MRI systematic biases due to site differences in MS

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BOOK REVIEWS  R.M. Quencer, Section Editor

Please visit www.ajnrblog.org to read and comment on Book Reviews.
Title: Echoes of (the) Sunset, 36” x 48” Oil on Canvas. This is an attempted abstraction of the beauty of the twilight hours, with dominance of oranges and reds. The colors melt into each other, a representation of the natural transition of time.

Anish Kapadia, Radiology Resident, University of Toronto, Toronto, Ontario, Canada
To tPA or Not to tPA, That Is the Question

T.M. Leslie-Mazwi, R.V. Chandra, and J.A. Hirsch

For decades, the acute treatment of stroke has centered on delivery of intravenous recombinant tissue plasminogen activator. Endovascular stroke therapy was historically dogged by a dearth of high-level evidence supporting its application. Refinements in imaging selection, improved treatment logistics, and increased reperfusion rates came together in 2015 with the publication of multiple randomized trials that changed that, unequivocally identifying the benefit of endovascular therapy combined with medical management over medical management alone for patients with proximal large vessel occlusions (LVO). With a number needed to treat of merely 2.6 to reduce disability (measured by the modified Rankin score), endovascular stroke therapy is now arguably one of the most effective treatments in medicine.6

Attention therefore turns to refinements and the remaining gaps in knowledge for this powerful therapy. This requires examination of every aspect of the care of patients with LVO. It is in this context that the role of IV tPA in patients with LVO undergoing endovascular therapy has come under scrutiny. Specifically, should IV tPA be administered at all?

The State of the Science

In the original 5 published randomized controlled trials (RCTs) demonstrating the superiority of endovascular therapy over medical management alone, IV tPA had no impact on the endovascular therapy results.1-5 Both the Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands (MR CLEAN)1 and Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours (REVASCAT)7 required IV tPA failure before randomization for endovascular treatment, selecting patients likely to do poorly with isolated medical management. However, the remaining 3 trials (Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke [ESCAPE], Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial [EXTEND-IA], and Solitaire With the Intention For Thrombectomy as PRIMary Endovascular Treatment for Acute Ischemic Stroke [SWIFT PRIME])2,3,5 were more selective and had no such requirement; 2 of these (EXTEND-IA and SWIFT PRIME) administered IV tPA to all participants. More recently the Trial and Cost Effectiveness Evaluation of Intra-Arterial Thrombectomy in Acute Ischemic Stroke [THRACE] trial, with wide inclusions, also reported similar findings: outcome was independent of IV tPA status.7

The HERMES meta-analysis aggregates these collective data at the individual patient level (excluding THRACE).6 For the endovascular cohort, 526/634 (83%) received tPA, compared with 87% of the control population. From the thrombectomy group, 108 patients were ineligible for IV tPA of 188 total. There was no treatment-effect heterogeneity across a range of prespecified variables; the administration of tPA caused neither benefit nor harm. The authors concluded that endovascular therapy should be pursued irrespective of tPA eligibility or status.

These are specific trial populations, and even in aggregate, there are reasons that generalizing to patients in everyday practice requires caution. However, several recent publications have explored this in typical clinical scenarios.

Weber et al8 retrospectively analyzed patients treated with combination therapy with IV tPA and thrombectomy (n = 105) compared to patients receiving thrombectomy alone (n = 145) during a 14-month period at a tertiary neurovascular center. Administration of IV tPA added a 36-minute delay in picture-to-puncture times. This finding is striking in an efficient, high-volume center. No significant differences existed in 90-day outcomes (modified Rankin Scale score, 0–2; 35.2% versus 40%; P = .444). Similarly, TICI 2b/3 (73.8% versus 73.1, P = .952) and symptomatic hemorrhage rates (5.9% versus 3.5%, P = .387) were equivalent.

A similar experience is reported during nearly 6 years in a high-volume stroke center.9 Like the groups in Weber et al,8 treatment decisions were individualized by the multidisciplinary treating team, excepting clear exclusions to IV tPA use. They reviewed 239 patients with anterior circulation stroke treated with mechanical thrombectomy alone and identified 40 IV tPA–eligible patients who were treated with thrombectomy alone. Multivariate matched-pairs analysis was used to compare these patients with controls treated with combination therapy. There were no significant differences in 90-day favorable outcome (mRS, 0–2; 42.5% versus 42.5%; P = 1.0), successful reperfusion (TICI 2b/3, 87.5% versus 77.5; P = .39), or symptomatic intracerebral hemorrhage (2.5% versus 2.5% P = 1.0). The patients who went directly to thrombectomy had lower rates of asymptomatic intracranial hemorrhage (12.5% versus 35%, P = .023) compared with those receiving bridging IV tPA.

Most recently, Coutinho et al10 published an analysis of 2 large prospective clinical trials, Solitaire FR Thrombectomy for Acute Recanalization (STAR) and Solitaire With the Intention for Thrombectomy (SWIFT), further questioning the role of IV tPA for patients with LVO eligible for thrombectomy.10 The authors analyzed 291 patients, 55% treated with combination therapy compared with thrombectomy alone. The groups were well-matched except that the baseline Alberta Stroke Program Early CT Score favored the combination therapy group (8 versus 9, P = .4). Outcomes between the 2 groups were the same at 90 days, as was symptomatic hemorrhage. Technical considerations were identical between groups, with no difference in clot fragmentation (measured by emboli to new territory). The authors concluded that IV tPA and thrombectomy offered no obvious benefit over thrombectomy alone.10
**IV tPA in Patients with LVO**

We have previously published on this topic, outlining the arguments both for and against IV tPA in this setting. IV tPA has distinct positives: It may produce recanalization without the need for mechanical thrombectomy. It may enhance the success of thrombectomy, by both making clot extraction easier and lysing smaller fragments that may embolize distally during the procedure. It may prevent microvascular thrombosis, maintaining cerebral perfusion distal to the occlusion. Finally, it offers a chance (albeit small) at recanalization for those patients who, for technical or logistic reasons, are unable to undergo mechanical thrombectomy or in whom this is delayed.

The arguments against the use of tPA are similarly varied. IV tPA has limited efficacy in the presence of large-volume clot, with an efficacy range of 8%–32%, depending on the occlusion level. Administration of tPA produces delays, both in the act of delivering the drug and tPA prioritization in the care delivery system. In comprehensive centers, thrombectomy may be accomplished before the tPA infusion has been completed. Moreover, the potential for hemorrhage in patients who receive IV tPA is difficult to ignore, despite the equivalent symptomatic hemorrhage rates in recent endovascular trials. At this stage, there is no clear clinical benefit or harm incurred by administering IV tPA. However, the routine use of IV tPA for patients with LVO does erode the overall health care value.

Both resource-intensive and expensive, endovascular stroke treatment makes an attractive target for organizations aiming to control expenditure. Maximizing value through cost-effectiveness and cost-utility, therefore, becomes a priority. One prominent question that remains to be answered in this new landscape of endovascular stroke therapy is about the most cost-effective method to deliver this care within our ever-more-constrained health care budget. Value is best viewed as the relationship between the cost of the treatment and outcome. In patients with LVO, this references overall expenditure (from onset to return to the community) weighted against the eventual patient outcome.

A recent cost-utility analysis using data with contemporary cost information found that combination therapy is approximately $17,000 more expensive than IV tPA alone in initial hospital costs. By 90 days, this difference had shrunken to $12,000 because of an average of $5000 saved in the combination therapy cohort through earlier hospital discharge and reduced rehabilitation costs. When lifetime projections were incorporated, however, mechanical thrombectomy was economically dominant, with substantial overall cost savings of more than $23,000 and both life-expectancy and quality-adjusted life expectancy gains. Effort to reduce the initial cost of thrombectomy treatment will further cement this economic dominance. The direct cost of IV tPA in the United States approximates $7000/100-mg vial. This reflects only the actual price of the drug and not the additional ancillary expenses of delivering it. This expense represents an area of potential savings for patients treated with combination therapy. Indeed, the questions may well be more nuanced than “Does tPA provide any value?” It may be more appropriate to ask, “In select patients, does IV tPA provide $7000 worth of value?”

A similar outcome at reduced cost improves value. Therefore, the concern that IV tPA adds little benefit to the patient with LVO should be evaluated in a randomized fashion. The RCT design would be pragmatic: direct to thrombectomy versus combination therapy in patients presenting early to centers with neuroendovascular capability. This would have important implications for future stroke treatment as episodic care, alternative payment, and physician-focused payment models grow increasingly important. Several trials have been proposed, and while published protocols are lacking, these trials are close to commencing.

The implications of a randomized trial proving that the addition of IV tPA carries no additional benefit for selected patients will be momentous. Resistance may be anticipated, but a well-designed trial would win over many in the stroke neurology community, overcoming the ethics of withholding a proved treatment. A particular concern will be to prevent undue interruption of current tPA delivery networks, which must be protected for the general stroke population. A randomized trial will raise these and more questions. The stroke community should embrace the opportunity.

**REFERENCES**

ischemic stroke: a pooled analysis of the SWIFT and STAR studies. JAMA Neurol 2017;74:268–74 CrossRef Medline
Dentate Update: Imaging Features of Entities That Affect the Dentate Nucleus

K.M. Bond, W. Brinjikji, L.J. Eckel, D.F. Kallmes, R.J. McDonald, and C.M. Carr

ABSTRACT

SUMMARY: The dentate nucleus is a cerebellar structure involved in voluntary motor function and cognition. There are relatively few entities that affect the dentate, and the clinical features of these conditions are often complex and nonspecific. Because these entities are rarely encountered, the formulation of a differential diagnosis can be difficult. Many of the conditions are reversible or treatable with early intervention. Therefore, it is important to recognize classic clinical presentations and their associated characteristic imaging findings. We provide a summary of entities that affect the dentate nucleus and a diagnostic workflow for approaching dentate nucleus imaging abnormalities.

ABBREVIATION: Gd³⁺ = free gadolinium

The deep cerebellar nuclei are key structures of the cerebrocerebellar circuitry that relay output from the cerebellar cortex to supratentorial cortical and subcortical targets. The dentate nucleus is the largest of the deep cerebellar nuclei, and it is involved in planning, initiating, and modifying voluntary movements as well as cognition. Because it is buried deep within cerebellar white matter, the dentate is uncommonly lesioned as a result of trauma or surgical interventions. However, a few entities specifically involve the dentate nuclei. Many of the conditions that affect the dentate are medically manageable, and prognoses can be favorable with early intervention. Despite the fact that they are rare entities, knowing the characteristic imaging findings for these conditions will allow the formulation of an appropriate differential diagnosis of dentate nucleus abnormalities and will assist in making a timely diagnosis. In this article, we review the clinical presentations and imaging features of many of the most common entities that involve the dentate. We also provide a summary of major inherited conditions and their presentations (On-line Table) and a diagnostic approach for evaluating dentate nucleus abnormalities (Fig 1).

Normal Anatomy and Function of the Dentate

The dentate nucleus is the largest and most lateral of the 4 deep cerebellar nuclei (Fig 2). The emboliform and globose nuclei, collectively referred to as the interposed nuclei, are positioned more medially, and the fastigial nucleus lies adjacent to the midline. The dentate nucleus is located within the cerebellar white matter and is directly adjacent to the vermis and the roof of the fourth ventricle bilaterally.1,2 While the dentate is classically known to be involved in planning and executing voluntary movements, it has also been implicated in higher level cognition and sensory processing.3–5 It contains anatomically separate domains that mediate these motor and nonmotor functions.6,7

The dentate receives ascending projections from the spinocerebellar tract via the inferior cerebellar peduncle, which convey proprioceptive information about the length and tension of muscle fibers. It also receives descending projections from the premotor and supplementary motor cortices, which are involved in planning and initiating voluntary movements.2 By integrating these 2 inputs, the dentate is able to compare intended movement with muscle feedback to maintain equilibrium and balance. Its efferent projections travel through the superior cerebellar peduncle and red nucleus to the ventrolateral thalamus, where it is involved in timing and fine-tuning voluntary movements.8

It is 1 of 3 interconnected structures collectively referred to as the myoclonic triangle or the triangle of Guillain-Mollaret. This triangular circuit comprises the red nucleus, the inferior olivary nucleus, and the dentate nucleus.9,10 Parvocellular red nucleus fibers project to the ipsilateral inferior olivary nucleus by way of the central tegmental tract. Efferents of the inferior olivary nu-
FIG 1. Diagnostic approach for dentate nucleus imaging abnormalities.

FIG 2. Illustration of the location of the dentate nucleus within the cerebellum. Used with permission of Mayo Foundation for Medical Education and Research, all rights reserved.
entities involving the dentate nuclei

hypertensive hemorrhages. Long-standing hypertension is associated with the formation and rupture of Charcot-Bouchard microaneurysms in small penetrating blood vessels of the cerebral circulation. Intracerebral hemorrhage is characterized by sudden onset of a focal neurologic deficit and may be associated with headache, altered consciousness, nausea, and vomiting. Cerbellar hypertensive hemorrhage is typically caused by rupture of the perforating arteries of the superior cerebellar artery. The most common symptoms of cerebellar hemorrhage are ataxia, vertigo, severe nausea, and vomiting. Bleeding often begins in the dentate nucleus and spreads throughout the ipsilateral hemisphere to include the cerebellar peduncles and fourth ventricle. There is a potential for the hemorrhage to extend through the vermis to the contralateral hemisphere.

As with all hemorrhages, CT can be used to quickly identify acute bleeding. On MR imaging, T2* sequences are key to identifying areas of prior microhemorrhage and hemosiderin deposition. These T2* hypointense microhemorrhages are characteristically concentrated in the dentate, basal ganglia, thalamus, and pons (Fig 3). Metronidazole toxicity. Metronidazole is an antibiotic indicated in the treatment of a variety of bacterial and protozoan infections. While it is generally a safe medication, it crosses the blood-brain barrier and can cause serious neurologic side effects at high doses and with prolonged use. Symptoms of metronidazole toxicity include ataxia, encephalopathy, peripheral neuropathy, and seizures. Symptoms often resolve completely following metronidazole discontinuation.

There have been reports of bilateral signal changes in the supratentorial white matter and the dentate nucleus (Fig 4) following the initiation of metronidazole therapy, both at doses within and above the recommended range. These lesions are symmetric and hyperintense on T2WI and can demonstrate associated restricted diffusion. Like the symptoms associated with metronidazole toxicity, edema is reversible and imaging studies return to baseline within a few weeks of metronidazole discontinuation.

Gadolinium deposition. Gadolinium-based contrast agents are frequently used in imaging studies. Because free gadolinium (Gd³⁺) is a cytotoxic element, it must be bound to a chelator that is eliminated by renal excretion when given as a contrast agent. From a safety standpoint, it is imperative that the gadolinium-chelator bond remain stable to ensure that free gadolinium is not deposited in tissues. However, Gd³⁺ deposition has been found in the bones of patients and animals with normal renal function following gadolinium-based contrast exposure.

The dentate nucleus and globus pallidus have also shown high signal intensity on unenhanced T1-weighted MR imaging following multiple contrast imaging studies. The number of previous contrast administrations is positively correlated with abnormal signal intensity. Recently, it has been confirmed that the high T1 signal in the dentate nucleus (Fig 5) and globus pallidus is...
due to Gd$^{3+}$ deposition. The mechanism by which Gd$^{3+}$ deposits preferentially in the dentate is not known, and to date, there have been no studies linking Gd$^{3+}$ deposition to deficits in neurocognitive function or movement disorders.

**Multiple Sclerosis.** Multiple sclerosis is an autoimmune disease of the central nervous system that affects 90 in every 100,000 individuals in the United States, with a higher prevalence in women. It is characterized by a cell-mediated autoimmune response against oligodendrocyte components, leading to demyelination and axonal degeneration in the brain and spinal cord. Although MS is classically known to be a disease of white matter, substantial damage and volume loss of gray matter structures can be present.

Prior studies have demonstrated high intrinsic T1 signal in the dentate nuclei of patients with MS. However, patients with MS tend to undergo multiple contrast-enhanced MRIs for both diagnosis and disease surveillance. Thus, the T1-weighted hyperintensity seen in the dentate nucleus in patients with MS may be a result of their large cumulative gadolinium load rather than a manifestation of their disease. Lesions demonstrating T1 hyperintensity and T2 hypointensity in deep gray matter structures, including the dentate nucleus, thalamus, striatum, and globus pallidus, can be present as well. Such lesions have been attributed to abnormal deposition of nonheme iron and evidence of MS progression.

It is possible that iron deposition is a by-product of neural degeneration rather than a true marker of MS progression. However, treatment with natalizumab decreases the rate of iron deposition in patients with MS, suggesting that MS-mediated inflammatory processes contribute to the phenomenon. Future studies would be needed to determine whether gadolinium or iron deposition is responsible for signal changes in the dentate of these patients.

**Iron Deposition in Neurodegenerative Conditions.** There are 10 inherited neurodegenerative diseases that are characterized by iron accumulation in the basal ganglia, substantia nigra, and deep cerebellar nuclei. These rare diseases are collectively referred to as neurodegeneration with brain iron accumulation, and their combined incidence is estimated to be <1 in 1,000,000. Their etiologies are heterogeneous and related to defects in iron metabolism and homeostasis, cell membrane integrity, and myelin synthesis. The clinical symptoms of neurodegeneration with brain iron accumulation depend on which structures are involved, but many present with extrapyramidal abnormalities and cognitive dysfunction during young adulthood. All neurodegeneration with brain iron accumulation subtypes are progressive, and treatment consists of symptom management because there are currently no cures for the underlying disorders.

The iron deposition is best visualized on 3D susceptibility-weighted imaging as symmetric hypointensity in the affected structures. Woodhouse-Sakati syndrome is a neurodegeneration with brain iron accumulation subtype characterized by iron deposition in the globus pallidus and dentate as well as white matter abnormalities.

**Fahr Disease.** Fahr disease is a rare, autosomal dominant disorder that affects <1 per 1,000,000 individuals. It most often presents in the fourth or fifth decade of life, with progressive extrapyramidal and neuropsychiatric symptoms such as spasticity, athetosis, dysarthria, and dementia. While the molecular underpinnings of Fahr disease are not well-elucidated, it has been associated with a number of endocrine disorders that affect circulating calcium levels. Treatment currently aims to alleviate symptoms and manage any coexisting hormone imbalances.

Fahr disease is characterized by idiopathic calcification of the basal ganglia and other brain regions involved in motor control, including the dentate nucleus (Fig 7) and thalamus.
tity has a characteristic appearance on CT of dense, symmetric calcification most commonly in the basal ganglia, but also within the dentate nucleus, thalamus, and subcortical white matter.38 The globus pallidus is typically the first structure to be affected.36 There is no correlation between the degree of calcification and the severity of symptoms. On MR imaging, these areas of calcification can have variable T1 and T2 signal intensities that relate to the stage of disease, the degree of calcium deposition, and variance in calcium metabolism. In general, these areas will be markedly hypointense on T2*-based imaging and hypointense on T2WI and have hyperintense regions on T1WI.40 In addition, MR imaging can depict associated inflammatory changes that can later calcify and may be responsible for current symptoms.39

Leigh Syndrome. Leigh syndrome, or subacute necrotizing encephalomyelopathy, is a rare mitochondrial disease that affects 1 in 50,000 neonates.41 It is most commonly associated with a mutation in SURF1, a gene necessary for cytochrome C oxidase assembly and a functional mitochondrial respiratory chain.32 Early signs of the disease usually present within the first year of life, though it can have a late onset in adolescents and adults.43 Infants typically present with developmental delay or regression.43,44 Other signs may include seizures, dysphagia, ophthalmoparesis, nystagmus, dystonia, and ataxia. The prognosis is poor, and affected children are expected to live for only a few months after diagnosis.43,44 There is no cure for Leigh disease, and treatment is targeted at symptom management.

