411–16 [CrossRef Medline](#)
 7. Beaulé V, Tremblay S, Lafleur LP, et al. **Cortical thickness in adults with agenesis of the corpus callosum.** *Neuropsychologia* 2015;77:359–65 [CrossRef Medline](#)
 8. Arnold SE, Trojanowski JQ. **Human fetal hippocampal development, II: the neuronal cytoskeleton.** *J Comp Neurol* 1996;367:293–307 [CrossRef Medline](#)
 9. Arnold SE, Trojanowski JQ. **Human fetal hippocampal development, I: cytoarchitecture, myeloarchitecture, and neuronal morphologic features.** *J Comp Neurol* 1996;367:274–92 [CrossRef Medline](#)
 10. Kier EL, Fulbright RK, Bronen RA. **Limbic lobe embryology and anatomy: dissection and MR of the medial surface of the fetal cerebral hemisphere.** *AJNR Am J Neuroradiol* 1995;16:1847–53 [Medline](#)
 11. Rousseau F, Oubel E, Pontabry J, et al. **BTK: an open-source toolkit for fetal brain MR image processing.** *Comput Methods Programs Biomed* 2013;109:65–73 [CrossRef Medline](#)
 12. Serag A, Aljabar P, Ball G, et al. **Construction of a consistent high-definition spatio-temporal atlas of the developing brain using adaptive kernel regression.** *Neuroimage* 2012;59:2255–65 [CrossRef Medline](#)
 13. Yushkevich PA, Piven J, Hazlett HC, et al. **User-guided 3D active contour segmentation of anatomical structures: significantly improved efficiency and reliability.** *Neuroimage* 2006;31:1116–28 [CrossRef Medline](#)
 14. Ge X, Shi Y, Li J, et al. **Development of the human fetal hippocampal formation during early second trimester.** *Neuroimage* 2015;119:33–43 [CrossRef Medline](#)
 15. Jacob FD, Habas PA, Kim K, et al. **Fetal hippocampal development: analysis by magnetic resonance imaging volumetry.** *Pediatr Res* 2011;69(5 Pt 1):425–29 [CrossRef Medline](#)
 16. Makropoulos A, Aljabar P, Wright R, et al. **Regional growth and atlasing of the developing human brain.** *Neuroimage* 2016;125:456–78 [CrossRef Medline](#)
 17. Rash BG, Richards LJ. **A role for cingulate pioneering axons in the development of the corpus callosum.** *J Comp Neurol* 2001;434:147–57 [CrossRef Medline](#)
 18. Richards LJ. **Axonal pathfinding mechanisms at the cortical midline and in the development of the corpus callosum.** *Braz J Med Biol Res* 2002;35:1431–39 [CrossRef Medline](#)
 19. Richards LJ, Plachez C, Ren T. **Mechanisms regulating the development of the corpus callosum and its agenesis in mouse and human.** *Clin Genet* 2004;66:276–89 [CrossRef Medline](#)
 20. Unni DK, Piper M, Moldrich RX, et al. **Multiple Slits regulate the development of midline glial populations and the corpus callosum.** *Dev Biol* 2012;365:36–49 [CrossRef Medline](#)
 21. Srivatsa S, Parthasarathy S, Britanova O, et al. **Unc5C and DCC act downstream of Ctip2 and Satb2 and contribute to corpus callosum formation.** *Nat Commun* 2014;5:3708 [CrossRef Medline](#)