Leigh disease characteristically presents on imaging as symmetric T2 hyperintensity (Fig 8) and restricted diffusion of the dentate nuclei, basal ganglia, thalamus, periaqueductal gray, substantia nigra, pons, and medulla.43,45,46 White matter is typically spared. The T2 hyperintensities and T1 hypointensities on MR imaging are reflective of vacuolation and spongiform changes.46 MR spectroscopy may demonstrate high levels of choline and lactate. Evidence of global atrophy can be seen as the disease progresses.46

Friedreich Ataxia. Friedreich ataxia is an autosomal recessive disease that affects approximately 2 in every 100,000 people.47 It is the most common type of inherited ataxia. Clinical presentation is variable because the disease has a variety of manifestations in the central and peripheral nervous system, heart, pancreas, and skeletal muscle. Friedreich ataxia typically presents during childhood and progresses with time, though there have been reports of onset as late as 75 years of age.47 The most common presenting symptom is progressive gait ataxia. Care is targeted at managing symptoms and addressing cardiac or endocrine manifestations of the disease.

The most common primary sites of pathologic changes in patients with Friedreich ataxia are the spinal cord and peripheral nerves.48 Thus, MR imaging consistently demonstrates atrophy of the cervical spine.49 Friedreich ataxia is also associated with selective atrophy of large neurons of the dentate nucleus with sparing of small neurons.50-52 It is unclear whether the high concentration of iron in the dentate nucleus makes it particularly susceptible to disease-mediated degeneration because other iron-rich structures, such as the substantia nigra, red nucleus, and globus pallidus, are spared.50 Wallerian degeneration of the superior cerebellar peduncle is supportive of a diagnosis of Friedreich ataxia because the efferent fibers of the dentate are carried by this tract. However, involvement of these nuclei and tracts is typically not visible with conventional imaging sequences. Diffusion-weighted and diffusion tensor imaging have been used to detect these changes that are not readily apparent.53

Canavan Disease. Canavan disease, or spongiform leukodystrophy, is an autosomal recessive disorder. The incidence of Canavan disease is estimated to be <1:100,000 in the general population and between 1:6000 and 1:14,000 in the Ashkenazi Jewish population.54,55 A mutation in the ASPA gene causes a deficiency of aspartoacyclase, resulting in a buildup of NAA, which impedes the production of new myelin and causes progressive damage to existing myelin.56,57 At postmortem examination, the white matter...
of brains with Canavan disease is described as edematous, gelatinous, and vacuolated, and these changes can be seen with imaging. Symptoms present within the first 3–6 months of life and prognosis is poor, with most affected children dying before 5 years of age. Treatment consists of symptom management and supportive care.

Diffuse cerebral atrophy and extensive white matter changes are characteristic of Canavan disease. The peripheral white matter is affected preferentially in the early stages of the disease. As the disease progresses, the globus pallidus is often atrophied, with sparing of the putamen. MR spectroscopy can be helpful in detecting elevated NAA ratios. There is variable involvement of the dentate, thalamus, brain stem, and dorsal pons. MR imaging is most helpful for evaluating the extensive white matter involvement characterized by bilaterally symmetric diffuse T2 hyperintensity and diffusion restriction.

Glutaric Aciduria Type 1. Glutaric aciduria type 1 is a rare autosomal recessive disorder that is estimated to affect 1 in every 100,000 neonates. In glutaric aciduria type 1, glutaric acid and 3-hydroxyglutaric acid accumulation causes neuronal hypoplasia. Glutaric aciduria type 1 usually has no signs or symptoms in the first few months of life except for microencephalic macrocephaly. Acute decompensation and rapid neurologic deterioration often occur following a febrile illness between 6 and 18 months of age. Symptoms include hypotonia, spasticity, dysphagia, and an increased propensity for bleeding. Chronic treatment involves a low lysine diet and carnitine supplementation. Many patients survive to adulthood with marked motor and coordination disability.

Even before the acute decompensation stage, patients with glutaric aciduria type 1 almost invariably have bilateral, cystlike widening of the Sylvian fissures and mesencephalic cistern, with atrophy of the frontotemporal cortices. During and after an acute decompensation event, T2-weighted hyperintensity on MR imaging and diffusion restriction on DWI are seen in the dentate nucleus, basal ganglia, periventricular white matter, and pontine medial lemniscus. These changes represent demyelination and edema following toxic metabolic by-product buildup. Subdural hemorrhage and hygroma can present following minor head trauma because these patients have a propensity for tearing bridging veins and arachnoid membrane fenestrations.

Maple Syrup Urine Disease. Maple syrup urine disease is an autosomal recessive disorder that has been estimated to affect 1 in 185,000 neonates worldwide. Mutations in the genes that encode for the branched-chain \( \alpha \)-keto acid dehydrogenase complex cause a defect in the catabolism of leucine, isoleucine, and valine. If left untreated, buildup of these branched-chain amino acids and their ketoacidotic by-products can lead to rapid neurologic decline, coma, and death. With the adoption of neonate screening for maple syrup urine disease, prognosis is good in the modern world.

Untreated patients with maple syrup urine disease show no abnormalities on CT or MR imaging during their asymptomatic first few days of life. The 4 deep cerebellar nuclei, dorsal brain stem, cerebral peduncles, and posterior limb of the internal capsule become severely edematous about 1 week after birth at the onset of symptoms. Generalized edema of the brain is often superimposed on these severe, localized changes. DWI will demonstrate markedly restricted diffusion within the affected structures. MR spectroscopy can demonstrate abnormal peaks corresponding to increased levels of leucine, isoleucine, and valine. Edema can persist for up to 7 weeks, even if treatment is initiated promptly after the onset of symptoms. If maple syrup urine disease is treated and edema subsides, MR imaging and DWI findings rarely return to normal. Residual abnormalities include diffuse atrophy, dysmyelination, and demarcated lesions in the dentate nuclei, hypothalamus, and cerebral white matter. MR spectroscopy may show decreased, but still abnormally high, peaks corresponding to the branched-chain amino acids.

Clues from Commonalities and Avenues for Future Research

The dentate nucleus is particularly susceptible to insults, whether demyelination, mineral deposition, or metabolic by-product buildup. The 3 other deep cerebellar nuclei and other deep gray matter structures are, for unclear reasons, often spared in these conditions. It may be that the dentate has innate biologic and metabolic characteristics that allow pathologic processes to preferentially affect it. The neurologic and pathologic effects of dentate involvement in the above-mentioned diseases have not been well-studied. Future studies examining disease-associated histopathologic changes, imaging characteristics, and natural history are needed to better characterize the pathophysiology and consequences of disease involvement of the dentate.

Conclusions

Relatively few inheritable diseases and pathologic processes affect the dentate nucleus. A summary of these diseases, their classic clinical presentations, and their radiographic features are provided in the On-line Table. The symptoms associated with these conditions can be nonspecific and complex, but the use of imaging can aid in narrowing wide differential diagnoses. Because some of these conditions are reversible or medically manageable if the diagnosis is made early enough, it is important to have a diagnostic approach for evaluating imaging features of the dentate (Fig 1).

References

6. Salamon N, Sicotte N, Drain A, et al. White matter fiber tractography...
and color mapping of the normal human cerebellum with diffusion tensor imaging. J Neuroadiol 2007;34:115–28 CrossRef Medline
9. Guillan G, Mollaret P. High signal intensity in the dentate nucleus and globus pallidus is dependent on the class of contrast agent. Radiology 2015;275:772–82 CrossRef Medline
19. White GW, Gibby WA, Tweedle MF. Comparison of Gd(DTPA-BMA) (Omniscan) versus Gd(HP-DO3A) (ProHance) relative to gadolinium retention in human bone tissue by inductively coupled plasma mass spectrometry. Invest Radiol 2006;41:272–78 CrossRef Medline
42. Zhu QZ, Yao JB, Johns T, et al. SURF1, encoding a factor involved in the biogenesis of cytochrome c oxidase, is mutated in Leigh syndrome. Nat Genet 1998;20:337–43 CrossRef Medline
50. Koeppen AH, Michael SC, Knuston MD, et al. The dentate nucleus in...


MR Imaging in Sudden Sensorineural Hearing Loss. Time to Talk

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ABSTRACT

SUMMARY: Sudden sensorineural hearing loss is defined as acute hearing loss of the sensorineural type of at least 30 dB over 3 contiguous frequencies that occurs within a 72-hour period. Although many different causative factors have been proposed, sudden sensorineural hearing loss is still considered “idiopathic” in 71%–85% of cases, and treatments are empiric, not based on etiology. MR imaging implemented with a 3D FLAIR sequence has provided new insights into the etiology of sudden sensorineural hearing loss. Herein, we review the current management trends for patients with sudden sensorineural hearing loss, from the initial clinical diagnosis to therapeutic strategies and diagnostic work-up. We focused primarily on MR imaging assessment and discuss the relevance that MR imaging findings might have for patient management, pointing out different perspectives for future clinical research.

ABBREVIATION: SSHL = sudden sensorineural hearing loss

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ccording to the guidelines of the Committee on Hearing and Equilibrium of the American Academy of Otolaryngology, sudden sensorineural hearing loss (SSHL) is defined as acute hearing loss of the sensorineural type of at least 30 dB over 3 contiguous frequencies occurring within a 72-hour period.1 SSHL occurs most often in the fourth decade of life, with an annual incidence that varies between 5 and 20 cases among 100,000 people. The severity of hearing loss is variable and is usually unilateral, though bilateral involvement has been reported in up to 4% of patients.2

Although SSHL has been attributed to many different causative factors,3 there are still no audiologic means of accurately assessing its etiology,4 so it is still considered “idiopathic” in 71%–85% of cases.5 Consequently, there is not a treatment that targets the etiology, which partly explains the inconsistent results of the various empiric drug protocols proposed, which include systemic steroids, antiviral medications, vasodilators, and carbogen or hyperbaric oxygen alone or in combination, none of which has been proved to be superior to the others.6–8

Over the past decade, MR imaging has provided new insights about SSHL etiology because of high-resolution sequences that are able to detect subtle changes in the inner ear.9–15 However, for many reasons, the use of this imaging technique for SSHL is still not widespread. First, many radiologists are not yet aware of the possibilities offered by advanced MR imaging studies of the inner ear and/or of the possible MR imaging findings in SSHL. Second, it is still unclear and is not yet addressed in the literature how MR imaging could change therapeutic strategies.

In this paper, we review the current management trends of patients with SSHL, from the initial clinical diagnosis to the therapeutic strategies, through the diagnostic work-up. Our work focuses particularly on MR imaging assessment. We discussed how MR imaging should be performed and the relevance that the possible MR imaging findings in the inner ear might have. Finally, we addressed the perspectives of possible changes in the therapeutic management of SSHL based on MR imaging findings, which could impact the patient’s prognosis.

Current Diagnostic Work-Up of SSHL

SSHL is suspected in patients with a sudden onset of generally unilateral decrease or loss of hearing, occurring instantaneously or rapidly developing over a period of hours or days.3 In other instances, primary care or emergency department physicians refer patients to an audiologist.16,17

The evaluation usually begins with a careful history and physical examination to look for potential causes such as infections,
systemic diseases, and exposure to known ototoxic medications. Otomicroscopy is generally negative for external and middle ear pathologies. Pure-tone audiometry is the main diagnostic tool used to differentiate between conductive and sensorineural hearing loss, which have very different management strategies. The physician can differentiate SSHL (symptoms occur within 3 days) from progressive or fluctuating SSHL. The presence of bilateral sudden hearing loss, recurrent episodes of sudden hearing loss, or focal neurologic findings suggests systemic disorders, autoimmune or metabolic disorders, bilateral Menière disease, or primary neurologic disorders.

If SSHL is diagnosed, an empiric treatment is started while the diagnostic work-up continues. A complete audiovestibular evaluation, including speech audiometry, speech in noise test, tympanometry, acoustic reflexes, and otocoustic emissions, is performed in an attempt to investigate whether the SSHL is cochlear or retrocochlear.8

Brain MR imaging with and without gadolinium is often used to exclude a vestibular schwannoma (reported in up to 10%–20% of patients with SSHL) as well as rarer causes of retrocochlear hearing loss such as other cerebellopontine tumors, brain stem infarctions, and demyelinating disease.3,8,18-21 A number of studies have advocated the use of MR imaging without gadolinium as the more appropriate means of screening patients with asymmetric SSHL suspected to be retrocochlear.22

In cases of suspected cochlear SSHL, different studies have proposed a tailored temporal bone MR imaging with 3D-FLAIR sequence to exclude abnormalities in the inner ear structures.9-15 MR imaging of the temporal bone can be negative, and the SSHL is therefore defined as idiopathic, or the MR imaging can show abnormalities in the inner ear structures, suggesting a specific etiopathogenesis (vascular or inflammatory).14 In both cases, because no trial has yet investigated different medical protocols guided by MR imaging findings, physicians continue with empiric therapy, so temporal bone MR imaging with a 3D-FLAIR sequence has not had any effect on the therapeutic management of cochlear SSHL in clinical practice. Nevertheless, in our opinion, it is important that radiologists perform temporal bone MR imaging with a 3D-FLAIR sequence to clarify the cochlear origin of SSHL, suggesting the probable pathogenesis, and provide prognostic information to physicians.

How We Perform MR Imaging in Patients with SSHL

MR imaging of the temporal bone is challenging because of the complexity and small dimensions of the anatomic structures. Thus, MR imaging should preferably be performed on a 3T scanner, which provides high-resolution images with a higher signal-to-noise ratio compared with a 1.5T scanner. The basic MR imaging protocol should include an axial precontrast 3D steady-state free precession sequence, a pre- and postcontrast T1-weighted sequence, and a pre- and postcontrast 3D-FLAIR sequence.4-15 The On-line Table summarizes the MR imaging scan parameters used in our department. It is recommended to use both postcontrast 3D-FLAIR and postcontrast T1-weighted FSE sequences because the former are more sensitive than a T1-weighted sequence in detecting intralabyrinthine contrast enhancement,11,14,23 and the latter can clarify the presence of a small schwannoma.

Postcontrast sequences should be acquired approximately 10 minutes after administration of the contrast agent.13,15 To cover part of the 10 minutes needed before the acquisition of postcontrast sequences, it is advantageous to inject a contrast agent before the acquisition of the 3D steady-state free precession sequence. Although the contrast enhancement of some structures can be seen on the 3D steady-state free precession sequence,24 the assessment of the inner ear anatomic structures and internal auditory canal on this sequence is usually not hindered by the presence of the contrast agent.

What Can MR Imaging Detect?

Neuroradiologists should review MRIs and look for asymmetry of the signal between the affected and unaffected sides. In the literature, abnormalities on MR imaging are reported in 27%–53% of SSHL cases.10,14 Two patterns can be recognized based on the MR imaging signal of the inner ear on precontrast T1-weighted and 3D-FLAIR images: 1) The vascular pattern shows hyperintensity on precontrast T1-weighted and 3D-FLAIR images because of the presence of methemoglobin in the inner ear (Fig 1); and

2) The inflammatory pattern shows hyperintensity only on 3D-FLAIR images because of the presence of proteinaceous exudate in the inner ear (Fig 2).

Regarding the vascular pattern, radiologists should be aware that pseudohyperintensity of the intralabyrinthine fluid can normally be detected on fat-suppressed T1-weighted images, which could hamper the diagnosis. This pseudohyperintensity has previously been described as an artifact25 and can be differentiated from methemoglobin because it is symmetrical and less evident on postcontrast fat-suppressed T1-weighted images (see Fig 3 for a detailed explanation).

Recent studies have investigated the relationship between precontrast 3D-FLAIR signals and clinical findings regardless of the hyperintensity on precontrast T1-weighted sequences.9-11,23 The rate of abnormalities on precontrast 3D-FLAIR images correlated
with the level of hearing loss at onset, resulting in fewer abnormalities in patients with mild to moderate hearing loss compared with patients with profound hearing loss.\textsuperscript{10,14,15} However, Yoshida et al\textsuperscript{11} did not observe similar results. Inflammatory diseases can also affect the vestibule, the semicircular canals, or cranial nerve VIII, and precontrast 3D-FLAIR images can detect signal abnormalities in these structures (Fig 3).\textsuperscript{10-14,23} Hyperintensity on precontrast 3D-FLAIR images of the vestibule or the semicircular canals has been associated with vertigo,\textsuperscript{11,14} which is reported in approximately 30% of SSHL cases.\textsuperscript{9}

The 2 MR imaging patterns are not always associated with inner ear enhancement on postcontrast 3D-FLAIR, which is consistent with blood-labyrinth barrier breakdown.\textsuperscript{14} The advantage of postcontrast 3D-FLAIR images is that they identify patients with more severe blood-labyrinth barrier breakdown when signal abnormalities are subtle on precontrast 3D-FLAIR images.\textsuperscript{23} However, the significance of the inner ear enhancement is still unclear. Viral infection, immune-mediated inner ear disease, and perilymphatic fistulas have been suggested as possible causes of cochlear enhancement.\textsuperscript{26,27}

Usually, the 3D T2-weighted steady-state free precession sequence does not show any pathologic findings\textsuperscript{23}; nevertheless, it is essential to investigate the morphology of the inner ear structures, cranial nerve VIII, internal auditory canal, and cerebellopontine angle.

**Prognostic Value of MR Imaging**

To the best of our knowledge, no published studies have investigated the difference in prognosis and outcome between the 2 MR imaging patterns mentioned above, though a vascular pattern has been associated with a poor prognosis.\textsuperscript{28} On the contrary, the published studies have concentrated on the prognostic value of 3D-FLAIR abnormalities and reported conflicting results. Two studies showed that a high signal in the affected inner ear on precontrast 3D-FLAIR was associated with a poor prognosis.\textsuperscript{11,15} In 2 other studies, the hearing outcome was worse in patients with multiple-location hyperintensities on precontrast 3D-FLAIR (cochlea plus vestibule) than in patients with a single-subsite hyperintensity (cochlea only).\textsuperscript{12,29} A recent study by Liao et al\textsuperscript{23} showed that the more asymmetric FLAIR signal between the affected ear and the normal one and presence of a high signal beyond the cochlea indicated a poorer prognosis. Lee et al\textsuperscript{10} demonstrated that precontrast 3D-FLAIR abnormalities do not affect the prognosis when the initial hearing loss is mild to moderate, whereas such abnormalities represent a negative prognostic factor in patients with initial profound hearing loss. However, Berrettini et al\textsuperscript{14} failed to find a correlation between the severity of precontrast 3D-FLAIR abnormalities and hearing improvement. Lee et al\textsuperscript{9} reported that a high signal on precontrast 3D-FLAIR did not significantly affect the final hearing ability.

These inconsistent results are partially explained by methodologic differences, including the time span between SSHL onset and MR imaging, method of MR imaging assessment, pharmacologic protocols of drug administration during follow-up, length of follow-up, and assessment criteria used to determine hearing improvement.\textsuperscript{30} A meta-analysis by Gao and Chi\textsuperscript{30} that included studies of patients without primary treatment before temporal bone MR imaging concluded that precontrast 3D-FLAIR abnormalities in the inner ear are associated with more severe initial hearing loss and a lower chance of recovery.

**Current Management of SSHL and Perspectives in MR Imaging Research**

The results of SSHL treatment are still largely unpredictable; a very large variability in responses has been reported, ranging
from no response to total recovery. Moreover, the high rate of spontaneous recovery, which varies from 45%–65%, should be considered.

Although cochlear vascular microthrombosis has been hypothesized as the main pathogenic mechanism, because there is no objective test that can detect the occlusion of microvessels, the pharmacologic treatment remains highly empirical, and its overall efficacy is controversial because of the absence of prospective double-blind studies. Pharmacologic treatment includes many drugs that, without a certain etiology of SSHL, are often prescribed in combination: oral and/or intratympanic corticosteroids, hyperbaric oxygen therapy, antivirals drugs, vasodilators, and vasoactive substances.

For decades, the “gold standard” treatment for SSHL has been the oral administration of corticosteroids. The exact mechanism by which steroids improve hearing is still unknown, though some of the major hypotheses are that they modulate cochlear function, decrease inflammation and edema, improve cochlear blood flow, and protect against cochlear ischemia. Although the evidence concerning the use of oral corticosteroids remains contradictory, it seems reasonable to offer them because of the potentially devastating disability caused by SSHL and the relatively low morbidity of the treatment. Intratympanic steroid treatment allows high steroid concentrations to be reached in the perilymph while avoiding the common side effects of systemic steroids. A recent meta-analysis has shown the benefits of intratympanic steroid treatment in combination with oral corticosteroids as the first-line therapy and salvage monotherapy in idiopathic SSHL. A recent meta-analysis has shown the benefits of intratympanic steroid treatment in combination with oral corticosteroids as the first-line therapy and salvage monotherapy in idiopathic SSHL. Hyperbaric oxygen treatment is also used as primary, adjuvant, or salvage therapy because it is thought to protect hair cells from ischemic damage by increasing oxygenation. However, cost/benefit issues, limited availability, and the absence of strong evidence because of the difficulties of organizing controlled randomized studies have halted its widespread application. Although there is no clear evidence supporting their use, antiviral drugs are often used in pharmacologic protocols for the treatment of SSHL because various viruses have been implicated in its etiology. Vasodilators and vasoactive substances are sometimes used because obstructed vascular flow to the cochlea is a theoretic cause of SSHL, but there is currently insufficient evidence to support their routine use.

Future research should investigate the role of MR imaging with a 3D-FLAIR sequence in the therapeutic management of SSHL (On-line Figure). Before future trials can investigate different medical protocols guided by MR imaging findings, longitudinal studies should investigate the effects of early steroid treatment and the time interval between disease onset and scanning on the sensitivity of MR imaging. In our opinion, its optimal timing would be upon admission to the emergency department or on the same day as a clinical assessment by an audiologist or otolaryngologist. We hypothesize that precontrast and contrast-enhanced MR imaging abnormalities are more easily detected before steroid treatment is started, so MR imaging should be performed as soon as possible, and preferably before the masking effect of steroids becomes apparent. In line with this suggestion, Berrettini et al have reported that the time interval between SSHL onset and MR imaging tended to be shorter in patients with 3D-FLAIR abnormalities than in those without 3D-FLAIR abnormalities (P = .06). However, this has not been confirmed by other authors.

**CONCLUSIONS**

MR imaging with 3D-FLAIR sequences provides new insights into SSHL etiology and may change current clinical and therapeutic practices. Radiologists should therefore be trained to perform tailored temporal bone MR imaging in the case of SSHL and recognize the common findings and pitfalls of the technique to provide clinicians with information useful for patient management.

**REFERENCES**

treatment of sudden hearing loss: a CHEER Network study. Otolar-

17. Coelho DH, Thacker LR, Hsu DW. Variability in the management of idiopathic sudden sensorineural hearing loss. Otolar-
yngol Head Neck Surg 2011;145:813–17 CrossRef Medline


phatic hydrops in Ménérie’s disease utilizing delayed postcontrast 3D FLAIR and fused 3D FLAIR and CISS color maps. Otol Neurotol 2014;35:e337–42 CrossRef Medline

22. Ryan M, Weissman JL, Kaylie D. Is Gadolinium contrast enhance-
ment necessary in screening MRI for asymmetric sensorineural hearing loss? Laryngoscope 2015;125:783–84 CrossRef Medline


yngol Head Neck Surg 2011;145:813–17 CrossRef Medline

yngol Head Neck Surg 2011;145:813–17 CrossRef Medline


27. Fitzgerald DC, Mark AS. Sudden hearing loss: frequency of abnor-
mal findings on contrast-enhanced MR studies. AJNR Am J Neuro-
radiol 1998;19:1433–36 Medline


30. Gao Z, Chi FL. The clinical value of three-dimensional fluid-atten-


34. Quaranta N, De Ceglie V, D’Elia A. Endothelial dysfunction in idio-


36. Wilson WR, Byl FM, Laird N. The efficacy of steroids in the treat-


38. Lavigne P, Lavigne F, Saliba I. Intratympanic corticosteroids injections: a systematic review of literature. Ear Arch Otorhinolar-
yngol 2016;273:2271–78 CrossRef Medline


40. Narozy W, Sicko Z, Przewozny T, et al. Usefulness of high doses of glucocorticoids and hyperbaric oxygen therapy in sudden senso-

41. Awad Z, Huins C, Pothier DD. Antivirals for idiopathic sudden senso-
rineural hearing loss. Cochrane Database Syst Rev 2012;8:CD006987 CrossRef Medline
Introduction of a Dedicated Emergency Department MR Imaging Scanner at the Barrow Neurological Institute

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ABSTRACT

SUMMARY: Use of advanced imaging in the emergency department has been increasing in the United States during the past 2 decades. This trend has been most notable in CT, which has increased concern over the effects of increasing levels of medical ionizing radiation. MR imaging offers a safe, nonionizing alternative to CT and is diagnostically superior in many neurologic conditions encountered in the emergency department. Herein, we describe the process of developing and installing a dedicated MR imaging scanner in the Neuroscience Emergency Department at the Barrow Neurological Institute and its effects on neuroradiology and the emergency department in general.

ABBREVIATION: ED = emergency department

In the United States, use of advanced imaging in the emergency department (ED) has been steadily increasing during the past 2 decades.1,2 This trend has outpaced the increasing number of ED visits, indicating that at least part of this rise is due to increasing demand for these imaging tests.3 While this increasing use has been successfully reversed in some centers with education programs, clinical decision support systems, pay-for-performance incentive systems, and other methods,3,4 national data continue to demonstrate growth, most notably in CT.1 Neuroimaging makes up a substantial portion of this use, constituting a large proportion of total CT imaging3,5 and most MR imaging ordered in the ED.2,5 These trends have led to increasing concern regarding the rising health care costs and the radiation dose attributable to increasing CT use. MR imaging provides a nonionizing alternative to CT for many neuroimaging indications; however, factors such as availability, scan length, and cost can limit its utility as a practical substitute for CT.

The dedicated Neuroscience Emergency Department at the Barrow Neurological Institute sees >18,500 patients per year, with >2500 hospital admissions per year for neurologic concerns. This number of patient encounters generates a high volume of neuroimaging. In an effort to increase access to MR imaging and create a viable alternative to CT in this patient population, the Barrow Neurological Institute installed a dedicated ED MR imaging scanner in 2015. Herein, we describe our experience with this process and the effects of a dedicated ED MR imaging scanner on neuroradiology and the emergency department.

Impetus for Change

On the basis of CT usage data from the early 1990s and extrapolation to 2007, Brenner and Hall6 estimated that 1.5%–2% of all cancers in the United States could be attributed to radiation from CT studies. Using BEIR VII data and CT head usage data from 2008, Smith-Bindman et al7 estimated that the risk of developing cancer from a CT of the head at age 40 is 1 in 8100 for women and 1 in 11,080 for men. This risk was estimated to double if the age at scanning was halved. Berrington de González et al8 suggested that CT head scans performed in the United States in 2007 caused approximately 4000 new cancers. These risks were qualified somewhat in a retrospective review by Sodickson et al9 in 2009, which suggested that while there was only an incrementally increased risk of CT-induced cancer for patients undergoing a limited number of scans, there was significantly increased risk to those undergoing recurrent scanning. Their data demonstrated that 33% of their cohort of 31,462 patients had undergone ≥5 CT scans during the 22-year study period and that 15% had a cumulative dose of >100 mSv.9

Multiple techniques are available to reduce the radiation dose from CT scans, particularly to radiosensitive tissues such as the lens of the eye and the thyroid gland. These include iterative reconstruction and organ-based dose-reduction algorithms specifically targeting the lens and thyroid glands. There is evidence that...
these strategies can result in moderate dose reduction (up to 50%) without compromising image quality. MR imaging offers an imaging solution that uses nonionizing radiation, eliminating radiation dose concerns associated with medical imaging.

While most acute neurologic encounters in the ED can be assessed with CT, MR imaging offers a more detailed assessment, given its superior soft-tissue contrast, without using ionizing radiation. Apart from trauma and conductive hearing loss, the Appropriateness Criteria of the American College of Radiology list MR imaging as the preferred examination for most neurologic symptoms. These include ataxia, cranial neuropathies, dementia, altered mental status, focal neurologic deficits, headache (except thunderclap headaches), seizure, and vision loss.13

MR imaging and specifically diffusion-weighted imaging have been shown to be more sensitive in diagnosing acute stroke compared with CT.14 Chalela et al conducted a prospective, blinded comparison of MR imaging and CT for the assessment of acute stroke in the emergency department and concluded that MR imaging was superior to CT for the detection of acute ischemia and could detect acute and chronic hemorrhage, suggesting that MR imaging should be the preferred test for the accurate diagnosis of patients with suspected acute stroke. Other studies have confirmed that MR imaging is as accurate as CT for acute hemorrhage and more accurate for chronic hemorrhage. Indeed, evidence suggests that the increased sensitivity of MR imaging for intracranial blood, and particularly microbleeds, may help identify those patients at higher risk for secondary intracerebral hemorrhage when considering intravenous thrombolytic therapy.18,19

Growing evidence suggests that the combination of fluid-attenuated inversion recovery pulse sequences and diffusion-weighted imaging is useful in determining which patients with strokes and unknown time of symptom onset or wake-up strokes are within the therapeutic window at presentation. Triaging patients with stroke to MR imaging instead of CT results in a better safety profile and a higher chance of favorable outcome when treating beyond 3 hours of symptom onset.24

When evaluating patients for possible endovascular therapy, contrast-enhanced MR angiography has been shown to be accurate in detecting stenosis of the carotid and vertebrobasilar circulations and correlates well with digital subtraction angiography for carotid stenosis. Contrast-enhanced MRA has also been shown to be equivalent or superior to time-of-flight angiography with much shorter scan times and to improve detection of carotid terminus occlusion.30

Although MR imaging is not the primary technique for assessing trauma, mounting evidence demonstrates that MR imaging offers considerable value as an ancillary test in the acute phase. Fluid-attenuated inversion recovery sequences have been shown to be equivalent or better than CT for the detection of acute subarachnoid hemorrhage, with increased sensitivity for acute and subacute hemorrhage with the addition of T2* sequences. MR imaging has also been shown to be superior to CT in detecting diffuse axonal injury. In acute spinal trauma, Morais et al demonstrated that MR imaging is superior to CT for the detection of bone swelling, posterior ligamentous complex injury, disc herniation, cord compression, and cord swelling.

Program Development
For use of MR imaging in the ED to achieve maximal success, it was thought that the turnaround times for MR imaging needed to be as close to CT as possible. Multiple factors, from placement of the equipment through training of technologists, were optimized to maximize efficiency and patient throughput.

The location of the MR imaging scanner within the ED itself was an extremely important achievement in the development of a viable ED MR imaging program because it permitted simplification of workflow from the multitransfer inpatient workflow to a no-transfer workflow, which more closely resembles the ED CT process.

Before the installation of the MR imaging scanner within the ED, patients requiring MR imaging would be entered into the hospital transport queue and would be taken to the inpatient scanners, accompanied by the responsible ED nurse. Once arriving at the inpatient scanner, care would be transferred to the MR imaging nurse for the duration of the scan, with all the potential delays that are inherent in any transfer-of-care process. Following the patient’s scan, this process was repeated in reverse, essentially doubling the potential for delays.

When the MR imaging scanner was placed in the ED, the use of the hospital transport queue was eliminated, with patients being moved by the dedicated ED transport system for more efficient transport. Both transfers of care were eliminated because the ED nurses are able to maintain care of their patients throughout the MR imaging process. Additionally, because the scanner was placed in the ED, only patients who would require nursing support for ED CT would require nursing support for ED MR imaging. These alterations essentially created an MR imaging workflow that was identical to the existing CT workflow, markedly reducing the previous temporal disadvantage of MR imaging. A comparison of the current and prior workflows can be seen in the Figure.

The next portion of the care process that required alteration was the scan itself. Barrow Neurological Institute inpatient MR imaging protocols last from 30 minutes to >1 hour; this timeframe is not conducive to high patient throughput. New ED scan protocols were created to limit scan time while providing adequate information to make emergent treatment and admit/discharge decisions. These protocols were designed to be completed in 10 minutes. A full listing of the sequences is detailed in the Table.

These new workflows and scan sequences necessitated education of referring physicians, nursing services, and technologists because they were substantially different from the inpatient protocols they were replacing. To this end, multiple meetings were held with the emergency physicians and the inpatient services (predominantly neurosurgery and neurology) before launch. Discussions were also held with the neurosurgery residents, nursing services, and technologists. The emergency physicians as a group were generally willing to transition from CT to MR imaging if the turnaround times would indeed be similar. There was some initial concern from the ED nurses that they would be forced to be away from their other patients for extended lengths of time. The nursing service was skeptical about the claim that the turnaround times for patients would be similar to those of CT. The inpatient services also expressed concern with the new processes, partic-
ularly relating to the loss of information secondary to the limited protocols. It was emphasized that these scans were for emergent treatment and admit/discharge decisions and that any additional information required could be obtained with an inpatient scan should the patient in question require admission.

Program Deployment
The installation of the MR imaging scanner in the ED took approximately 2 years from the time it was initially approved. This process was substantially expedited because the ED had preexisting space available to house the scanner, avoiding extensive renovations/additions to the existing structure of the ED. Overall, there were no lengthy or unexpected delays, and the scanner went live in May 2015.

The new scan protocols were deployed in 2 phases. In phase 1, ordering guidelines were created with MR imaging replacing CT of the head as the primary imaging technique for all non-trauma, nonstroke indications in the ED. This phase was initiated in May 2015. Phase 2 was initiated in July 2016, when MR imaging of the head and contrast-enhanced MRA of the head and neck replaced CT of the head and CT angiography of the head and neck as the primary imaging technique for acute stroke. Scan data were collected from August through November in 2015 and 2016 and were compared with baseline data collected from August through November in 2014. Statistical significance was calculated by using the \( \chi^2 \) test. Results are reported as the percentage change between phases (number of CT scans/number of total scans, \( P \) value).

Before the installation of the ED MR imaging scanner, 86% (5538/6430) of the monthly scans performed in the emergency department were CT. Following initiation of phase 1, there was a statistically significant drop in the percentage of CT studies to 62% (4518/7288, \( P < .001 \)). The distribution of these CT scans changed slightly with fewer CT angiography studies (22% to 15%) and an associated increase in the proportion of time-of-flight MRAs (5% to 13%). There was also a large increase in the percentage of unenhanced MR imaging of the brain (17% to 29%).

Following the initiation of phase 2, there was an additional statistically significant drop in the overall CT scan percentage to 48% (4161/8669, \( P < .001 \)). The distribution of CT scans again changed slightly, with a continued decrease in the proportion of CTA studies (15% to 9%) and a marked increase in contrast-enhanced MRA, accounting for 11% of MR imaging studies. This change was associated with an increase in the proportion of enhanced MR imaging of the brain related to the new stroke protocol.

Throughput following phase 1 averaged between 25 and 26 scans per day during the 4-month period. This number increased
to between 39 and 40 scans per day in phase 2, a 65% increase in daily throughput. Because phase 1 occurred when the workflows and protocols were new, this increase was likely due to an increase in ordering and improving familiarity with the new workflows for both nurses and technologists.

The culture shift associated with these changes, with an emphasis on throughput as opposed to completeness, was challenging for the technologists. Before the addition of the ED MR imaging scanner, technologists had been working for years in a setting where attention to detail and completeness were routinely applauded. Adding extra sequences based on already completed series or additional patient history was helpful and reduced the need for separate, additional scans. However, in the new ED environment where efficiency was paramount, the addition of extra sequences or deviation from the established protocols had a profoundly negative effect on patient throughput and turnaround times. This transition was substantially more difficult than anticipated and required continued communication following the launch of the new protocols. In hindsight, increased effort on education of technologists, focusing on this culture shift, would likely have eased this transition and increased initial patient throughput.

Conversely, the concerns expressed before launch by the ED nursing staff regarding the amount of time the new workflow would require them to be away from their patients were alleviated very shortly following launch. Once the 10-minute scan time was established as a reality, the temporal difference between MR imaging and CT from a nursing perspective was minimal and the ED nursing staff adapted to the new routine within a few weeks.

The initiation of the new scanner and subsequent increase in MR imaging volume from the ED necessitated some reordering of scan allocations among the neuroradiology fellows to compensate for the changing distribution of scans. The average MR imaging turnaround time (time from when a scan is ordered to when the scan is started) for the ED changed from 3 hours 51 minutes before phase 1 to 1 hour 50 minutes following phase 1 and 2 hours 26 minutes following phase 2. We hypothesize that this increase in turnaround time seen between phases 1 and 2 was related to the overall increase in MR imaging volume in the ED seen in phase 2. When we specifically selected for patients imaged for acute stroke, MR imaging in phase 2 had an average turnaround time of 15 minutes 30 seconds, lower than the CT turnaround time for phase 1 of 19 minutes 9 seconds.

Reactions from the attending neuroradiologists were varied, with some lauding the efficiency and decreased read time of the new scans, while others expressed concern over the limitations of the new sequences. A good example of these concerns is the decreased sensitivity of contrast-enhanced MRA for aneurysms. There were also concerns raised that the new, limited examinations would not meet the expectations of referring physicians and patients who expect a thorough and detailed examination from a specialized center like the Barrow Neurological Institute. In response to these concerns, statements detailing the purpose and limitations of the new ED protocols were included in reporting templates for these studies.

The effects on referring physicians were also varied. ED physicians have been satisfied with the turnaround and throughput and have expressed greater confidence with decisions to both admit and discharge patients. Concerns from inpatient services over missing diagnostic information have translated into persistent ordering of time-intensive scans despite the prelaunch education. These scans generally come in 2 variations: either large-area scans such as MR imaging of the brain and cervical, thoracic, and lumbar spine with and without contrast for investigation of multiple sclerosis, or small-FOV, thin-section imaging such as pituitary or orbit scans. Continued effort to emphasize the purpose of the ED scans is ongoing, including collaborative research projects to establish the value of certain scans in admit/discharge decisions. During our data collection, there were no instances of patients being recalled for additional images due to insufficient diagnostic information.

While the challenges with respect to the day-to-day ordering trends of the inpatient services were anticipated, the effects on the learners, particularly the neurosurgery residents, were not. Through hours of on-call work, the neurosurgery residents at Barrow Neurological Institute had become extremely proficient in extracting the information they needed to make decisions on call from inpatient MR imaging sequences with which they were familiar. The addition of ED MR imaging scan protocols optimized to reduce scan time replaced these familiar sequences with new sequences and severely undermined the residents’ confidence in their on-call decision-making. The magnitude of this disruption was much greater than anticipated before launch and required additional education sessions with the neurosurgery residents to familiarize them with the new scan protocols and draw parallels between the sequences they knew and the corresponding new sequences. Provided with this foundation, the residents acclimated within 2–3 months to the new protocols and concerns regarding the ED scanner became infrequent.