 22. Shu T, Richards LJ. **Cortical axon guidance by the glial wedge during the development of the corpus callosum.** *J Neurosci* 2001;21:2749–58 [CrossRef Medline](#)
 23. Fothergill T, Donahoo AL, Douglass A, et al. **Netrin-DCC signaling regulates corpus callosum formation through attraction of pioneering axons and by modulating Slit2-mediated repulsion.** *Cereb Cortex* 2014;24:1138–51 [CrossRef Medline](#)
 24. Innocenti GM, Price DJ. **Exuberance in the development of cortical networks.** *Nat Rev Neurosci* 2005;6:955–65 [CrossRef Medline](#)
 25. Humphrey T. **The development of the human hippocampal formation correlated with some aspects of its phylogenetic history.** *Evolution of the Forebrain* 1966:104–06 https://link.springer.com/chapter/10.1007/978-1-4899-6527-1_11
 26. Kostović I, Seress L, Mrzljak L, et al. **Early onset of synapse formation in the human hippocampus: a correlation with Nissl-Golgi architectonics in 15- and 16.5-week-old fetuses.** *Neuroscience* 1989;30:105–16 [CrossRef Medline](#)
 27. Atlas SW, Zimmerman RA, Bilaniuk LT, et al. **Corpus callosum and limbic system: neuroanatomic MR evaluation of developmental anomalies.** *Radiology* 1986;160:355–62 [CrossRef Medline](#)
 28. Magee KR, Olson RN. **The effect of absence of the corpus callosum on the position of the hippocampus and on the formation of Probst's bundle.** *J Comp Neurol* 1961;117:371–82 [CrossRef Medline](#)
 29. Sato N, Hatakeyama S, Shimizu N, et al. **MR evaluation of the hippocampus in patients with congenital malformations of the brain.** *AJNR Am J Neuroradiol* 2001;22:389–93 [Medline](#)
 30. Baker LL, Barkovich AJ. **The large temporal horn: MR analysis in developmental brain anomalies versus hydrocephalus.** *AJNR Am J Neuroradiol* 1992;13:115–22 [Medline](#)
 31. Küker W, Mayrhofer H, Mader I, et al. **Malformations of the midline commissures: MRI findings in different forms of callosal dysgenesis.** *Eur Radiol* 2003;13:598–604 [Medline](#)
 32. Donmez FY, Yildirim M, Erkek N, et al. **Hippocampal abnormalities associated with various congenital malformations.** *Childs Nerv Syst* 2009;25:933–39 [CrossRef Medline](#)
 33. Bohlen MO, Bailoo JD, Jordan RL, et al. **Hippocampal commissure defects in crosses of four inbred mouse strains with absent corpus callosum.** *Genes Brain Behav* 2012;11:757–66 [CrossRef Medline](#)
 34. Kappeler C, Dhenain M, Phan Dinh Tuy F, et al. **Magnetic resonance imaging and histological studies of corpus callosal and hippocampal abnormalities linked to doublecortin deficiency.** *J Comp Neurol* 2007;500:239–54 [CrossRef Medline](#)
 35. Nakata Y, Barkovich AJ, Wahl M, et al. **Diffusion abnormalities and reduced volume of the ventral cingulum bundle in agenesis of the corpus callosum: a 3T imaging study.** *AJNR Am J Neuroradiol* 2009;30:1142–48 [CrossRef Medline](#)