**Future Directions**

Continued evaluation and improvement of the ED MR imaging workflows and protocols are ongoing to ensure that patients in the ED receive the maximal benefit from their imaging study. An example of this improvement is the development of a new T2*-weighted sequence to replace the currently used gradient-echo sequence in the MR imaging brain protocol, which will provide improved spatial resolution with approximately 60-second shorter scan times. Additional fine-tuning of the protocols will

<table>
<thead>
<tr>
<th>Scan</th>
<th>Sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unenhanced brain</td>
<td>Sagittal T1, axial DWI, axial FLAIR, axial T2 GRE</td>
</tr>
<tr>
<td>Enhanced brain</td>
<td>Sagittal T1, axial DWI, axial FLAIR, 3D-T1 with and without contrast</td>
</tr>
<tr>
<td>Unenhanced C/T spine</td>
<td>Sagittal T1, sagittal mDixon T2, axial T2 GRE</td>
</tr>
<tr>
<td>Enhanced C/T spine</td>
<td>Sagittal T1, sagittal STIR, sagittal and axial mDixon T1 with contrast</td>
</tr>
<tr>
<td>Unenhanced L spine</td>
<td>Sagittal T1, sagittal mDixon T2, axial T2 TSE, coronal T1</td>
</tr>
<tr>
<td>Enhanced L spine</td>
<td>Sagittal T1, sagittal mDixon T2, axial T2 TSE, sagittal and axial mDixon T1 with contrast</td>
</tr>
<tr>
<td>Unenhanced MRA</td>
<td>Axial 2D TOF of the neck, 3D TOF of the head</td>
</tr>
<tr>
<td>Enhanced MRA</td>
<td>3D bolus dynamic contrast-enhanced</td>
</tr>
</tbody>
</table>

Note: —GRE indicates gradient-echo; mDixon, modified Dixon; C, cervical; T, thoracic; L, lumbar.
continue as more experience is gained with a dedicated ED MR imaging scanner.

There are currently no plans to add additional MR imaging scanners to the emergency department. However, 2 new inpatient MR imaging scanners are scheduled to be installed adjacent to the ED, which will allow decompression of the ED scanner should ED scan volumes continue to rise and outstrip current capacity.

While we were able to significantly reduce the proportion of CT imaging studies ordered in the ED (86% to 48%), a 56% relative reduction, the overall volume of imaging rose continuously during the 2-year period, from 6430 per 4-month period in 2014, to 7288 in 2015, and 8609 in 2016. Based on this rise, the absolute reduction in CT scans performed was 1379 studies per 4-month period, a 25% reduction. Concern has been raised that the installation of an MR imaging scanner in the ED has simply replaced inappropriately ordered CT scans with inappropriately ordered MRIs and that the underlying problem of rising use remains unaddressed. This argument merits attention, and other interventions such as persistent physician education, clinical decision support, updated guidelines, and pay-for-performance systems have been shown to be effective in decreasing use in academic centers.

However, the issue of increased use is multifactorial, and a permanent solution would likely require systematic changes to payment structures and extensive alterations in the medicolegal landscape, both of which are extremely complex environments. Fast access to MR imaging from the ED has, at least in the interim, provided a safer and diagnostically superior replacement for CT.

CONCLUSIONS

The installation of a dedicated ED MR imaging scanner significantly reduced the number of CT scans performed in the ED by providing a diagnostically superior and safer imaging alternative with a drastically improved turnaround time. This was achieved by altering the MR imaging workflow and existing scan protocols with an emphasis on efficiency and patient throughput. This change has resulted in increased confidence in clinical decision-making for the ED physicians and, with the exception of the unanticipated severity of the culture shift on the MR imaging technologists and neurosurgery residents, has been relatively well-received. Whether this change has resulted in improved patient outcomes was not addressed and further investigation is required.

ACKNOWLEDGMENTS

We thank Kevin King and Jana Mahl for their tireless assistance with data collection for this project.

REFERENCES

patients with unknown onset time. *Radiology* 2010;257:782–92 CrossRef Medline
ABSTRACT

BACKGROUND AND PURPOSE: Gadolinium-enhanced MR imaging is currently the reference standard for detecting active inflammatory lesions in patients with multiple sclerosis. The sensitivity of MR imaging for this purpose may vary according to the physicochemical characteristics of the contrast agent used and the acquisition strategy. The purpose of this study was to compare detection of gadolinium-enhancing lesions or active disease following a single or cumulative dose of a macrocyclic gadolinium-based contrast agent with different image acquisition delays in patients with clinically isolated syndrome or relapsing multiple sclerosis.

MATERIALS AND METHODS: All patients received a first dose (0.1 mmol/kg) of gadobutrol and, 20 minutes later, a second dose (0.1 mmol/kg), with a cumulative dose of 0.2 mmol/kg. Two contrast-enhanced T1-weighted sequences were performed at 5 and 15 minutes after the first contrast administration, and 2 additional T1-weighted sequences at 5 and 15 minutes after the second contrast administration with a 3T magnet.

RESULTS: One hundred fifteen patients were considered evaluable. A significantly larger number of lesions were detected in scans obtained at 5 and 15 minutes after the second contrast injection compared with scans obtained at 5 and 15 minutes after the first injection (P < .001). The number of patients with active lesions on MR imaging was significantly higher after the second dose administration (52.0%, first dose versus 59.2%, second dose; P < .001).

CONCLUSIONS: Cumulative dosing of a macrocyclic gadolinium-based contrast agent increases detection of enhancing lesions and patients with active lesions. These data could be considered in the design of MR imaging protocols aimed at detecting active multiple sclerosis lesions.

ABBR EVIAT IONS: CIS = clinically isolated syndrome; GBCA = gadolinium-based contrast agent; GRE = gradient recalled-echo
MATERIALS AND METHODS

Patients

From January 2010 to December 2011, a prospective, single-center, open-label experimental phase IV study was performed at Vall d’Hebron University Hospital. The study compared a single dose and cumulative double dose of a macrocyclic gadolinium-based contrast agent (GBCA) (gadobutrol, Gadovist; Bayer Schering Pharma, Berlin, Germany) administration with different delay times at 3T to detect enhancing lesions in patients with CIS and relapsing MS using blinded, centralized MR imaging assessment.

Patients 18–50 years of age with CIS suggestive of central nervous system demyelination not attributable to other diseases and those with a diagnosis of relapsing MS based on the McDonald 2010 criteria17 showing at least 2 brain T2 lesions of the type seen in MS were eligible for inclusion in the study.

The exclusion criteria were as follows: pregnant or nursing women, patients having a pacemaker or any other factor that would preclude proximity to a strong magnetic field, those with severe claustrophobia or a known allergy to GBCAs, previous participants in a clinical trial of an investigational drug within 30 days before MR imaging, those with any medical condition that might decrease the chance of obtaining reliable data, and patients with known impaired renal function (glomerular filtration rate, <60 mL/min/1.73 m²).

The study protocol and consent documents were approved by the Clinical Research Ethics Committee of Hospital Vall d’Hebron, and the procedures were in accordance with the ethical standards of the Declaration of Helsinki, as revised in 2000. The blinded read was conducted in compliance with the International Conference on Harmonization of Good Clinical Practice guidelines and all applicable regulatory requirements. Before participation, eligible patients were informed of all aspects of the study and provided written informed consent.

Study Design and MR Imaging Protocol

Two visits took place before MR imaging acquisition. During the initial visit, consecutive patients with CIS (demonstrating on a previous MR imaging at least 2 focal brain lesions suggestive of MS) or relapsing MS were identified. All these patients were referred to the MR imaging unit as part of the diagnostic work-up in patients with CIS and of the monitoring process in patients with relapsing MS with suspected disease activity or progression.

A total of 122 patients were initially identified, though 7 (6%) were excluded because 5 did not have either CIS or relapsing MS and 2 had exclusion criteria. Ultimately, 115 patients were included in the study and analyzed; approximately one-quarter had CIS and three-quarters had relapsing MS.

During the second visit (visit 0), a pregnancy test was performed within 24 hours before MR imaging acquisition in women with childbearing potential, and demographic and clinical data were recorded. These included the patient’s medical history, CIS or relapsing MS diagnosis, current medication, and neurologic examination results, including the Expanded Disability Status Scale score.

During visit 1, the MR imaging acquisition visit, all patients were examined on a 3T MR imaging scanner equipped with a 12-channel phased array head coil. The imaging protocol included the following sequences: 1) transverse proton density and T2-weighted fast spin-echo (TR, 2500 ms; TE, 16–91 ms; NEX, 1); and 2) transverse fast T2-FLAIR (TR, 9000 ms; TE, 100 ms; TI, 2500 ms; NEX, 2; flip angle, 120°). Both sequences were acquired with an FOV of 250 mm, and contiguous, 3-mm sections covering the whole brain (voxel size, 0.78 × 0.78 × 3.0 mm³).

In patients in whom the previous sequences confirmed the presence of at least 2 T2 lesions, an unenhanced 2D GRE T1-weighted sequence was performed before the first GBCA dose, which was manually administered as an intravenous bolus at a rate of 1 mL/s. This first 0.1-mmol/kg dose (equivalent to 0.1 mL/kg) was followed by a 20-mL saline flush, and a first contrast-enhanced 2D GRE T1-weighted sequence was performed 5 minutes after contrast administration (scan A), and a second contrast-enhanced 2D GRE T1-weighted sequence was performed 10 minutes after scan A (scan B). Twenty minutes after the start of the first contrast administration, a second dose of GBCA (0.1 mmol/kg) was administered, followed by another saline flush, resulting in a cumulative dose of 0.2 mmol/kg (0.2 mL/kg). A third contrast-enhanced 2D GRE T1-weighted sequence was performed 5 minutes later (scan C), and a fourth contrast-enhanced 2D GRE T1-weighted sequence, 10 minutes after scan C (scan D).

The following parameters were used in all the 2D GRE T1-weighted sequences: TR, 297 ms; TE, 2.46 ms; NEX, 3; flip angle, 70°; FOV, 250 mm, acquiring contiguous 3-mm sections covering the whole brain (voxel size, 0.78 × 0.78 × 3.0 mm³).

Image Analysis

To determine the number of enhancing lesions, we independently evaluated each of the 4 sets of contrast-enhanced 2D GRE T1-weighted images in a random fashion. Three neuroradiologists with >10 years of experience (not affiliated with the center where the scans were obtained) read the images, blinded to the time point at which the enhanced T1-weighted sequences had been obtained and using proton density/T2, T2-FLAIR, and unenhanced T1-weighted sequences as references.

The 3 readers independently recorded the number and topography of enhancing lesions in each contrast-enhanced T1-weighted scan. The number of lesions per patient was restricted to a maximum of 20 lesions for each scan. Patients with MR imaging–active lesions were defined as those showing at least 1 enhancing lesion in any of the contrast-enhanced T1-weighted sequences. In addition, the readers graded the quality of the images in 3 groups, good, average, or poor, and expressed their level of confidence in the detection of each enhancing lesion in each scan as very confident, confident, or not confident.

Efficacy Analysis: End Points

The end points of the study were the number of enhancing lesions and the number of patients with MR imaging–active lesions detected with a cumulative dose of a macrocyclic GBCA versus a single dose obtained at different time delays.

Adverse Events

Adverse events were recorded and classified into mild, moderate, or severe. The observation period for recording adverse events ran...
from the start of administration of the first gadolinium dose up to 24 hours after administration of the second dose.

**Sample Size Calculation**
To assess differences in active lesion detection in the 2 types of patients following administration of a single or cumulative contrast dose, we would have to include a minimum of 115 patients in the study. The sample size was determined on the basis of an expected mean of 2.1 enhancing lesions detected with a single dose of gadolinium (1.5 lesions in CIS and 2.7 in relapsing MS) and a 15% minimum increase in the number of lesions detected after the second dose, considering that 15% of patients initially included in the study would be excluded from the final analysis.

**Statistical Analysis**
Descriptive analyses (mean, median, SD, minimum, and maximum) were performed for the quantitative variables, and frequency counts by category were calculated for the qualitative variables. Confidence intervals, given when appropriate, were 2-sided in each case and provided 95% confidence.

The total number of enhancing lesions per patient between each time point was compared with Poisson regression based on generalized estimations. The number of patients with active lesions at each time point was compared using a $\chi^2$ test. Statistical significance was set at a $P$ value of <.05. $\kappa$ coefficients were calculated to assess the agreement among the readers’ assessments in pair-wise comparisons. Statistical analyses were performed with SAS, Version 9.3 (SAS Institute, Cary, North Carolina).

**RESULTS**
Baseline demographic and clinical characteristics were homogeneous between the groups, with more women than men in both the CIS and relapsing MS groups (Table 1). Six (5.2%) patients had ≤8 T2 lesions, whereas 109 patients (94.8%) had >8 T2 lesions. Three (11.5%) patients with CIS and 47 (52.8%) with relapsing MS were under a disease-modifying treatment at the time of the study. There was 1 mild adverse event (nausea after the first contrast injection), which did not require any treatment other than observation.

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### Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Patients with CIS (n = 26)</th>
<th>Patients with MS (n = 89)</th>
<th>Total (n = 115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (No.) (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>17 (65.4)</td>
<td>66 (74.2)</td>
</tr>
<tr>
<td>Male</td>
<td>9 (34.6)</td>
<td>23 (25.8)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>32.9 (7.1)</td>
<td>36.0 (6.5)</td>
</tr>
<tr>
<td>Median</td>
<td>31.0</td>
<td>36.0</td>
</tr>
<tr>
<td>Min, max</td>
<td>(25.0, 47.0)</td>
<td>(23.0, 50.0)</td>
</tr>
<tr>
<td>EDSS score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>1.6 (1.1)</td>
<td>3.0 (1.7)</td>
</tr>
<tr>
<td>Median</td>
<td>1.5</td>
<td>3</td>
</tr>
<tr>
<td>Min, max</td>
<td>(0.0, 4.0)</td>
<td>(0.0, 7.5)</td>
</tr>
</tbody>
</table>

**Note:** EDSS indicates Expanded Disability Status Scale; Min, minimum; max, maximum.

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### Table 2: Enhancing lesion count per scan and reader

<table>
<thead>
<tr>
<th>Scan</th>
<th>Lesion No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reader 1</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>243</td>
</tr>
<tr>
<td>B</td>
<td>238</td>
</tr>
<tr>
<td>C</td>
<td>362</td>
</tr>
<tr>
<td>D</td>
<td>379</td>
</tr>
<tr>
<td>Reader 2</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>260</td>
</tr>
<tr>
<td>B</td>
<td>308</td>
</tr>
<tr>
<td>C</td>
<td>373</td>
</tr>
<tr>
<td>D</td>
<td>402</td>
</tr>
<tr>
<td>Reader 3</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>325</td>
</tr>
<tr>
<td>B</td>
<td>358</td>
</tr>
<tr>
<td>C</td>
<td>455</td>
</tr>
<tr>
<td>D</td>
<td>490</td>
</tr>
</tbody>
</table>

**Total lesion No. (mean)**

| | 828 (2.4) |
| A | |
| B | 904 (2.6) |
| C | 1190 (3.3) |
| D | 1271 (3.7) |

*a The number of enhancing lesions detected in each MRI scan did not significantly differ among the 3 readers (P = .4200).

*b A, early single dose; B, delayed single dose; C, early cumulative dose; D, delayed cumulative dose.

**Contrast-Enhancing Lesions**
All 115 evaluable patients received the first and second gadolinium injections. The mean time interval between the first and second injections was 20.3 ± 1.7 minutes (19.8 ± 1.0 in CIS and 20.4 ± 1.8 in relapsing MS). After the first gadolinium dose, the 2D GRE T1-weighted scans were obtained at a mean postinjection time of 5.0 ± 0.2 minutes (scan A) and 15.1 ± 0.7 minutes (scan B). After the second dose, the scans were obtained at a mean postinjection time of 5.0 ± 0.0 minutes (scan C) and 15.1 ± 0.8 minutes (scan D).

The number of enhancing lesions detected on each MR imaging scan did not significantly differ among the 3 readers (Table 2). The total number of enhancing lesions was similar in images obtained at 5 (scan A) and 15 minutes (scan B) after the first contrast injection (276 versus 301) and at 5 (scan C) and 15 (scan D) minutes after the second dose (397 versus 424) (Fig 1). However, a significantly larger number of lesions were detected in scans obtained at 5 (mean, 5.8) and 15 minutes (mean, 6.2) after the second contrast injection than at 5 (mean, 4.5) and 15 minutes after the first injection (mean, 4.9) ($P < .001$). The increase in total lesion count between the single-dose scan obtained at 5 minutes and the cumulative scan at 15 minutes was 58% (Table 3). This increase was only 8.7% between the 5- and 15-minute single-dose scans, and 6.6% between the 5- and 15-minute cumulative-dose scans, but an increase of 27.3% was seen between the 5- and 15-minute single-dose scan and the 5-minute cumulative-dose scan.

Examples of lesion detection on images obtained at different time points are shown in Figs 2–4.

The number of patients showing at least 1 gadolinium-enhancing lesion (MR imaging–active) increased from 52% in the single-dose scans to 58.9%–59.2% in the 2 cumulative-dose scans ($P < .001$ (Fig 5).

As to reproducibility in the assessment of patients with active lesions, agreement between readers 1 and 2 was highest for scan D.
Readers expressed a higher percentage of very confident assessments for scans performed after the second injection and 15 minutes’ delay (reader 1, 93.97%; reader 2, 84.95%; and reader 3, 97.20% of the total). The readers showed no differences in their quality of image sets obtained under different conditions of contrast dose and delay, whereas they conveyed higher confidence for detecting contrast-enhancing lesions with the cumulative-dose delayed scan. Moreover, a higher concordance in identifying patients with active lesions was observed between the first and second readers with the cumulative-dose delayed scan, but not between the third reader and the other 2, with a low level of concordance observed in all 4 scans. These discrepant results are because reader 3 detected a larger number of active lesions in each scan compared with readers 1 and 2, though this difference did not reach significance.

The results of our study are in line with those in previous studies, in which greater lesion detection was found with the use of higher gadolinium doses or time delays on 2D spin-echo sequences at 1.5T. However, this study is the first to demonstrate this effect with 2D GRE sequences at 3T, a common scanning strategy used in clinical practice. In the present study, we selected a 2D GRE sequence because it reduces the flow artifacts seen with 2D spin-echo sequences, which are more problematic at 3T, leading to a decrease in background noise and better lesion detection.

**Postcontrast Image Quality**

Image quality was rated as good for most images in all 4 scans obtained: reader 1, 93.97%; reader 2, 84.95%; and reader 3, 97.20% of the total. The readers showed no differences in their rating of image quality among the 4 scans. No scan was rated as poor; therefore, all images obtained were included in the analysis. Readers expressed a higher percentage of very confident assessments for scans performed after the second injection and 15 minutes’ delay (reader 1, $P = .022$; reader 2, $P = .004$; and reader 3, $P = .005$) (Table 3). Also across readers, significant differences were found between the image sets and the readers’ assessment ($P < .001$), but not for the interaction between image set and reader.

The mean percentages of enhancing lesions in the 4 sets of images for which the observers rated identification as very confident were 41%, 45%, 54%, and 54% (A, B, C, and D, respectively), with higher values in the sets with longer delay times and higher doses ($P < .001$).

**DISCUSSION**

This study shows that a cumulative dose (0.2 mmol/kg) of a macrocyclic GBCA resulted in a significant increase in the sensitivity of contrast-enhanced 3T MR imaging for detecting active lesions in patients with CIS or relapsing MS, compared with a single contrast dose. Furthermore, this approach led to a higher percentage of patients with active lesions—that is, showing at least 1 gadolinium-enhancing lesion, which is an essential feature in the initial evaluation of patients suspected of having MS and a highly relevant prognostic marker, particularly in patients with MS under disease-modifying treatments. The readers found no differences in the quality of image sets obtained under different conditions of contrast dose and delay, whereas they conveyed higher confidence for detecting contrast-enhancing lesions with the cumulative-dose delayed scan. Moreover, a higher concordance in identifying patients with active lesions was observed between the first and second readers with the cumulative-dose delayed scan, but not between the third reader and the other 2, with a low level of concordance observed in all 4 scans. These discrepant results are because reader 3 detected a larger number of active lesions in each scan compared with readers 1 and 2, though this difference did not reach significance.

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Gadolinium-enhanced brain MR imaging is the most sensitive tool for detecting focal inflammatory activity in MS and is essential for establishing an early MS diagnosis and for predicting the disease course. Furthermore, the existence and degree of inflammatory activity are often used as an outcome measure in clinical trials, to select patients for initiation of disease-modifying treatment, to predict the risk of disability progression, and to monitor and predict treatment effect. In fact, several studies have attempted to define criteria and models for the early identification of incomplete response in individual patients via a combination of clinical and MR imaging measures during the first 6–12 months after treatment initiation, which are partially or completely based on the detection of disease activity. All these data support the pivotal role of the presence and number of gadolinium-enhancing lesions to assess radiologic disease activity, which is used, in turn, for diagnosing and guiding therapeutic strategies and as a surrogate marker to evaluate treatment efficacy.

![Total number of enhancing lesions per scan performed and reader](image)

**Table 3: Number of enhancing lesions in patients with active lesions by scan and reader**

<table>
<thead>
<tr>
<th>Reader, Scan</th>
<th>No.</th>
<th>Total (mean)</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 A 69 325 2.0 (4.7) 1.000 20.000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 B 67 358 3.0 (5.3) 1.000 20.000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 C 76 452 3.0 (6.0) 1.000 20.000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 D 79 490 3.0 (6.2) 1.000 20.000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* A higher number of enhancing lesions was detected for cumulative-versus-single dose scans ($P < .001$).

* A, early single dose; B, delayed single dose; C, early cumulative dose; D, delayed cumulative dose.

* No., number of patients with active lesions.

* The number of lesions was restricted to a maximum of 20 per patient.

* A higher number of enhancing lesions was detected for cumulative-versus-single dose scans ($P < .001$).

* A, early single dose; B, delayed single dose; C, early cumulative dose; D, delayed cumulative dose.
in clinical trials. Thus, reliable detection of enhancing lesions is an important clinical and research goal in patients with CIS and MS, and considerable effort is required to optimize the parameters used in standard techniques to maximize the sensitivity of MR imaging for this purpose.

One strategy to increase the sensitivity of enhanced MR imaging for detecting active brain lesions in patients with MS is the use of high doses of contrast agent. Our findings indicate that this factor is the main driver of the improved sensitivity found. In our patients with CIS and MS, the sensitivity increase was mainly due to cumulative contrast dosing, whereas the influence of time was much weaker: Significant differences were detected between scans performed with single and cumulative doses, but not between the different delay times (5 and 15 minutes) used in each of the dosing regimens.

In a previous study, use of 1.0 mol/L (0.2 mmol/kg) of GBCA allowed detection of a larger number of enhancing lesions and patients with active disease than the use of 0.5 mol/L at the same dose, but the number of enhancing lesions did not differ significantly between images obtained 5 and 10 minutes after the injec-
In addition, the design used in this study would be very difficult to implement in clinical practice (2 consecutive injections of gadolinium to achieve the cumulative double dose). However, on the basis of the results of the present study that show a significant increase in the detection of active lesions and scans showing active lesions after the second injection of contrast, we may suggest the use of a single injection of a double dose of gadolinium and a minimum delay of 5 minutes before the acquisition of the T1-weighted sequence. This “dead” time can be used to perform the T2-FLAIR sequences, so that the total acquisition time is not lengthened. This suggestion can facilitate the use of this strategy in clinical practice.

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We also have to consider recent literature showing that with repeat contrast administration, gadolinium accumulates in the brain despite an intact blood-brain barrier and normal renal function, producing an increase in signal intensity in certain areas, such as the dentate nucleus and globus pallidus. This effect, which has not been associated with histopathologic findings, has mainly been detected with linear GBCAs. Only 1 study has shown signal changes in the dentate nucleus and globus pallidus after several administrations of a macrocyclic GBCA. However, in this study, signal changes could not be detected visually (only quantitatively), and the design of the study could not control for or exclude the use of other GBCAs, including linear agents. Moreover, the results of this study contradict other clinical studies that could not find signal-intensity changes in patients receiving several doses of the same macrocyclic GBCA used in our study. All these data have been recently analyzed in a systematic review article based on the analysis of 25 original publications, showing that the signal changes in certain central nervous system structures identified with MR imaging correlated positively with the exposure to linear agents but negatively with the stability of contrast agents, which is higher with macrocyclic agents. Nonclinical studies have indicated that all types of gadolinium can be deposited in different tissues, though the detected residual gadolinium concentration in the brain is approximately 1- to 15-fold higher for linear than for macrocyclic GBCAs.

Although no symptoms or diseases linked to brain gadolinium deposition have been reported, data on long-term effects are still limited.

This study has limitations. First, the design did not enable us to establish the relative influences of cumulative dose and delayed scanning on the increase in sensitivity, though the results obtained indicate that the differences were mainly driven by the cumulative gadolinium dose. Second, the high variability in the detection of active lesions by one of the readers limits the interpretation of the higher concordance observed in cumulative and delayed scans compared with single-dose early scans between the 2 other readers.

CONCLUSIONS
The results of this study indicate that a cumulative dose (0.2 mmol/kg) of macrocyclic GBCA administered as an intravenous bolus in 2 injections of 0.1 + 0.1 mmol/kg is a safe procedure that significantly increases the detection rate of gadolinium-enhancing lesions in patients with CIS or relapsing MS. Furthermore, this approach enables identification of a larger number of patients with active lesions and provides higher confidence in lesion detection. On the basis of these results, the use of a single injection of a double dose of macrocyclic gadolinium-based contrast and a delay time of 5 minutes could be considered in brain MR imaging studies aimed at detecting active MS lesions whenever this purpose could have relevant therapeutic implications. However, on the basis of the limited data on the long-term effects of gadolinium deposition in the brain, which could also occur with macrocyclic GBCAs, the use of this strategy in all routine MR imaging examinations of patients with MS is not recommended.
Disclosures: Alex Rovira—RELATED: Grant: Bayer HealthCare. Comments: This research was funded by Bayer HealthCare Pharmaceuticals*; UNRELATED: Board Membership: Biogen Idec. Novartis, Sanofi Genzyme, Omea Medical; Consultancy: Biogen Idec, Novartis, Sanofi Genzyme, Omea Medical; Payment for Lectures Including Service on Speakers Bureaus: Bayer HealthCare Pharmaceuticals, Sanofi Genzyme, Bracco, Merck Serono, Teva Pharmaceutical Industries Ltd, Novartis, Biogen Idec; Payment for Development of Educational Presentations: Bayer HealthCare Pharmaceuticals, Bracco, Teva Pharmaceutical Industries Ltd, Novartis, Biogen Idec. Cristina Auger—RELATED: Grant: Bayer HealthCare Pharmaceuticals*; UNRELATED: Payment for Lectures Including Service on Speakers Bureaus: Novartis, Biogen Idec, Stendhal America SA. Elena Huerga—RELATED: Grant: Bayer HealthCare Pharmaceuticals.* Juan Francisco Corral—Grant: RELATED: Stendhal America SA. Elena Huerga—Grant: RELATED: Tre-Garriga.* Mar Tintore—Grant: RELATED: Bayer HealthCare Pharmaceuticals.* Jaume Sas—Grant: RELATED: Bayer HealthCare Pharmaceuticals.*

References:

38. Runge VM. Safety of the gadolinium-based contrast agents for magnetic resonance imaging, focusing in part on their accumulation in the brain and especially the dentate nucleus. Invest Radiol 2016; 51:273–79 Medline
Diffusional Kurtosis Imaging of the Corticospinal Tract in Multiple Sclerosis: Association with Neurologic Disability


ABSTRACT

BACKGROUND AND PURPOSE: Multiple sclerosis is an autoimmune disorder resulting in progressive neurologic disability. Our aim was to evaluate the associations between diffusional kurtosis imaging–derived metrics for the corticospinal tract and disability in multiple sclerosis.

MATERIALS AND METHODS: Forty patients with MS underwent brain MR imaging including diffusional kurtosis imaging. After we masked out T2 hyperintense lesions, the fractional anisotropy, mean diffusivity, radial diffusivity, axial diffusivity, mean kurtosis, radial kurtosis, and axial kurtosis were estimated for the corticospinal tract. Disability was quantified by using the Expanded Disability Status Scale at the time of MR imaging and 12 months post-MR imaging. The Pearson correlation coefficient and linear regression analyses were conducted to evaluate the associations between diffusion metrics and disability.

RESULTS: Significant correlations were found between the Expanded Disability Status Scale scores during the baseline visit and age ($r = 0.47$), T2 lesion volume ($r = 0.38$), corticospinal tract mean diffusivity ($r = 0.41$), radial diffusivity ($r = 0.41$), axial diffusivity ($r = 0.34$), fractional anisotropy ($r = -0.36$), and radial kurtosis ($r = -0.42$). Significant correlations were also found between the Expanded Disability Status Scale scores at 12-month follow-up and age ($r = 0.38$), mean diffusivity ($r = 0.45$), radial diffusivity ($r = 0.41$), axial diffusivity ($r = 0.45$), mean kurtosis ($r = -0.42$), radial kurtosis ($r = -0.56$), and axial kurtosis ($r = -0.36$). Linear regression analyses demonstrated significant associations among radial kurtosis, age, and Expanded Disability Status Scale score during the baseline visit, while radial kurtosis was the only variable associated with Expanded Disability Status Scale score for the 12-month follow-up.

CONCLUSIONS: Radial kurtosis of the corticospinal tract may have an association with neurologic disability in MS.

MULTIPLE SCLEROSIS

Multiple sclerosis is an autoimmune disorder of the central nervous system characterized by recurrent episodes of inflammation, demyelination, edema, and axonal loss, which can result in a progressive accumulation of neurologic disability. MR imaging is routinely performed to assess the burden of disease in patients with MS to guide therapeutic decisions. Conventional MR imaging is widely used to evaluate macrostructural changes such as T2 hyperintense lesions, T1 black holes, gadolinium-enhancing lesions, and brain volume loss. Although conventional MR imaging analysis has been used for years to assess the disease burden, it cannot fully explain the degree of neurologic dysfunction. The lack of correlation between neurologic disability and conventional MR imaging measures is commonly described as the “clinicoradiologic paradox.”

DTI has been previously used to assess the integrity of brain tissue and to probe specific white matter tracts. Prior studies have evaluated microstructural changes of the corticospinal tract (CST) in MS and the association between diffusivity of the CST and measures of neurologic disability. However, a fundamental limitation of DTI is that the data analysis approximates the water diffusion dynamics within brain tissue as being a Gaussian...
process, though considerable non-Gaussian diffusion effects are observed throughout the brain. Hence, DTI does not fully characterize water diffusion in the brain. Diffusional kurtosis imaging (DKI)\(^\text{18}\) is a clinically feasible diffusion MR imaging method, which extends the DTI model to include non-Gaussian diffusion effects.\(^\text{18-20}\) As a result, DKI has the potential to provide more sensitive biomarkers for probing microscopic structural changes occurring in the normal-appearing white matter (NAWM), which could lead to better predictive biomarkers for disease progression. Although DKI has been applied to MS in a few preliminary studies,\(^\text{18-22}\) the potential of DKI to aid in the assessment of neurologic disability in MS is still not well-established.

The aim of this study was to examine the associations between DKI-derived diffusion metrics of the corticospinal tract and physical disability in patients affected by MS, as measured by the Extended Disability Status Scale (EDSS).\(^\text{23}\) Our hypothesis was that DKI-derived metrics have stronger associations with neurologic dysfunction than DTI metrics.

**MATERIALS AND METHODS**

**Participants**

The study was approved by the institutional review board, who exempted the study from requiring individual patient consent. We retrospectively reviewed the PACS for all patients with multiple sclerosis who underwent brain MR imaging during an 18-month period. Inclusion criteria were the following: 1) age between 18 and 70 years; 2) diagnosis of multiple sclerosis according to established diagnostic criteria;\(^\text{2}\) 3) brain MR imaging performed according to our standard multiple sclerosis protocol, including DKI; and 4) neurologic evaluation within 1 month of the MR imaging available in the electronic medical record (baseline visit). On the basis of the clinical phenotype, patients were categorized as having clinically isolated syndrome, relapsing-remitting MS, primary-progressive MS, secondary-progressive MS, or unknown type of MS.\(^\text{24}\) We excluded patients with history of neurologic disorders other than multiple sclerosis. We also excluded all imaging datasets degraded by bulk head motion or other artifacts. The degree of neurologic impairment was assessed by using the Kurtzke EDSS during the baseline visit (EDSS\(_b\)). If subsequent clinical neurologic encounters were documented in the electronic medical record, then we recorded the EDSS score for the neurologic visit 12 months after brain MR imaging (EDSS\(_{12\,m}\)).

**MR Imaging**

Brain MRIs were performed on a 1.5T Avanto MR imaging scanner (Siemens, Erlangen, Germany). A sagittal T1-weighted MPRAGE (TR/TE/TI = 1900/2.91/1100 ms, flip angle = 15°, acquisition matrix = 225 × 199, FOV = 256 × 256 mm\(^2\), section thickness = 1 mm) and an axial FLAIR sequence (TR/TE/TI = 8000/88/2372 ms, flip angle = 180°, matrix = 424 × 512, FOV = 220 × 220 mm\(^2\), section thickness = 5 mm) were performed. Axial diffusion-weighted images were acquired with 3 b-values (0, 1000, and 2000 s/mm\(^2\)) along 30 diffusion-encoding directions with a single-shot twice-refocused spin-echo EPI sequence with NEX = 1 (NEX = 10 for b = 0). Imaging parameters of the diffusion sequence were the following: voxel size = 3 × 3 × 3 mm\(^3\), number of sections = 40, TR/TE = 5500/99 ms, FOV = 222 × 222 mm\(^2\), acquisition matrix = 74 × 74, bandwidth/pixel = 1325 Hz, acceleration factor = 2, acquisition time = 7 minutes.

**Data Processing**

The Lesion Segmentation Tool toolbox (http://www.applied-statistics.de/ls1.html), an open-source toolbox for SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12), specifically the lesion-growth algorithm, was used to segment T2 hyperintense lesions from the MPRAGE and FLAIR images (\(\kappa = 0.2\)).\(^\text{25}\) Then, a neuroradiologist blinded to all clinical information inspected each lesion mask to ensure accurate lesion segmentation. With MRcron software (http://www.nitrc.org/projects/mrcron/),\(^\text{26}\) we calculated total white matter lesion volume for each patient.

With Diffusional Kurtosis Estimator software\(^\text{27}\) (Version 2.6, https://www.nitrc.org/projects/dke/) implemented in Matlab (MathWorks, Natick, Massachusetts), we calculated the diffusion and kurtosis tensors on a voxel-by-voxel basis. Parametric maps for the following metrics were obtained from the DKI dataset: 1) diffusivity metrics: fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (\(\lambda_1\)), and radial diffusivity (\(\lambda_2\) and \(\lambda_3\)); 2) kurtosis metrics: mean kurtosis (MK), axial (\(K_{ax}\)) and radial (\(K_{rad}\)) kurtosis. MK is the average kurtosis over all diffusion directions, \(K_0\) is the kurtosis in the direction of the diffusion tensor eigenvector with the largest diffusion eigenvalue (typically along the direction of the axons), and \(K_x\) is the average kurtosis over all directions perpendicular to the diffusion eigenvector with the largest eigenvalue (typically all directions perpendicular to the axons).\(^\text{18}\) FA maps were normalized to the Montreal Neurological Institute standard space FA template, a high-resolution average of 58 well-aligned good-quality FA images from healthy male and female subjects between 20 and 50 years of age, at 1 × 1 × 1 mm\(^3\) resolution. The resulting normalization parameters were then applied to the remaining diffusion maps and to the lesion masks. The white matter skeleton was obtained by using Tract-Based Spatial Statistics (TBSS; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS) in FSL (FA threshold, \(\geq 0.4\)).\(^\text{28}\) The corticospinal tract volumes of interest were obtained from the WM skeleton with the Johns Hopkins University White Matter Tractography Atlas,\(^\text{29}\) after masking out T2 hyperintense areas of individual patients (Fig 1). As a result, the CST VOI only included the NAWM of the CST. Then, average diffusion values of the CST VOIs were computed for all diffusion metrics and subjects by using Matlab.

Statistical analyses were conducted with SPSS (Version 22; IBM, Armonk, New York). Due to the small number of men in the study, sex differences in EDSS were examined with an independent-samples Mann-Whitney U test. Pearson correlations were examined between CST diffusion metrics and EDSS at baseline and at the 12-month follow-up to characterize basic relations among variables. Results of the Pearson correlations were considered statistically significant with \(P < .05\), corrected for multiple comparisons with the false discovery rate method.\(^\text{30}\) A linear regression equation with the stepwise method was calculated to evaluate the relationships among EDSS at baseline, the dependent variable, and the independent variables entered in the following order: age, white matter lesion volume, and CST diffusion param-
parameters. Additional linear regressions were also calculated to evaluate the associations between the same independent variables and EDSS at the 12-month follow-up and changes in the EDSS score between baseline and 12-month follow-up. Before the linear regression equation calculation, multicollinearity among independent variables was assessed with the variance inflation factor (VIF). Independent variables were excluded from the analysis when the VIF was >10. The results of the linear regression analyses were considered statistically significant at \( P < .05 \).

RESULTS

Demographic and Clinical Characteristics

Forty patients with MS were included in this study. Table 1 shows demographic, clinical, and conventional MR imaging characteristics of the entire cohort and of the subgroup of 28 patients with 12-month follow-up. There was no significant difference in EDSS scores between men and women at baseline (women: median = 3, range = 1–8, \( n = 33 \); men: median = 3, range = 1–3.5, \( n = 7 \); \( U = 138.5, P = .421 \)) and at the 12-month follow-up (women: median = 3, range = 0–9, \( n = 24 \); men: median = 6, range = 1–6, \( n = 4 \); \( U = 39.5, P = .590 \)). Patients had a disease duration of at least 1 year since their first symptom before the brain MR imaging. The exact duration of disease was not documented in the chart for 3 patients. Of the 40 patients, 25 were receiving disease-modifying treatments, which included interferon \( \beta \) (\( n = 13 \)), glatiramer acetate (\( n = 8 \)), natalizumab (\( n = 3 \)), and fingolimod (\( n = 1 \)).