Celebrating 35 Years of the AJNR

March 1984 edition

MR Imaging of Pituitary Adenomas Using a Prototype Resistive Magnet: Preliminary Assessment

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Magnetic resonance (MR) images were obtained with a prototype resistive magnet system in 10 patients, all of whom had been shown to have pituitary tumors by enhanced high-resolution computed tomography (CT). Histologic verification was obtained in eight cases. Inversion-recovery (IR) T1-weighted images revealed the tumor in six of nine cases; saturation-recovery (SR) images with less T1 weighting identified seven of nine tumors; Carr-Purcell-Meiboom-Gill (CPMG) spin-echo T2-weighted images revealed two of four tumors. MR images failed to demonstrate three microadenomas: 5 × 5 × 5 mm, 6 × 6 × 6 mm, and one less than 5 mm in estimated size. In the last pretreatment study, CT had demonstrated a 13 mm maximum diameter adenoma. Repeat CT at the time of MR imaging also showed a partially empty sella and did not resolve the residual adenoma. The larger adenomas were identified readily by MR imaging, which, unlike CT, suggested old tumor hemorrhage in two cases, which was confirmed at surgery and histologic examination. MR and CT images were also compared for relative effectiveness in identifying important peritumoral structures.

The introduction of computed tomography (CT) has revolutionized the imaging of intracranial neoplasms. High-resolution CT has been shown to have high sensitivity in detecting pituitary tumors and represents the standard against which any new imaging method must be measured. Previous publications dealing with magnetic resonance (MR) imaging of intracranial lesions have generally included examples of a wide variety of pathologic conditions [1-9]. To date, none have dealt exclusively with a series of cases of a single tumor type. Very few MR images of pituitary adenomas or apparently normal pituitary glands have been presented [4, 7, 10-12]. Our study represents an evaluation of MR imaging in a consecutive series of 10 patients with pituitary adenomas, using a prototype resistive magnet MR system. Effectiveness of MR imaging was compared with that of CT.

CT is dependent for image contrast upon variations of x-ray attenuation, produced largely by variations in electron density of tissues. Further, detection and evaluation of pituitary adenomas require the use of intravenous contrast enhancement and, occasionally, intrathecal contrast methods. Proton (¹H) MR imaging exploits the interactions of static and dynamic magnetic fields, radiofrequency (RF) energy, and hydrogen nuclei, yielding information about proton density and the local physicochemical environment of protons, to the extent that this can be inferred from the relaxation time constants T1 (spin-lattice) and T2 (spin-spin). While proton density variations between different soft tissues are rather small, it has been shown that variations in the T1 and T2 relaxation times between normal and abnormal tissues are frequently very large. Suitable choices of RF pulse sequences to optimize these differences result in images with high tissue contrast (up to several hundred percent).

Subjects and Methods

Ten patients with pituitary adenomas were studied (table 1). Before MR imaging, each



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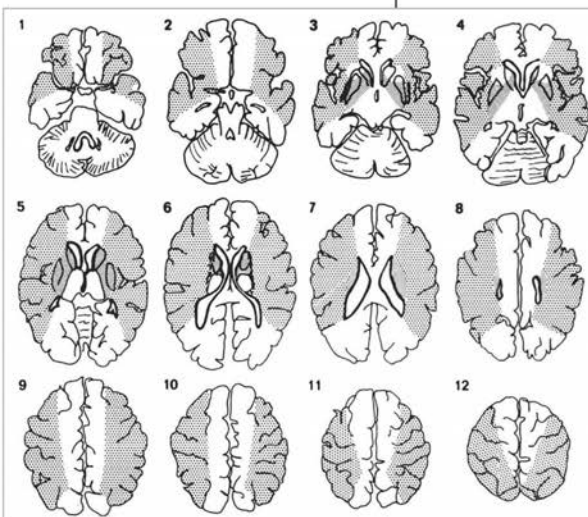
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Correlation of CT Cerebral Vascular Territories with Function: 3. Middle Cerebral Artery

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Schematic displays are presented of the cerebral territories supplied by branches of the middle cerebral artery as they would appear on axial and coronal computed tomographic (CT) scan sections. Comparison diagrams of regional cortical function and a discussion of the fiber tracts are provided to simplify correlation of clinical deficits with coronal and axial CT abnormalities.



This report is the third in a series designed to correlate cerebral vascular territories and functional anatomy in a form directly applicable to computed tomography (CT). The illustrations are intended to simplify analysis of CT images in terms of clinical signs and symptoms and vascular territories in everyday practice. The anterior and posterior cerebral arteries have been described [1, 2]. This report deals with the middle cerebral arterial territory.

Knowledge of cerebral vascular territories can help in differentiating between infarction and other pathologic processes. For example, if the position and extent of a lesion and the usual position and extent of a vascular territory are incongruous, infarction should receive relatively low diagnostic priority and vice versa. Knowledge of vascular territories can also facilitate correct interpretation of cerebral angiograms by pinpointing specific vessels for particularly close attention.

Knowledge of functional neuroanatomy applied to a patient's clinical findings can improve detection of subtle lesions by pinpointing specific areas for special attention on CT and specific vessels for attention on angiograms.