Imaging Data

Table 2 demonstrates the correlations among age, T2 lesion volume, CST diffusion metrics, EDSS\(_0\) and EDSS\(_{12 \text{ m}}\) (Fig 2). Analyses of the multicollinearity among independent variables resulted in inclusion in the regression model of the following independent variables with a VIF of <10: age (VIF = 1.30), T2 white matter lesion volume (VIF = 1.42), CST MK (VIF = 5.89), CST K\(_1\) (VIF = 2.21), and CST K\(_{\perp}\) (VIF = 5.43). FA, MD, \( \lambda_1 \), and \( \lambda_4 \) were excluded from the analyses due to a VIF of >10. Then, a linear regression analysis was performed to evaluate the relationship between EDSS\(_0\) and the following variables: age, T2 white matter lesion volume, MK, K\(_0\), and K\(_{\perp}\). A significant regression equation was found \(( F [2,37] = 8.875, \ P = .001 \) with an \( R^2 \) of 0.324, \( K_0 = -0.329, P = .023 \) and age \( (\beta = .399, P = .007 \)) were the only variables significantly associated with EDSS\(_0\) (Table 3). A linear regression analysis was performed to evaluate the relationship between EDSS\(_{12 \text{ m}}\) and the same variables (age, T2 lesion load, and CST diffusion metrics obtained at baseline). A significant regression equation was found \(( F [1,26] = 12.014, P = .002 \) with an \( R^2 \) of 0.316. K\(_{\perp}\) \( (\beta = -0.562, P = .002 \) was the only variable to have a significant association with EDSS\(_{12 \text{ m}}\) (Table 3). A linear re-

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**Table 1: Patient clinical characteristics and imaging metrics**

<table>
<thead>
<tr>
<th>Metrics</th>
<th>Entire Cohort</th>
<th>Patients with 12-Month Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>40</td>
<td>28</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>33/7</td>
<td>24/4</td>
</tr>
<tr>
<td>Age (mean) (yr)</td>
<td>42.9 ± 12.5</td>
<td>42.1 ± 13.1</td>
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<tr>
<td>EDSS(_0) (mean)</td>
<td>3.4 ± 1.9</td>
<td>3.6 ± 2</td>
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<tr>
<td>EDSS(_{12 \text{ m}}) (mean)</td>
<td>4.2 ± 2.3</td>
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</tr>
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<td>MS type (RR/SP/unknown/PP)</td>
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<td>23/1/3/1</td>
</tr>
<tr>
<td>Disease duration (mean) (yr)</td>
<td>8.0 ± 6.4</td>
<td>6.9 ± 4.5</td>
</tr>
<tr>
<td>T2 lesion load (mean) (mL)</td>
<td>21.3 ± 22.8</td>
<td>23.3 ± 26.0</td>
</tr>
<tr>
<td>CST FA (mean)</td>
<td>0.44 ± 0.03</td>
<td>0.44 ± 0.03</td>
</tr>
<tr>
<td>CST MD (mean)</td>
<td>0.94 ± 0.06</td>
<td>0.93 ± 0.06</td>
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<tr>
<td>CST ( \lambda_1 ) (mean)</td>
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<td>0.70 ± 0.06</td>
</tr>
<tr>
<td>CST (mean)</td>
<td>1.41 ± 0.07</td>
<td>1.40 ± 0.07</td>
</tr>
<tr>
<td>CST MK (mean)</td>
<td>1.17 ± 0.06</td>
<td>1.17 ± 0.06</td>
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<tr>
<td>CST K(_{\perp}) (mean)</td>
<td>1.60 ± 0.15</td>
<td>1.60 ± 0.14</td>
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<tr>
<td>CST K(_1) (mean)</td>
<td>0.96 ± 0.05</td>
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</table>

**Table 2: Correlations between EDSS and age, T2 lesion volume, and diffusion metrics**

<table>
<thead>
<tr>
<th>Metrics</th>
<th>( r )</th>
<th>( P ) Value*</th>
<th>( r )</th>
<th>( P ) Value*</th>
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<td>Age</td>
<td>0.47</td>
<td>.009</td>
<td>0.38</td>
<td>.003</td>
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<tr>
<td>T2 lesion volume</td>
<td>0.38</td>
<td>.018</td>
<td>0.23</td>
<td>.177</td>
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<td>MD</td>
<td>0.41</td>
<td>.018</td>
<td>0.45</td>
<td>.018</td>
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<tr>
<td>( \lambda_1 )</td>
<td>0.34</td>
<td>.023</td>
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<tr>
<td>( \lambda_4 )</td>
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<td>.018</td>
<td>0.41</td>
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<tr>
<td>FA</td>
<td>-0.36</td>
<td>.022</td>
<td>-0.30</td>
<td>.063</td>
</tr>
<tr>
<td>MK</td>
<td>-0.29</td>
<td>.046</td>
<td>-0.42</td>
<td>.023</td>
</tr>
<tr>
<td>K(_0)</td>
<td>-0.25</td>
<td>.063</td>
<td>-0.36</td>
<td>.040</td>
</tr>
<tr>
<td>K(_{\perp})</td>
<td>-0.42</td>
<td>.018</td>
<td>-0.56</td>
<td>.009</td>
</tr>
</tbody>
</table>

* \( P \) values were corrected for multiple comparisons with the false discovery rate method.
gression analysis was also performed to evaluate the relationship between change in the EDSS score (baseline EDSS versus 12-month follow-up EDSS) and the same independent variables. None of the variables had significant associations with change in the EDSS score.

DISCUSSION

We conducted a retrospective study designed to explore the hypothesis that DKI-derived metrics of the CST have stronger associations with physical disability than DTI-derived metrics in patients with MS. We have preliminarily found that $K_{1}$ of the CST has an association with physical disability. Associations were found between DKI-derived metrics and neurologic disability at the time of brain MR imaging, as well as with the degree of disability at 12-month follow-up. Due to the retrospective nature of our study, however, our results will require validation with future prospective studies. If our preliminary observations are confirmed, DKI-derived metrics may play an important role in improving our understanding of physical disability and prognosis, as well as in guiding treatment considerations in multiple sclerosis.

The correlations between DTI-derived measures of CST integrity and functional disability in MS have been previously evaluated. Lin et al. found greater MD and radial diffusivity in the normal-appearing CST in patients with MS than in healthy controls. Prior studies found significant associations between DTI-derived measures of CST integrity and functional disability. Bergsland et al. found significant correlations between the EDSS and diffusivity measures, including FA, MD, $\lambda_{1}$, and $\lambda_{2}$ for the NAWM CST. Tovar-Moll et al. found an inverse association between CST FA and EDSS when correcting for lesion volume. Other authors found only trends for an inverse correlation between EDSS and CST FA in

![FIG 2. Scatterplots for the Expanded Disability Status Scale at the time of the brain MR imaging versus radial diffusivity (A) and radial kurtosis (C) of the corticospinal tracts, and EDSS at the follow-up visit 12 months after the brain MR imaging versus radial diffusivity (B) and radial kurtosis (D) of the corticospinal tracts in patients with MS.

Table 3: Linear regression analyses: coefficients table

<table>
<thead>
<tr>
<th></th>
<th>EDSS$_{0}$</th>
<th>P Value</th>
<th>EDSS$_{12}$m</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Constant)</td>
<td>.022</td>
<td>&lt;.001</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>.399</td>
<td>.022</td>
<td>.172</td>
<td>.347</td>
</tr>
<tr>
<td>CST MK</td>
<td>.074</td>
<td>.811</td>
<td>.257</td>
<td>.432</td>
</tr>
<tr>
<td>CST $K_{1}$</td>
<td>.055</td>
<td>.774</td>
<td>.006</td>
<td>.979</td>
</tr>
<tr>
<td>CST $K_{2}$</td>
<td>-.329</td>
<td>.023</td>
<td>-.562</td>
<td>.002</td>
</tr>
<tr>
<td>T2 lesion volume</td>
<td>.353</td>
<td>.355</td>
<td>-.141</td>
<td>.491</td>
</tr>
</tbody>
</table>
MS\textsuperscript{14,15} or found weak correlations between EDSS and DTI metrics of the CST (MD, λ⊥, and λ//)\textsuperscript{9}. Reich et al\textsuperscript{16} did not find significant differences in FA, MD, λ⊥, and λ// for the CST among patients with various degrees of ankle dorsiflexion impairment. Harrison et al\textsuperscript{13} found that DTI indices of the CST were not able to predict EDSS scores. Overall, prior study results demonstrated that conventional DTI measures may have an association with physical disability, but this relationship has not been consistently demonstrated in the literature. Here, we report associations of conventional DTI metrics for the CST with EDSS, which confirm prior studies, and extend prior investigations by demonstrating significant correlations between kurtosis metrics, especially $K_\perp$, and EDSS.

The diffusional kurtosis metrics are complementary to the diffusion tensor metrics and provide microstructural information that more comprehensively characterizes brain tissue microstructure.\textsuperscript{18} A few studies have previously evaluated the use of DKI-derived metrics in the characterization of demyelinating disease in animal models and in patients affected by MS. Using the cuprizone mouse model of CNS demyelination, Falangola et al\textsuperscript{34} evaluated the associations between DKI-derived metrics in cuprizone-induced chronic demyelination of the corpus callosum and morphologic WM alterations associated with myelin pathology. DKI-derived metrics were found to have greater sensitivity than conventional DTI parameters in the detection of cuprizone-induced demyelination of the anterior corpus callosum. Guglielmetti et al\textsuperscript{15} found that MK and $K_\perp$, but not DTI-derived parameters, were sensitive to cuprizone-induced cortical alterations. Yoshida et al\textsuperscript{19} have conducted ROI-based quantitative analyses of MK for 24 cerebral NAWM regions in 11 patients with MS. The average MK for the NAWM was found to be lower in patients with MS than in healthy controls. Raz et al\textsuperscript{31} evaluated the signal characteristics of the spinal cord by using DKI and found that MK was lower in patients with MS than in healthy controls. Abnormal DKI-derived metrics of the NAWM were found in patients with MS but not in individuals with neuromyelitis optica.\textsuperscript{22} Bester et al\textsuperscript{20} applied DKI to the evaluation of cortical gray matter microstructural changes and found that decreased cortical MK was associated with poor performance on the Delis–Kaplan Executive Function System test ($r = 0.66$). De Kouchkovsky et al\textsuperscript{17} assessed white matter integrity in MS by using DKI-derived white matter integrity metrics, specifically axonal water fraction, intra-axonal diffusivity, radial and axial extra-axonal diffusivity, and tortuosity of the extra-axonal space. The authors found a moderate association between axonal water fraction in the corpus callosum and the EDSS score ($p = 0.39$). Our study design differs from the methodology used by de Kouchkovsky et al. In fact, our approach was to study the associations between physical disability and pure diffusion metrics of the CST, such as mean kurtosis and radial kurtosis, as opposed to model-dependent quantities such as axonal water fraction.

These prior studies have shown that kurtosis parameters provide more comprehensive information about brain tissue microstructure than that available with conventional DTI.\textsuperscript{18} It is important to determine whether this enhanced sensitivity to microstructural changes provided by DKI translates into improved disability prediction. Our work demonstrates promising relations between DKI-derived diffusion metrics for the CST and clinical disability. In this retrospective cohort, age and $K_\perp$ were associated with neurologic disability and accounted for approximately 32% of the variability of EDSS scores at baseline. We also found that $K_\perp$ was the only parameter significantly associated with disability at the 12-month follow-up examination and accounted for about 32% of the variability of EDSS scores. If the associations between $K_\perp$ and disability are validated in future larger prospective studies, these metrics may ultimately prove to be powerful adjuncts to the clinical assessment of patients with MS.

Histopathology and MR imaging studies have shown that the NAWM is affected, to a lesser extent, by the same pathologic processes that are found in MS lesions, specifically inflammation, demyelination, microglial activation, axonal injury, Wallerian degeneration, and macrophage infiltration.\textsuperscript{36-39} The pathologic basis of the stronger association between $K_\perp$ and physical disability in MS requires further determination. $K_\perp$ is the average kurtosis over all directions perpendicular to the diffusion eigenvector with the largest eigenvalue (typically all directions perpendicular to the axons). We hypothesized that the stronger association between physical disability and $K_\perp$ than between other diffusion metrics may reflect a greater sensitivity of $K_\perp$ to early pathologic changes of the NAWM, possibly myelin breakdown resulting in demyelination or hypomyelination or an increase of membrane barriers due to microgliosis.\textsuperscript{34,35} Unfortunately, pathologic findings for the NAWM are not available for this patient cohort. Future studies on the correlations between DKI parameters and pathologic findings for the NAWM in MS will help clarify the histopathologic basis of our preliminary observations.

An alternative approach to DKI for quantifying diffusional non-Gaussianity is to fit the diffusion MR imaging signal to a stretched exponential model.\textsuperscript{40} However, this model does not allow the estimation of kurtosis,\textsuperscript{18} and it is less appropriate for white matter because incorporating the effects of diffusion anisotropy is challenging.\textsuperscript{41} Biexponential fitting of the diffusion MR imaging signal is also feasible. This is fully consistent with DKI but requires the acquisition of more diffusion-weighted data than the truncated cumulant expansion signal model conventionally used with DKI (as in the present study).\textsuperscript{18}

This study has limitations. First, it was a retrospective study that evaluated a relatively limited number of 40 patients, which precluded analysis of data in patients with relapsing-remitting, primary-progressive, and secondary-progressive MS separately. Twelve-month clinical follow-up information was available for only 28/40 patients (70%). We also did not evaluate the subsequent temporal evolution of the observed CST diffusion measures. Finally, while the EDSS is an effective tool widely used in clinical trials to assess the severity of MS, it is heavily weighted toward ambulation, and the multiple sclerosis functional composite may be a more sensitive method to evaluate disease progression.\textsuperscript{28}

\section*{CONCLUSIONS}

We have found significant associations between the $K_\perp$ of the CST and disability in MS. DKI metrics were found to have stronger
associations than DTI metrics with measures of disability in MS. It is important that this work be validated in future prospective studies with larger sample sizes.

**ACKNOWLEDGMENTS**

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Disclosures: Jens H. Jensen—OTHER RELATIONSHIPS: I am a coinventor on US Patent 8870706 that covers one of the imaging methods investigated in this article [DK]. The patent is owned by a former employer (New York University), but I could be entitled to a share of any royalties at some point. To date, I have not received royalties from this patent. Joseph A. Helpern—UNRELATED: Grant: The Litwin Foundation. Neal U. Hatch—UNRELATED: Support for Travel to Meetings for the Study or Other Purposes: partial reimbursement of travel expenses provided by the department. *Money paid to the institution.

**REFERENCES**


Volumetric Analysis from a Harmonized Multisite Brain MRI Study of a Single Subject with Multiple Sclerosis

ABSTRACT

BACKGROUND AND PURPOSE: MR imaging can be used to measure structural changes in the brains of individuals with multiple sclerosis and is essential for diagnosis, longitudinal monitoring, and therapy evaluation. The North American imaging in Multiple Sclerosis Cooperative steering committee developed a uniform high-resolution 3T MRI imaging protocol relevant to the quantification of cerebral lesions and atrophy and implemented it at 7 sites across the United States. To assess intersite variability in scan data, we imaged a volunteer with relapsing-remitting MS with a scan-rescan at each site.

MATERIALS AND METHODS: All imaging was acquired on Siemens scanners (4 Skyra, 2 Tim Trio, and 1 Verio). Expert segmentations were manually obtained for TI-hypointense and T2 (FLAIR) hyperintense lesions. Several automated lesion-detection and whole-brain, cortical, and deep gray matter volumetric pipelines were applied. Statistical analyses were conducted to assess variability across sites, as well as systematic biases in the volumetric measurements that were site-related.

RESULTS: Systematic biases due to site differences in expert-traced lesion measurements were significant (P < .01 for both T1 and T2 lesion volumes), with site explaining >90% of the variation [range, 13.0–16.4 mL in T1 and 15.9–20.1 mL in T2] in lesion volumes. Site also explained >80% of the variation in most automated volumetric measurements. Output measures clustered according to scanner models, with similar results from the Skyra versus the other 2 units.

CONCLUSIONS: Even in multicenter studies with consistent scanner field strength and manufacturer after protocol harmonization, systematic differences can lead to severe biases in volumetric analyses.

ABBREVIATIONS: NAIMS = North American Imaging in Multiple Sclerosis Cooperative; T1LV = TI-hypointense lesion volume; T2LV = T2 lesion volume

Conventional MR imaging is an established tool for measuring CNS lesions and tissue compartment volumes in vivo in individuals with multiple sclerosis. In the brain and spinal cord, inflammatory demyelinating lesions appear hyperintense on T2-weighted images. Total cerebral T2 lesion volume (T2LV) is a key metric for the longitudinal monitoring of disease severity, as well as a standard outcome in clinical trials of MS therapeutics. Many T2 lesions exhibit pulse-sequence-dependent hypointensity on T1-weighted images, which has been shown to be associated with more severe (destructive) histopathology and worse clinical outcomes. MR imaging is also used to measure cerebral

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atrophy, a commonly used supportive outcome measure of the neurodegenerative aspects of the disease in both relapsing-remitting and progressive forms of MS. Together, lesion and atrophy measures provide complementary quantitative information about disease progression that are considered central to patient assessment.

Unfortunately, differences in acquisition methods have the potential to bias MR imaging metrics. Factors such as equipment manufacturer, magnetic field strength, and acquisition protocol can affect image contrast and resultant volumetric data. Indeed, several groups have investigated the reliability of volumetric measurements across scanners, but little is understood about the variability in volumetric measurements of lesions and atrophy in individuals with MS. Furthermore, many automated segmentation algorithms depend on statistical atlases or models that are built with healthy volunteers or atrophy in individuals with MS. Furthermore, automated segmentation algorithms depend on statistical atlases or models that are built with healthy volunteers or atrophy in individuals with MS. Together, lesion and atrophy measures provide complementary quantitative information about disease progression that are considered central to patient assessment.

The North American Imaging in Multiple Sclerosis Cooperative (NAIMS) was established to accelerate the pace of imaging research. As a consortium, our first aim was to facilitate multicenter imaging studies by creating harmonized MR imaging protocols across sites. In this article, we describe initial results from our pilot study, which tested the feasibility of multisite standardization of MR imaging acquisitions for the quantification of lesion and tissue volumes. We compare inter- to intrasite scan-rescan variability in various MR imaging output metrics with consistently acquired 3T acquisitions.

### MATERIALS AND METHODS

#### Participant

A 45-year-old man with clinically stable relapsing-remitting MS and mild-to-moderate physical disability was imaged at 7 NAIMS sites across the United States (Table). He developed the first symptoms of the disease 13 years before study enrollment and had been relapse-free in the previous year after starting dimethyl fumarate. His last intravenous corticosteroid administration was 5 years previously. His timed 25-foot walk at study entry was 5.3 seconds. His Expanded Disability Status Scale score was 3.5, both at study entry and exit, without any intervening relapses on-study. The participant signed informed consent for this study, which was approved by the institutional review board of each site.

### Scan Acquisition

Through consensus agreement in the Cooperative, NAIMS developed a standardized high-resolution 3T MR imaging brain scan protocol. All imaging was acquired with Siemens scanners, which, at the time of the study, were used by most NAIMS sites. Scan-rescan pairs were acquired on these scanners; the most relevant acquisition sequences are shown in the Table. At each site, the scan-rescan experiment was performed on the same day, with the participant removed and repositioned between scans. None of the participant’s scans were coregistered to each other, to replicate a “real world” clinical trial setting. The volunteer was also imaged at the National Institutes of Health NAIMS site at the beginning and end of the study (5 months later) to assess disease stability. Raw MR imaging scans were distributed to 4 NAIMS sites for postprocessing.

### Expert Lesion Tracing

De-identified images underwent manual quantification to assess total cerebral T1-hypointense lesion volume (T1LV) and T2LV from the native 3D FLAIR and T1 images by the consensus of trained observers (G.K., F.Y.) under the supervision of an experienced observer (S.T.). For T2LV, this process involved manually identifying all lesions on the FLAIR images. For T1LV, lesions were required to show hypointensity on T1-weighted images and at least partial hyperintensity on FLAIR images. The lesions were then segmented by 1 observer (G.K.) with a semiautomated edge-finding tool in Jim (Version 7.0; http://www.xinapse.com/home.php) to determine lesion volumes. Images were presented to the same reading panel for all of the above steps in random order in 1 batch and mixed into a stack of 50 other MS images to reduce scan-to-scan memory effects and preserve blinding.