Discussion

The largest area of the brain that is normally supplied by the vessel(s) of the middle cerebral territory is indicated in figures 1 and 2. An occlusion of the middle cerebral artery will rarely produce a CT lesion larger than that defined in these illustrations. In fact, collateral supply, which often interfaces at the periphery of an infarction, may cause the area of involvement to be smaller than that schematically defined. Furthermore, the area of involvement may have a patchy appearance because only selected branches within the territory are occluded by emboli or fall victim to failure of collateral circulation. Very rarely occlusion may result in infarction of an area that is larger than the territory ascribed to it in figures 1-3. In these cases the territory supplied by the infarcted vessel has "extended" via collateral vessels into adjacent territory(s), the natural supply of which has previously been compromised. Thus when the rescuing vessel is compromised, territory outside the usual vascular limit is also compromised.

The vascular territory generally supplied by the middle cerebral artery and the neurologic functions ascribed thereto are mapped on schematic axial and coronal

Robert H. Ackerman, MD, MPH (1935–2018)

Robert Harold Ackerman, MD, MPH, Emeritus Director of the Massachusetts General Hospital Neurovascular Laboratory and Associate Professor at Harvard Medical School, died on December 18 at 83 years of age after a long and productive career in the Departments of Neurology and Radiology. He was a pioneer in stroke imaging and prevention, who devoted his professional life to studying blood flow to the brain for the diagnosis and treatment of stroke and stroke-prone patients.

Bob grew up in New York City, attending Horace Mann School in Bronx-Riverdale. He received his BA degree from Brown University in 1957 and his MD degree from the University of Rochester in 1964. His immediate postcollege years—just at the start of the “Sputnik” era—were spent largely as a journalist in Great Britain; it was the subsequent “space race” however that, at least in part, sparked his enthusiasm for science. He interned at the Mary Imogene Bassett Hospital in Cooperstown, New York, and completed residencies in neurology (1970) and radiology (1975) at the Massachusetts General Hospital (MGH). Bob was unique in having earned Board Certification from both the American Boards of Radiology and Psychiatry and Neurology; he continued to practice clinically in these departments throughout his tenure at MGH.

Dr Ackerman trained under Drs C. Miller Fisher and Michael Moskowitz to become an international expert in the imaging evaluation of carotid disease and cerebral blood flow and metabolism; during his lengthy career he, in turn, served as a mentor to many of the leading stroke neurologists and neuroradiologists worldwide. He was an MGH Dalton Scholar at the Neurologic Institute Queen Square, London, from 1970 to 1971, where he studied cerebral blood flow techniques. In 1974, back at MGH, he founded the first consultative noninvasive neurovascular lab in the country. Since then, his research interests continued to focus on building a “diagnostic armamentarium” of noninvasive tools for the detection and management of patients with acute stroke or at risk of stroke.¹

From 1977 to 2009, Dr Ackerman served as Co-Principal Investigator with Dr Moskowitz on a National Institute of Neurological Disorders and Stroke-funded Interdepartmental Stroke Program Project Grant and was one of the first to image acute cerebral ischemia in vivo with positron-emission tomography. His seminal, highly cited 1981 article, “Positron Imaging in Ischemic Stroke Disease Using Compounds Labeled with Oxygen 15: Initial Results of Clinicophysiology Correlations,” reported alterations in brain tissue metabolism following stroke that are still highly relevant to current, novel “late window” (6–24 hours postonset) treatment trials.² He reported that in acute stroke, PET data on oxygen metabolism correlated better with tissue viability than data reflecting cerebral blood flow.

Dr Ackerman’s bibliography includes nearly 100 scientific publications on neurovascular disease. Bob helped develop and champion the use of extracranial and transcranial Doppler sonography as a safer, noninvasive alternative to conventional angiography for the diagnosis and monitoring of carotid artery stenosis.



FIG 1. Robert Ackerman.

He was also among the first to advance the “new” technology of head CT scanning—as an extension of the neurologic physical examination—when, in 1974, MGH installed what was then the second CT scanner in North America.