### Automated Analysis

Several fully automated pipelines were also used to estimate T2LV and the volumes of total brain, normal-appearing white matter, and both cortical and deep gray matter structures. To prevent overfitting, we used all pipelines with their default settings, according to published recommendations for each
method separately, in which appropriate images were inhomogeneity corrected, rigidly aligned across sessions from each scan session, processed for removal of extracerebral voxels for all processing pipelines, and intensity normalized. For lesion measurements, several algorithms were applied by the laboratories that developed or codeveloped the various methods: Lesion-TOADS (TOpology-preserving Anatomical Segmentation; https://www.nitrc.org/projects/toads-cruise/), a fuzzy C-means-based segmentation technique with topologic constraints; Automated Statistical Inference for Segmentation (OASIS), a logistic-regression-based segmentation method leveraging statistical intensity normalization; Subject Specific Sparse Dictionary Learning (S3DL; https://www.nitrc.org/projects/s3dl/), a patch-based dictionary learning multiclass method; and White Matter Lesion Segmentation (WMLS; https://www.nitrc.org/projects/wmls/), a local support vector machine-based segmentation algorithm developed for vascular lesions that also uses corrective learning. To estimate the volume of gray matter structures, we used Lesion-TOADS; FMRIB Integrated Registration and Segmentation Tool (FSL-FIRST; http://fsl.fmrib.ox.ac.uk/fsl/fswiki/FIRST) (a Bayesian appearance method); Multi-atlas Segmentation with Brain Surface Estimation (MaCRUISE) (a combined multiatlas segmentation and cortical reconstruction algorithm); and Multi-atlas region Segmentation utilizing Ensembles of registration algorithms (MUSE) (an ensemble multiatlas label-fusion method). The FSL-FIRST analysis was applied directly to the raw T1 images according to common practice, and OASIS was applied to the T1, FLAIR, and a 3D T2 high-resolution sequence after preprocessing; all other pipelines were applied to appropriately preprocessed T1 and FLAIR images. Not all algorithms measured volumes of the same set of structures. Lesion-filling was not performed. Lesion-TOADS, MaCRUISE, and MUSE also yielded estimates for total brain volume.

**Statistical Analysis**

All statistical analyses were conducted in the R software environment (http://www.r-project.org/). To compare estimated volumes within and across sites, we computed mean volumes and SDs. T tests were also used for differences in within-site averages between scanner platforms. Correlations between these averages across segmentation algorithms were also explored. The proportion of variation explained by site was computed, and the association with site was assessed with permutation testing. The coefficients of variation were also estimated across sites. To assess associations between session-average measured total brain and lesional volumes and time of day (morning versus afternoon), we used Wald testing within a linear model framework, both marginally and adjusting for scanner platform.

**RESULTS**

The participant was found to be stable regarding cerebral lesion load during the study. When we compared images acquired at the National Institutes of Health at study entry and exit, the manually measured T2LV in the participant was similar (17.9 mL in September 2015 versus 17.8 mL in February 2016). The T1LV was also stable (15.5 versus 15.1 mL). This imaging stability paralleled his clinical stability (see “Materials and Methods”).

The manually estimated T1LV and T2LV for each scan is shown in Fig 1. Site explained 95% of the variation observed in the estimated T2LV and 92% of the variation in the estimated T1LV, indicating marked scanner-to-scanner differences despite protocol harmonization, which clearly exceeded scan-rescan variability within sites. The range of T2LVs was 15.9 to 20.1 mL, indicating that differences of up to 25% of the lesion volume were observed across sites. The range of T1LVs was similarly wide, ranging from 13.0 to 16.4 mL. Further inspection of these volumes across platforms indicated that Skyra (Magnetom Skyra; Siemens, Erlangen, Germany) scanners showed larger lesion volumes compared with other Siemens platforms both on T1LV (Skyra: mean T1, 15.2 mL; non-Skyra: mean T1, 13.8 mL; P < .05) and T2LV (Skyra: mean T2, 18.9 mL; non-Skyra: mean T2, 16.6 mL; P < .01). An example of the segmented lesions across scanners is provided in Fig 2.

Results from the automated techniques for delineating and measuring
suring T2LV are shown in Fig 3. The automated lesion segmentations showed marked disagreement in the average lesional volume measurements compared with the manually assessed volumes, and all methods showed large site-to-site differences (in some cases up to 7.5 mL, or almost 50% of the manually measured lesion volume), except for Lesion-TOADS (range, 10.5–11.0 mL), which was more stable. For all methods, site explained 50% of the observed variation; 53% of the variation was explained by site (permutation \( P < .005 \)) for S3DL, 54% for Lesion-TOADS (\( P = .41 \)), 44% for OASIS (\( P = .57 \)), and 83% for WMLS (\( P = .002 \)), which clearly was most prone to site-related variation.

To measure brain structure volumes, we used several automated methods. As an example, results for the thalamus are shown in Figs 4 and 5. While Lesion-TOADS estimated smaller volumes, MUSE, FSL-FIRST, and MaCRUISE yielded similar average measurements. Nonetheless, site was strongly associated with measured thalamic volume, explaining 96% of the Lesion-TOADS volume variation (\( P < .01 \)), 89% of MUSE (\( P < .01 \)), 84% of FSL-FIRST (\( P = .04 \)), and 65% of MaCRUISE (\( P = .17 \)). Similar results for the putamen, caudate, cortical gray matter, normal-appearing white matter, and total brain volume were found, as provided in On-line Figs 1–5. Summaries of the coefficient of variation give an intuitive measure of the scale of the combined scan-rescan and across-site variation as shown in Fig 6.
Finally, the proportion of variation explained by site is shown in Fig 7. Note that in almost all cases, site explained >50% of the variation, with most measurement techniques showing >80% variation due to site for all structures assessed.

While all images were acquired on 3T Siemens scanners, the model type appeared to influence the results; there was evidence of systematic differences in many measurements between Skyra and non-Skyra scanners. Figure 8 shows the negative log P values for the comparison of volumes averaged across scan-rescan measurements, with larger values indicating more systematic differences between platforms. The largest platform-associated differences were observed in MacCRUISE measurements of normal-appearing white matter, cortical gray matter, and, consequently, total brain volume. Lesion-TOADS also showed large differences in total brain volume attributable to cortical gray matter, as did S3DL for T2LV measurements. MUSE showed major differences in thalamic volume across scanner models, and FSL-FIRST showed similar discrepancies in the thalamus and caudate. The correlation between site-averaged measurements varied dramatically, especially for lesional and total brain volume measurements (On-line Fig 6); this variation indicates that site differences resulted in contrasting effects on output from the different algorithms. While the other measurements showed less scanner model-related variation, most still showed prominent differences between Skyra and non-Skyra scanners.

The time of day of scan acquisition was not associated with manually segmented T1 lesion volumes ($t = 0.45$) or T2 lesion volumes ($t = 0.38$) or total brain volume, as measured by any of the automated algorithms (On-line Figs 7 and 8).

**DISCUSSION**

Clinical MS therapeutic trials have traditionally used 1.5T MR imaging platforms to provide metrics on cerebral lesions and atrophy as supportive outcome measures. However, there is growing interest in the use of high-resolution 3T imaging to assess disease activity and disease severity in MS. Such 3T imaging has the potential for increased sensitivity to lesions and atrophy, higher reliability, and closer relationships to clinical status compared with scanning at 1.5T. The purpose of this study was to evaluate the consistency of metrics obtained from a single MS participant with a high-resolution 3T brain MR imaging protocol distributed to 7 sites. The results of our study indicate that even in multicenter acquisitions from the same scanner vendor after careful protocol harmonization, systematic differences in images led to severe biases in volumetric analyses. These biases were present in manually and automatically measured volumes of white matter lesions, as well as in automatically measured volumes of whole-brain and gray and white matter structures. These biases were also highly dependent on scanning equipment, which resulted from a higher sensitivity to lesions in newer scanners from the same manufacturer compared with earlier models, even at the same field strengths.
In comparison with past estimates of reliability of volumetric measurements of brain structures, our findings point to higher between-site variation than previously documented. In particular, Cannon et al.27 reported that between 3% and 26% of the observed variation in global and subcortical volumes were attributable to site; this was a study of 8 healthy participants imaged on 2 successive days across 8 sites with 3T Siemens and GE Healthcare scanners. However, the proportion of explained variation has a different interpretation from that reported here. The total variation in Cannon et al. consisted of 4 contributors to variance: first, across-site differences; second, across-scan differences; third, across-day differences; and fourth, across-subject differences. In our single-participant study, we isolated only the first 2 variance components, allowing us to compare variation because it is relevant for precision medicine (subject-specific) applications.

Previous work indicated that the observed variation attributable to scanning occasion was small25,27; indeed, Cannon et al.27 found this to constitute <1% of the variation. Thus, we did not scan our participant on subsequent days but rather simply repositioned the participant between scans during the same imaging session. A notable difference between our study and that of Cannon et al. is that we did not use data from a standardized phantom concurrently acquired for correction of between-scanner variations in gradient nonlinearity and scaling. Cannon et al. found that this correction improved between-site intra-class correlations and greatly reduced differences between scanner manufacturers. Similarly, Gunter et al.41 reported the usefulness of a phantom for scanner harmonization and quality control in the Alzheimer’s Disease Neuroimaging Initiative (http://www.adni-info.org/).

In future studies, we will focus on applying phantom calibrations across NAIMS sites to extend our current observations. Despite the growing literature on the importance of diurnal variation and hydration status for volumetric analyses,42-45 we found no significant associations between time of day and measured volumes. This may indicate that in single-participant analyses, time of day and day-to-day variation may be of less concern than the much larger source of variation of scanner platform. Most interesting, Cannon et al. also found that measurements acquired with scanners receive coils had higher reliability. In our study, we found that even scanner models (ie, Skyra versus non-Skyra) from the same manufacturer varied markedly in their estimates of lesion volume; this variation highlights the importance of between-scanner differences for assessing MS-related structural changes.

To assess differences across processing pipelines, we used a variety of techniques for automated segmentation of lesion and white and gray matter volumes. Different segmentation algorithms showed a range of variability in their estimates, as well as their sensitivity to differences between scanners. For example, Lesion-TOADS showed much less variable lesion measurements...
between scanning equipment and scanner software versions have also been noted in past studies of reliability, but their implications for the assessment of pathology remain unclear. In particular, repeat acquisitions on scanners with different receive coils could provide additional insight concerning reliability. In addition, our study was from a single time point across scanners, whereas clinical trials rely on the quantification of intra-subject longitudinal change. Each participant is typically scanned on the same platform, which may limit the variability in on-study change between participants. Further studies are necessary to assess whether scan platform introduces the same level of acquisition-related variability when assessing longitudinal changes.

Given the intersite differences observed in lesion volumes, across-site-inference statistical adjustment for site is clearly necessary when analyzing volumetrics from multisite studies, even when images are acquired with a harmonized protocol on 3T scanners produced by the same manufacturer. From a single participant, it is unclear what the role of differential sensitivity to lesions might be across individuals with heterogeneity in lesion location. For example, while lesion detection in the supratentorial white matter might be more straightforward and comparable across individuals, detection of lesions in the brainstem, cerebellum, and spinal cord may be more sensitive to differences in equipment.

New statistical methods for measuring and correcting systematic biases are warranted, especially for studies in which patient populations may differ across sites. Indeed, intensity normalization and scan-effect removal techniques\(^5\) (akin to batch-effect removal methods in genomic studies\(^5\)) are an active area of methodologic research and promise to improve comparability of volumetric estimates from automated segmentation methods. After volumes are measured, statistical techniques for modeling estimated volumes from multicenter studies are also rapidly evolving.\(^1\) These techniques bring the potential to mitigate site-to-site biases in group-level analyses, with better external validity at the cost of increased sample size.

**CONCLUSIONS**

By imaging the same subject with stable relapsing-remitting MS during 5 months, we assessed scanner-related biases in volumetric measurements at 7 NAIMS centers. Despite careful protocol harmonization and the acquisition of all imaging at 3T on Siemens scanners, we found significant differences in lesion and structural volumes. These differences were especially pronounced when comparing Skyra scanners with other Siemens 3T platforms. The results from this study highlight the potential for interscanner and intersite differences that, unless properly accounted for, might

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**FIG 8.** Negative logarithm (base 10) P value from t tests describing the difference in average volume between Skyra-versus-non-Skyra platforms explained by site with various segmentation methods for different structures in the brain. cGM indicates cortical gray matter; NAWM, normal-appearing white matter; TBV, total brain volume.
confound MR imaging volumetric data from multicenter studies of brain disorders.

Our findings raise a key issue of the interpretability of MR imaging measurements in the context of personalized medicine, even in carefully controlled studies with harmonized imaging protocols.

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REFERENCES

measures of hippocampus and other brain structures using MRI. Magn Reson Imaging 1993;11:993–1006 CrossRef Medline
ABSTRACT

BACKGROUND: Diffusion tensor imaging has been widely used to measure HIV effects on white matter microarchitecture. While many authors have reported reduced fractional anisotropy and increased mean diffusivity in HIV, quantitative inconsistencies across studies are numerous.

PURPOSE: Our aim was to evaluate the consistency across studies of HIV effects on DTI measures and then examine the DTI reliability in a longitudinal seropositive cohort.

DATA SOURCES: Published studies and investigators.

STUDY SELECTION: The meta-analysis included 16 cross-sectional studies reporting fractional anisotropy and 12 studies reporting mean diffusivity in the corpus callosum.

DATA ANALYSIS: Random-effects meta-analysis was used to estimate study standardized mean differences and heterogeneity. DTI longitudinal reliability was estimated in seropositive participants studied before and 3 and 6 months after beginning treatment.

DATA SYNTHESIS: Meta-analysis revealed lower fractional anisotropy (standardized mean difference, −0.43; \( P < .001 \)) and higher mean diffusivity (standardized mean difference, 0.44; \( P < .003 \)) in seropositive participants. Nevertheless, between-study heterogeneity accounted for 58% and 66% of the observed variance (\( P < .01 \)). In contrast, the longitudinal cohort fractional anisotropy was higher and mean diffusivity was lower in seropositive participants (both, \( P < .001 \)), and fractional anisotropy and mean diffusivity measures were very stable during 6 months, with intraclass correlation coefficients all >0.96.

LIMITATIONS: Many studies pooled participants with varying treatments, ages, and disease durations.

CONCLUSIONS: HIV effects on WM microstructure had substantial variations that could result from acquisition, processing, or cohort-selection differences. When acquisition parameters and processing were carefully controlled, the resulting DTI measures did not show high temporal variation. HIV effects on WM microstructure may be age-dependent. The high longitudinal reliability of DTI WM microstructure measures makes them promising disease-activity markers.

ABBREVIATIONS: AD = axial diffusivity; cART = combination antiretroviral therapy; CPE = CNS penetration effectiveness; FA = fractional anisotropy; MD = mean diffusivity; RD = radial diffusivity; SMD = standardized mean difference

The advent of combination antiretroviral therapies (cART) for HIV has resulted in both increases in life expectancy and decreases in mortality.1 While cART successfully controls HIV viremia and reconstitutes immune function,2 the effects of persisting HIV infection and its treatments on brain structure and function are less clear. The incidence of HIV-associated dementia declines following cART initiation,3 and cART is sometimes asso-
associated with improved cognitive function. Nevertheless, cognitive deficits can persist in treated HIV infection, with some suggesting that the neuropsychological impairment pattern changes, rather than its prevalence. Factors such as comorbidity burden, cognitive reserve, nadir T-helper (CD4) cell count, and age may also contribute to cognitive impairment.

While CD4 cell count and viral load are generally used to diagnose infection and monitor treatment response, they do not necessarily reflect the direct and indirect brain effects of HIV infection. HIV enters the central nervous system soon after infection and persists after treatment. Before the cART era, CSF HIV RNA levels correlated with the severity of cognitive impairment but cART reduced CSF levels of HIV-1 RNA. Nevertheless, with cART there is no strong association between cognitive impairment and concurrent CSF or peripheral viral load, and several studies have shown that cognitive impairment may develop during viral suppression.

Neuropsychological testing is often used to estimate HIV CNS effects, even though assessment is time-intensive and possibly subject to practice effects. Nevertheless, the HIV neuropsychological profile associated with cognitive impairment is debated, suggesting that behavioral measures may not be optimal for measuring the ongoing CNS involvement.

The absence of measurable, consistent cognitive changes related to HIV disease activity motivates the search for objective biomarkers of the CNS effects of HIV infection. Histopathologic evidence of HIV infection effects ranges from inflammation associated with gliosis and increased perivascular macrophages to degenerative pathology manifested as diffuse myelin pallor and axonal damage. This evidence of white matter involvement has led to cross-sectional studies with diffusion tensor imaging to study WM microarchitecture following HIV infection, with many finding decreased fractional anisotropy (FA) and increased mean diffusivity (MD). However, there have also been puzzling inconsistencies, with studies demonstrating results of opposite polarity, namely increased FA and decreased MD in the corpus callosum or other WM tracts. It would be useful to have consistency estimates of any serostatus effects across studies and temporal reliability estimates of these effects in individuals to evaluate the utility of using WM microstructure measures for tracking the progression of HIV infection in the brain.

These issues prompted us to first do a meta-analysis of studies reporting callosal microstructure changes following HIV infection and then to examine the longitudinal stability of WM microstructural measures in seropositive participants before the initiation of cART and 3 and 6 months thereafter.

**MATERIALS AND METHODS**

**Meta-Analysis of HIV Effects in the Corpus Callosum**

To summarize the literature on WM microstructure changes associated with HIV infection, we performed a computerized literature PubMed search on April 25, 2016, by using the terms “(‘hiv’[MeSH Terms] OR ‘hiv’) AND (‘brain’[MeSH Terms] OR ‘brain’[All Fields]) AND (‘diffusion tensor imaging’[MeSH Terms] OR (‘diffusion’[All Fields] AND ‘tensor’[All Fields] AND ‘imaging’[All Fields]) OR ‘diffusion tensor imaging’[All Fields]),” yielding 82 records. Of these, 28 studies were excluded for the following reasons: 1) Studied participants were not infected with HIV, 2) studies were performed in animal models, 3) they were review articles, 4) they were case reports, or 5) they examined participants with perinatal HIV exposure who were not infected. Given the variability in the ROIs from which FA and MD were measured, we chose to focus on the corpus callosum because it is the largest WM fiber tract in the brain and was the most frequent measurement target.

Of the 54 eligible full-text articles, 16 cross-sectional studies of patients with HIV infection and controls that were completed between 2001 and 2016 were included in the meta-analysis, with 12 studies reporting both FA and MD values and 4 studies reporting only FA values. Because 3 articles did not report complete FA and MD values, the results were obtained from the authors. The remaining studies were excluded for the following reasons: 1) Numeric values for FA and MD were not reported for either seropositive or seronegative participants (authors of these articles were contacted in an effort to obtain the missing values); 2) only whole-brain FA or MD was reported; 3) the studies examined the relationships of clinical variables, biomarkers, or treatment on DTI measures without including a seronegative control group; 4) FA and MD were not measured in the corpus callosum; 5) prior published DTI data were used for fMRI connectivity analysis ROI selection; 6) a single case-control pair was reported; 7) the study focused on imaging measures other than diffusion parameters; or 8) the article reported a new processing algorithm for DTI data (Fig 1). See the On-line Appendix for excluded study references. Mean FA and MD values and their SDs were taken from the article tables, or the corresponding author was contacted if results were presented in a different form.