From July 1991 to June 1992, Dr Ackerman was selected as Distinguished Scientist in the Department of Radiologic Pathology at the Armed Forces Institute of Pathology, where he made important contributions to research and education.³ In 2013, he was honored at an MGH Ether Dome ceremony, where it was announced that the Neurovascular Laboratory would be renamed the R.H. Ackerman Neurovascular Lab; Ackerman served as its director until 2001, and subsequently as emeritus director.

The list of trainees and colleagues who rotated through Bob’s neurovascular lab reads like a “Who’s Who” of vascular neurology. Notables include but are not limited to “first ever” cerebral blood flow fellow Dr Jean-Claude Baron, followed closely by IV-tPA and Mobile Stroke Unit innovator Dr Jim Grotta—both members of the “original” MGH “stroke team”—as well as Dr Stephen Davis, Director of the Melbourne Brain Centre at the Royal Melbourne Hospital and Immediate Past President of the World Stroke Organization. Dr Ackerman mentored and helped advance the neurology-related careers of numerous other former neurovascular lab fellows, among them Dr Viken Babikian (Boston University Medical Center Vascular Diagnostic Lab), Dr Kevin Barrett (Mayo Clinic, Jacksonville), and Drs Shin, Romero, and Lev (all currently at MGH). Through his many collaborations



FIG 2. Javier Romero, Robert Ackerman, and Michael Lev.



FIG 3.



FIG 4. The “first-ever” MGH stroke team, from left to right and top to bottom: Goulamos (2nd CBF fellow), Nat Alpert, Jack Correia, Mrs Taveras, Prof Juan Taveras, Bob’s Doppler technician, Bob Ackerman, Jean Claude Baron (1st CBF fellow), Wang (physicist/IT engineer), John (2nd CBF technician on the PET stroke grant).

and during his several years leading the Boston Stroke Society, Bob remained a highly valued and respected member of the vascular neurology community and interacted closely with such luminaries as Drs C. Miller Fisher, Juan Taveras, Ken Davis, Jay P. Mohr, J. Philip Kistler, Louis Caplan, Geoffrey Donnan, Gordon Brownell, Carlos Kase, Walter Koroshetz, Ferdi Buonanno, Lee Schwamm, Gil Gonzalez, and Michael Pessin.⁴

Bob’s achievements and contributions were celebrated at a dinner he attended last October, hosted by MGH Neuroradiology Division Chief Dr R. Gil Gonzalez. In tributes posted this past week, his friends, patients, and fellow members of the Cambridge



FIG 5.

Rowing Club praised his thoughtful and caring nature, positive attitude and intellect, and skill and persistence in tracking down and treating the “causes of illness”; many remarked that Bob was a “true gentleman” who “took care of friends near and far,” and “always made me feel good.” Perhaps Dr Stephen Davis best summed up the feelings of all when he observed:

“He was a wonderful mentor and highly valued friend. He has contributed hugely to the developments in stroke diagnosis and treatment. He performed early seminal work on the imaging of ischemic penumbra at the Massachusetts General Hospital and Harvard University. He was a leader in the evaluation of carotid artery disease and its clinical significance. He has been a great teacher and mentor to many stroke neurologists. He was a renaissance man, a lover of literature and music. He will also be remembered for his enthusiasm for rowing and of course his beloved home in Gloucester. He will be sorely missed.”

Dr Ackerman will be remembered by friends, colleagues, and family as a devoted teacher, scholar, and mentor, as well as an avid rower who competed for decades in the Head of the Charles Regatta and a raconteur with a deep knowledge of medical history. His wit, wisdom, gentle humor, and keen insights will indeed be sorely missed by his patients and by all who knew him; his impact and legacy will continue.

REFERENCES

1. Ackerman RH. Neuroimaging looks to the future. *J Neurol Sci* 1995; 128:117–21 CrossRef Medline
2. Ackerman RH, Correia JA, Alpert NM, et al. Positron imaging in ischemic stroke disease using compounds labeled with oxygen 15: initial results of clinicophysiological correlations. *Arch Neurol* 1981;38: 537–43 CrossRef Medline
3. Buck JL. Robert H. Ackerman, MD, Distinguished Scientist, Department of Radiologic Pathology, Armed Forces Institute of Pathology. *Radiology* 1991;180:281 <https://doi.org/10.1148/radiology.180.1.281>. Accessed 23 December, 2018
4. Ackerman RH. Celebrating the life of C. Miller Fisher. *Int J Stroke* 2012;7:444–46 CrossRef Medline

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Engorged Medullary Veins in Neurosarcoidosis: A Reflection of Underlying Phlebitis?

We read with interest the recent article describing the engorgement of deep medullary veins (DMV) in patients with neurosarcoidosis (NS).¹ The findings of DMV engorgement on susceptibility-weighted imaging have also intrigued us, and we recently published our experience in such cases.² We agree with some of the findings reported in this article, such as occurrence of perivascular enhancement (PVE) in about half of these patients, increased occurrence of microhemorrhages, and a tendency toward worse neurologic outcomes. Even though the latter was not statistically significant, we suspect that it may, at least partially, be related to the small sample size.

Even though the authors mention that the DMV engorgement is not secondary to downstream venous occlusion, they agree that the pathophysiology of these findings remains unclear. This issue is further compounded by the absence of any correlation with neural tissue biopsy, conventional angiography studies, or any changes in DMV with time, especially with regard to immunosuppressive therapy, which limits any educated extrapolation or inference of the presented data.

We suspect that the engorged DMVs, as seen on SWI, reflect underlying venous phlebitis. This is based on the previously reported postmortem literature, which showed that the venous involvement was most common in the paraventricular region, and our own experience, in which we evaluated 4 patients with engorged DMVs.^{2,3} In all of our patients, we also had conventional angiography data as well as neural tissue biopsy. The venous phase of the angiographic studies confirmed the presence of tortuous and engorged veins, and the brain biopsy also found a predominant venous involvement.

Even though venous involvement in NS is fairly well-recognized in the postmortem literature, the under-recognition on imaging is likely due to lack of sequences such as SWI, which are more sensitive to tissue susceptibility. The introduction of SWI as a routine clinical sequence has more recently led to greater recognition of this imaging finding. In some ways, we wonder if SWI has provided the missing link that connects the postmortem literature and in vivo findings. Another reason for

our suspicion is based on our anecdotal experience with patients with NS, in which mild cases of engorged DMVs do improve when patients receive immunosuppressive therapy and also appear worse when patients present with NS flare. In patients in whom they have been present for a while, such fluctuations, however, tend to be less frequent, possibly secondary to irreversible injury. The presence of PVE in a similar distribution also supports the possibility that there is a superimposed component of perivascular inflammation. We agree with the authors that this may be a combination of engorged vessels and perivascular involvement. In fact, we recently performed vessel wall imaging in 1 such case and noted that the cortical veins did show circumferential enhancement, corresponding to the SWI findings, a likely reflection of underlying vascular inflammation.⁴

An interesting question here, if SWI does indeed reflect venous involvement, is whether SWI findings can be used as a surrogate biomarker for ongoing vascular inflammation in NS cases. Even though this is open to further research, on the basis of our experience with limited patients, we suspect that vessel wall imaging and SWI are reflecting different components of venous involvement. One, therefore, may not be substituted for the other, especially because the SWI findings may become irreversible in chronic cases. Nevertheless, the possibility that SWI findings likely reflect underlying NS-associated phlebitis does add a new dimension to the NS imaging spectrum. Even though a lack of any neural tissue banks in NS would preclude retrospective evaluation of imaging and postmortem data and the overall uncommon nature of NS would limit a prospective single-center study, the significance of SWI findings may be better clarified through multicenter pooling of cases in which neural biopsy and conventional angiography data are available.

REFERENCES

1. Zamora C, Hung SC, Tomingas C, et al. **Engorgement of deep medullary veins in neurosarcoidosis: a common-yet-underrecognized cerebrovascular finding on SWI.** *AJNR Am J Neuroradiol* 2018;39:2045–50 [CrossRef Medline](#)
2. Bathla G, Watal P, Gupta S, et al. **Cerebrovascular manifestations in neurosarcoidosis: how common are they and does perivascular**

enhancement matter? *Clin Radiol* 2018;73:907.e15–907.e23 CrossRef Medline

3. Bathla G, Watal P, Gupta S, et al. **Cerebrovascular manifestations of neurosarcoidosis: an underrecognized aspect of the imaging spectrum.** *AJNR Am J Neuroradiol* 2018;39:1194–1200 CrossRef Medline
4. Bathla G, Dandapat S, Soni N, et al. **Neuroimaging findings in intracranial sarcoid phlebitis: a case report.** *J Stroke Cerebrovasc Dis* 2019; 28:369–70 CrossRef Medline

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REPLY:

We thank Dr Bathla and colleagues for their comments and for sharing their experience with cerebrovascular findings in patients with neurosarcoidosis. Some of the figures in their recent article¹ show engorged and tortuous deep medullary veins that are similar to what we have described. We are glad to see that their study and ours share some common observations and agree that larger studies may be able to elucidate the clinical significance of this finding. As Dr Bathla and colleagues point out, it is reasonable to think that venous engorgement may be an effect of inflammation; however, we could not prove this in our study due to lack of histologic data. Their anecdotal experience of patients with

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mild engorgement showing improvement after therapy is also interesting. Although we do not have sufficient long-term data, the 5 cases that we could follow did not show any change in venous engorgement after treatment. This is something that could be explored in a future study.

REFERENCE

1. Bathla G, Watal P, Gupta S, et al. Cerebrovascular manifestations in neurosarcoidosis: how common are they and does perivascular enhancement matter? *Clin Radiol* 2018;73:907.e15–23 CrossRef Medline

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High-Resolution Vessel Wall MR Imaging as an Alternative to Brain Biopsy

We commend Zeiler et al¹ for their study entitled “Vessel Wall MRI for Targeting Biopsies of Intracranial Vasculitis,” recently published in *American Journal of Neuroradiology*, in which the authors tested the applicability of contrast-enhanced, high-resolution 3D vessel wall MR imaging for the detection of vascular inflammation and assistance with direct open biopsies of intracranial vessels and adjacent brain parenchyma. The authors concluded that this MR imaging technique could be used to identify inflamed intracranial vessels, enabling precise biopsy localization guidance.

Traditionally, biopsy is considered essential for a definitive diagnosis of central nervous system vasculitis and exclusion of similar-appearing conditions.² Given the invasiveness of biopsy, we believe there should be consideration of whether it may be replaced with high-resolution vessel wall MR imaging, especially in patients with secondary vasculitis. In this context, we present the case of a 37-year-old man with a history of headache, right hemiparesis, and reduced consciousness. He had no skin lesions. A 3T MR imaging study in this patient showed an acute stroke in the left nucleocapsular region and vasogenic edema in the brain parenchyma around the horizontal segment of the left middle cerebral artery. MR angiography showed no changes. High-resolution vessel wall imaging showed smooth and concentric wall thickening and enhancement of the left MCA. White blood cell and protein levels were elevated in the patient’s CSF. Polymerase chain reaction for Varicella zoster virus was positive in the CSF. The patient was treated for presumed Varicella zoster virus vasculitis with acyclovir and pulse therapy with corticosteroids. After the treatment, the patient recovered clinically with headache alleviation and an improvement in his level of consciousness. Posttreatment high-resolution vessel wall MR imaging showed a reduction in the arterial wall thickening and enhancement (Figure).

Brain biopsy retains an essential role in the diagnosis of CNS vasculitis and is the criterion standard for the diagnosis of primary CNS vasculitis. Some authors even recommend that a biopsy, including cortical and meningeal tissue, be performed in all sus-

picious cases if possible.² However, these articles were published when high-resolution vessel wall MR imaging was an emergent technique and larger studies examining it had yet to be reported. Since then, vessel wall imaging has become an important tool for evaluating vascular diseases and physicians are becoming increasingly familiar with changes revealed by this technique. Furthermore, an open cranium operation, even for a simple biopsy, has serious risks, including infection, skull fracture, and hemorrhage. Such complications can increase the morbidity and mortality risks, prolong postoperative recovery, and delay treatment. Avoiding an operation eliminates the risk of surgical complications and reduces the cost of care.

Similar to our patient, patient number 6 of Zeiler et al¹ had brain vasculitis secondary to Varicella zoster virus. However, we did not perform a biopsy to confirm the diagnosis in our patient. Other authors have also published cases of Varicella zoster brain vasculitis without brain biopsy data or with inconclusive biopsy results in which high-resolution intracranial vessel wall MR imaging was used to diagnose and track the treatment response.³ Although Obusez et al⁴ have seen inconsistent results in follow-up vessel wall imaging findings after treatment of primary CNS vasculitis, the potential role of this technique as a marker of treatment response in CNS vasculitis should continue to be investigated because there is a heterogeneity of disease activity and patient response to treatment. Also, there is a lack of longitudinal studies evaluating the role of this technique in tracking treatment response in secondary CNS vasculitis.

Hence, the growing clinical applicability of intracranial vessel wall imaging has contributed to making this technique part of a state-of-the-art MR imaging protocol for vascular disease diagnosis. Physicians should be aware that vessel wall imaging may be used to avoid invasive procedures such as brain biopsy and to track treatment response.

REFERENCES

1. Zeiler SR, Qiao Y, Pardo CA, et al. **Vessel wall MRI for targeting biopsies of intracranial vasculitis.** *AJNR Am J Neuroradiol* 2018;39:2034–36 CrossRef Medline

2. Dutra LA, de Souza AW, Grinberg-Dias G, et al. **Central nervous system vasculitis in adults: an update.** *Autoimmun Rev* 2017;16:123–31 CrossRef Medline
3. Mossa-Basha M, Alexander M, Gaddikeri S, et al. **Vessel wall imaging for intracranial vascular disease evaluation.** *J Neurointerv Surg* 2016; 8:1154–59 CrossRef Medline
4. Obusez EC, Hui F, Hajj-Ali RA, et al. **High-resolution MRI vessel wall imaging: spatial and temporal patterns of reversible cerebral vasoconstriction syndrome and central nervous system vasculitis.** *AJNR Am J Neuroradiol* 2014;35:1527–32 CrossRef Medline

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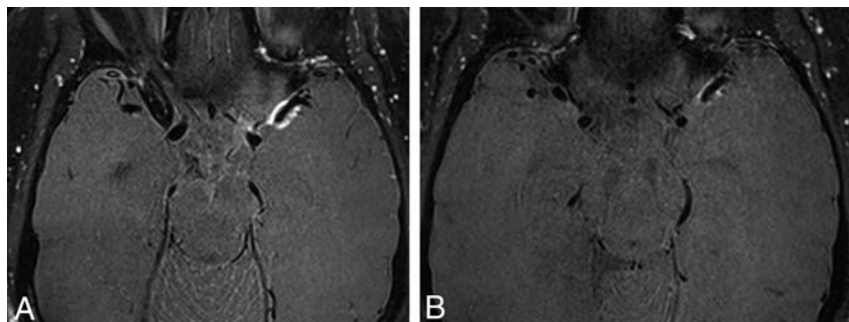


FIGURE. Brain vasculitis secondary to Varicella zoster virus infection. A, Intracranial vessel wall imaging after intravenous contrast injection revealing smooth, concentric arterial wall thickening and enhancement of the horizontal segment of the left MCA, compatible with inflammatory vasculopathy. B, Posttreatment intracranial vessel wall imaging shows diminished vessel wall thickening and enhancement.