We used the R meta-analysis library meta to estimate the standardized mean difference (SMD) in FA or MD for each study and then calculated a weighted average of these estimates across studies. If multiple values for callosal subregions were reported in a study, we used their average in inverse-variance–weighted random-effects models, estimating the mean effect and incorporating estimates of between-study variation in the weighting of each study. Study bias was checked by examining plots of sample size versus effect size. Meta-regression was used to examine imaging protocol effects.

**Meta-Analysis of Callosal Regional Variation in HIV Serostatus Effects**

Eight of the selected studies reported FA, MD, axial diffusivity (AD), and radial diffusivity (RD) for callosal subregions, including the genu, body, and splenium. Because qualitative examination of the values revealed anatomic variation in diffusion measures, we performed a separate repeated-measures, mixed-effects regression analysis, examining regional and serostatus effects on callosal diffusion measures. If the callosal microstructure exhibited regional variation, differential regional sampling across studies could result in high experimental error.
Comparison Study

To compare the meta-analysis serostatus effects with a new sample and to characterize within-subject temporal variations in diffusion measures, we collected longitudinal DTI in seropositive participants before the initiation of cART and 3 and 6 months thereafter, comparing the results with those in a seronegative control group.

After we obtained Temple University institutional review board approval and consent, 10 seropositive participants, 22–50 years of age, cART-naive but ready to begin antiretroviral therapy, were studied. Nine were followed longitudinally for 6 months. We excluded participants who met the Diagnostic and Statistical Manual of Mental Disorders-IV criteria for substance dependence or abuse in the past 6 months and/or who had other major psychiatric disorders, neurologic illnesses unrelated to HIV, MR imaging contraindications, cancer, hepatic disease, renal disease, cardiac disease, or pulmonary disease.

The serologic status of HIV participants was confirmed by positive HIV enzyme-linked immunoassay and Western blot or detection of plasma HIV RNA by the polymerase chain reaction. Plasma viral load, CD4, and CD8 T-cell counts were collected before initiation of cART and from 0.5 to 6.0 months after beginning therapy. Urine toxicology was collected before each imaging visit, testing the presence of marijuana, cocaine, opiates, methamphetamines, barbiturates, benzodiazepines, and phencyclidine. Participants testing positive for any of these substances with the exception of marijuana were excluded.

For comparison, 12 seronegative participants 21–26 years of age were studied once. None of this group reported past or present symptoms of a major psychiatric or neurologic disorder or head injury with loss of consciousness or were taking psychoactive medications.

To assess posttreatment cognitive and motor performance, we gave participants a brief test battery for psychomotor function, dexterity, learning, and memory skills, including the International HIV Dementia Scale, the Hopkins Verbal Learning Test, the HIV-Dementia Motor Scale, the Unified Parkinson’s Disease Rating Scale motor examination, and the Grooved Pegboard Test.

Neuroimaging was performed with a 3T Verio MR imaging system (Siemens, Erlangen, Germany) equipped with a 12-channel matrix head coil. We performed the following scans: a high-resolution, 3D sagittal T1-weighted, magnetization-prepared rapid acquisition of gradient echo (TR/TE/flip angle = 1600 ms/2.5 ms/9°, 256 × 256 matrix, 1-mm³ voxels); a 2D multislice oblique axial T2-weighted fast spin-echo (TR/TE = 3000 ms/85 ms, 320 × 320 matrix, 5-mm³ voxels); and DTI for WM microstructure assessment (2.0 × 2.0 × 2.2 mm voxels, TR/TE/flip angle = 14,700 ms/95 ms/90°, and 30 diffusion gradient directions with b-values of 0 and 1000). Images were inspected at the time of scanning, and a repeat scan was performed if motion artifacts were observed.

DTI data were preprocessed with a script implementing gradient direction, head motion, and eddy current correction by using the FMRIB 5.0 Diffusion Toolbox (FDT; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT). Quality assurance involved visual inspection of the individual images and elimination of corrupted images. FA, MD, RD, and AD values were computed for all voxels after we fitted a tensor model to the corrected diffusion data with FDT.

The FA map for each subject was then aligned with an FA atlas FMRIB58_FA (www.fmrib.ox.ac.uk/fsl/data/FMRIB58_FA) with the FMRIB Nonlinear Registration Tool (FNIRT; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FNIRT). Next, a mean FA image was created and thinned to create a mean FA skeleton representing the centers of all tracts common to the group. Then each subject’s aligned FA data were projected onto the mean skeleton. The skeleton-creation steps are part of the Tract-Based Spatial Statistics (TBSS; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS) procedure.

To increase the robustness of the measures and to facilitate the interpretation of the results, we averaged the different measures over the skeleton delimited by ROIs obtained from the ICBM-152 atlas, previously aligned with the FNIRT procedure in the

**FIG 1.** Flow diagram showing selection of articles examining WM microstructure changes in HIV infection for the meta-analysis.
RESULTS

Meta-Analysis

Meta-analysis of serostatus effects on callosal microstructure revealed a small reduction in FA (SMD = −0.43; 95% CI, −0.65 to −0.21) related to serostatus (test of SMD = 0: z = −3.82, P < .001), with high study heterogeneity (Q = 40.7, df = 17, P = .001, and I² [variation in SMD attributable to heterogeneity] = 58%). The r² of between-study variance was 0.12. Eleven of the 16 studies had confidence intervals that included zero (Fig 2A).

Meta-analysis of MD revealed a significant increase (SMD = +0.44; 95% CI, 0.15–0.72) related to serostatus (test of SMD = 0: z = 3.00, P = .003), with high study heterogeneity (Q = 38.4, df = 13, P = .0003, and I² = 66.0%). The estimate of between-study variance r² was 0.18 (Fig 2B). Therefore, meta-analysis of both FA and MD revealed a small but statistically significant, change related to serostatus. Nevertheless, the observed high study heterogeneity suggests the existence of other unexplained experimental effects.

Because both FA and MD serostatus group differences were associated with high between-study heterogeneity, it was possible that the observed group differences in WM microstructure resulted from variations in image-acquisition parameters or biologic variables. For image-acquisition parameters reported by the constituent publications, mixed-effects meta-regression revealed no significant effects on callosal FA and MD from variations in field strength (range, 1.5T–4T), voxel volume (range, 1.5–20 mm³), and diffusion direction number (range, 6–64).

Mixed-effects meta-regression also revealed no significant effects of the biologic variables age (range, 27–53 years) and CD4 count (range, 211–678). In addition, there was no apparent trend in the DTI measures during the period spanned by the studies (2001–2016). Perhaps due to the relatively small sample of available studies, none of the variables examined appear to explain the high heterogeneity seen in the meta-analyses of FA or MD effects. Examination of funnel plots did not reveal asymmetries suggestive of bias.

To investigate the possibility that the high between-study heterogeneity arose from DTI processing variations, we coded studies according to whether the FSL/TBSS method was used, because it uses a unique step in which the FA maps are “skeletonized” to reduce potential partial volume effects. Meta-regression revealed a nonsignificant (P = .08) trend for FSL/TBSS processing being associated with higher FA values. Details of acquisition and processing for each study can be found in Online Table 1.

Comparison Study

For comparison with the meta-analysis, we collected DTI data from seropositive and seronegative participants for cross-sectional and longitudinal examination of WM microstructure changes.

Nine of 10 seropositive participants in our sample successfully completed 3 imaging visits, and 12 seronegative controls completed 4 visits (On-line Table 1). Given some regional variation in measures, the observed between-study heterogeneity in callosal FA and MD group differences might also have resulted from sampling and combining diffusion measures from different callosal segments in different studies. To more closely examine callosal regional variations in FA and MD related to serostatus, we used repeated-measures multilevel models with region and serostatus as fixed effects and study as a random effect in the 8 studies providing all 4 diffusion measures for 3 callosal subregions. For both FA and MD, we found significant regional effects, with the splenium having higher FA and lower MD than the body and splenium. Thus, the callosal region sampled appears to have a strong effect on group estimates of WM microstructure (On-line Appendix, On-line Tables 2 and 3, and On-line Figs 1 and 2).
To examine the regional pattern of diffusion changes following HIV infection but before treatment began, we compared the seropositive pretreatment ROI values with the seronegative control values, with repeated-measures multilevel models treating serostatus and hemisphere (left hemisphere, midline, and right hemisphere) as fixed effects and subject and ROI as random effects. With FA as the dependent measure, the seropositive group had higher FA values [F(2,21.06) = 19.31, P < .0001]. For RD, we found an effect of hemisphere [F(2,19.92) = 18.45, P < .001] and an effect of hemisphere by serostatus interaction [F(2,17.40) = 15.16, P < .001] and an effect of hemisphere by serostatus by hemisphere interaction [F(2,287.58) = 13.31, P < .001], with a significant serostatus by hemisphere interaction [F(2,287.58) = 3.77, P = .027] (Fig 3A). For RD, we found an effect of serostatus, with the seropositive group showing lower values [F(1,17.40) = 15.16, P < .001] and an effect of hemisphere [F(2,287.58) = 13.31, P < .001], with the midline having a higher RD than the hemispheres. There was also a significant serostatus by hemisphere interaction [F(2,287.58) = 3.77, P = .027] (Fig 3C). For AD, we found an effect of serostatus [F(1,92.12) = 7.03, P = .0095], with the seropositive group exhibiting lower AD and an effect of hemisphere [F(2,298.73) = 0.30, P < .001], with the midline showing higher values than the hemispheres (Fig 3D). Thus, spective participants began cART immediately after their first visit. All 9 seropositive participants were treated with at least 3 antiretroviral medications, including nucleoside reverse transcriptase inhibitor and a nucleoside analog, which were taken in combination with nonnucleoside reverse transcriptase inhibitors or an integrase inhibitor. The CNS penetration effectiveness (CPE) rank of each participant’s cART regimen was calculated on the basis of a modified version of the CPE, which includes rilpivirine (personal communication, S. Letendre, January 14, 2015). Six participants were on regimens with a CPE rank of 6, and 3 participants had a CPE rank of 7, 1 of whom switched to a regimen with a rank of 6 after 4 months of therapy, and then to one with a rank of 8 after 5 months.

Laboratory testing included serial CD4 and CD8 T-cell counts and viral load, both assessed before initiation of cART and from 0.5 to 6.0 months after the initiation of cART (On-line Table 4). During 24 weeks of therapy, seropositive participants averaged CD4 cell count increases of 68.8 cells/week (P < .001) and accompanying decreases in the log viral load (P < .001), with no change in CD8 cell counts (P = .64). These results are typical responses to cART.

Behavioral assessments revealed that while none of our subjects met the criteria for HIV dementia, a few exhibited mild-to-moderate degrees of impairment in verbal learning, with some subjects exhibiting mild degrees of impairment in motor function (On-line Table 5).

Although HIV infection can result in macroscopic changes in WM, visual inspection of the T1- and T2-weighted images revealed that our participants were generally free of these effects. One seropositive participant exhibited a mild degree of T2 prolongation in the periatrial WM bilaterally. T1- and T2-weighted images were otherwise unrevealing, with no parenchymal lesions, ventriculomegaly, or brain atrophy of the sort frequently reported before the widespread introduction of cART.49,50

Seropositive participants had higher FA and lower MD, RD, and AD. Measurements from 28 white matter ROIs were aggregated into left hemisphere (L), midline (MID), and right hemisphere (R) regions.

Seropositive participants began cART immediately after their first visit. Although the mean age for our seropositive subjects (30.7 ± 9.5 years) was greater than that of controls (23.3 ± 1.8 years), age variations over this range are not known to result in variations in diffusion measures,48 a finding consonant with the negative age meta-regression results reported above. While we would expect that the slightly older age of our seropositive cohort could potentially decrease the FA, this decrease was not observed. Seropositive participants had fewer years of education (11.9 ± 0.5 years) than controls (17.2 ± 1.7 years). On entry into the study, 6 of the 9 participants were seropositive during screening for sexually transmitted disease. The other 3 participants had signs and symptoms of clinical AIDS, with all 3 presenting with Pneumocystis pneumonia and 1 additionally having herpes zoster and esophageal candidiasis.

To examine the regional pattern of diffusion changes following HIV infection but before treatment began, we compared the seropositive pretreatment ROI values with the seronegative control values, with repeated-measures multilevel models treating serostatus and hemisphere (left hemisphere, midline, and right hemisphere) as fixed effects and subject and ROI as random effects. With FA as the dependent measure, the seropositive group had lower FA values [F(2,21.06) = 14.31, P = .0011]. FA values were also higher in the midline than the hemispheres [F(2,707.98) = 15.16, P < .001]. MD values were also higher in the midline than the hemispheres [F(2,81.52) = 10.92, P < .001] (Fig 3A). For RD, we found an effect of hemisphere [F(2,81.52) = 3.31, P = .042] (Fig 3B). For RD, we found an effect of serostatus, with the seropositive group showing lower values [F(1,17.40) = 15.16, P < .001] and an effect of hemisphere [F(2,287.58) = 13.31, P < .001], with the midline having a higher RD than the hemispheres. There was also a significant serostatus by hemisphere interaction [F(2,287.58) = 3.77, P = .027] (Fig 3C). For AD, we found an effect of serostatus [F(1,92.12) = 7.03, P = .0095], with the seropositive group exhibiting lower AD and an effect of hemisphere [F(2,298.73) = 0.30, P < .001], with the midline showing higher values than the hemispheres (Fig 3D). Thus,
compared with seronegative controls, in the seropositive group, we observed higher FA and lower MD, RD, and AD.

To examine the within-subject reliability of FA, MD, RD, and AD measures, we examined temporal variations in the 4 diffusion measures during 6 months with a 2-way random-effects intraclass correlation coefficient model. Averaging across all 28 WM sampling regions, we observed excellent internal consistency, with Cronbach α scores of FA = 0.91, MD = 0.96, AD = 0.98, and RD = 0.96. Cronbach α indicates the degree to which items measure a single unidimensional latent variable. Intraclass correlation coefficient estimates were also high, with FA intraclass correlation coefficient = 0.97 (95% CI, 0.96–0.97), MD = 0.96 (95% CI, 0.96–0.99), AD = 0.98 (95% CI, 0.98–0.99), and RD = 0.96 (95% CI, 0.95–0.97) (Fig 4A). In addition, examination of individual subject time plots of FA, MD, RD, and AD revealed that all subjects exhibited consistent mean WM architecture estimates across time (Fig 4B).

### DISCUSSION

**Summary of Results**

Meta-analysis of HIV effects on WM microstructure revealed relatively small changes in FA and MD related to serostatus and high between-study heterogeneity. Variation in image-acquisition parameters across studies did not explain the high heterogeneity. More detailed examination of callosal WM microstructure measures revealed regional variations that could contribute to between-study differences if the same callosal regions were not sampled in each study. In our comparison study, HIV infection was associated with widespread changes in WM microstructure, with increases in FA and decreases in MD, RD, and AD. During a 6-month span, these measures showed excellent reliability, suggesting that within-subject experimental variation does not contribute substantially to high between-study heterogeneity.

**HIV Effects on White Matter Microstructure**

HIV infection affects cerebral WM through a range of mechanisms. Histopathologic evidence includes inflammation associated with gliosis, an increased numbers of perivascular macrophages, and a type of degenerative pathology, manifested as myelin pallor, which is thought to result from breakdown of the blood-brain barrier with resulting vasogenic edema. WM metabolite alterations detected with MR spectroscopy paralleled those seen in subcortical gray matter, including elevated Cho/Cr, elevated mIns/Cr, and decreased NAA/Cr ratios, with these metabolite differences increasing with disease progression. Macrostructural evidence of HIV infection includes cerebral WM volume loss and focal hyperintensities seen with T2-weighted imaging.

DTI revealed changes associated with seropositivity, believed to reflect WM injury from both direct or indirect effects of infection. While these studies have generally found elevated MD and reduced FA in the WM of seropositive participants relative to controls, results vary among the published accounts. These inconsistencies could arise from a number of sources, including pooling observations from both...
treated and untreated participants, diffusion imaging protocol variations, study sample variations in the duration of infection, age, premorbid and comorbid substance use, comorbid illness such as hepatitis, length and effectiveness of antiretroviral therapy treatment, CNS medication penetration, CD4 nadir, premorbid intelligence, and ethnicity.

**Meta-Analysis of HIV Effects on White Matter Microstructure**

Meta-analysis of HIV DTI studies revealed wide variation in seropositivity effects on diffusion parameter estimates. If DTI is ever used as a diagnostic marker for HIV infection, high consistency in regional measurements will be required. In addition, there are growing concerns about the reproducibility and reliability of biomedical research, prompting the National Institutes of Health to focus on initiatives to reduce the frequency and severity of irreproducibility. There are many potential sources for the study heterogeneity effects we observed.

The specific choice of MR imaging acquisition parameters, with related SNR variation, might bias measurements of diffusion measures, particularly in higher magnetic fields. Nevertheless, meta-regression of acquisition parameters across studies did not account for variation in diffusion measures, suggesting that the range of SNR values arising from variation in voxel volume, field strength, and diffusion direction number did not strongly influence FA and MD estimates. Keeping acquisition parameters constant in the comparison study, we observed high within-subject reproducibility across time.

While differences in DTI data-processing techniques may contribute to diffusion measure heterogeneity, many of the studies included in the meta-analysis did not report data-processing details in sufficient detail to examine their specific effects by using meta-regression or subgroup analysis. Nevertheless, we were able to compare the effects using DTI processing methods that involved skeletonization of diffusion parameter maps with those that did not and observed a trend for FA values being higher when FSL/TBSS style processing was used. The skeletonization step that is a unique aspect of TBSS results in voxel selections that are more likely to contain pure WM, thereby having less contamination from partial volume effects, which might be expected to reduce the apparent directionality of diffusion. This preliminary finding will be explored in a subsequent subject-level meta-analysis of the effects of processing strategy on diffusion parameter estimates in HIV.

While HIV globally affects WM, regional variations in myelination, axon orientation, packing density, and membrane permeability may affect regional measurements. Meta-analysis of callosal diffusion measures revealed regional variability, with FA consistently highest in the splenium. Therefore, between-study variation in the selection of subsequently aggregated sampling regions could result in higher between-study heterogeneity.

Differences in cohort characteristics, such as the duration of infection, age, premorbid and comorbid substance use, comorbid illness such as hepatitis, the length and effectiveness of treatment with antiretroviral therapy, CNS penetration effectiveness of the cART regimen, nadir CD4, premorbid intelligence, and ethnicity, may also contribute to a lack of reproducibility. Many studies in our meta-analysis excluded subjects with current drug or alcohol use, but premorbid drug or alcohol use was often not addressed. Chronic alcoholism has been shown to reduce the corpus callosum FA. Studies have also shown corpus callosum FA decreases following cocaine, methamphetamine, and opiate use.

WM microstructure cross-sectional studies have shown that FA is lower and MD is higher in older compared with younger adults. More recently, annual decreases in FA and annual increases in MD, AD, and RD have been shown in a longitudinal healthy cohort, with changes beginning in the fifth decade. While we found no evidence for age effects in our meta-analysis, the maximum mean age in these studies was below the age when WM microstructural changes generally begin, highlighting the need to further explore age effects in older patients with HIV.

Higher general intelligence indices have been associated with higher FA and lower MD and RD, in typical middle-aged and older adults, with these findings confirmed in studies involving younger adults. Some studies used in our meta-analysis had control groups with more years of education than the seropositive participants.

Antiretroviral treatments may be injurious to brain cell elements. To our knowledge, there are no studies examining the effects of cART regimen CPE on WM microstructure. Nevertheless, in a study comparing simple motor task performance in seropositive participants on low- and high-CPE cART regimens, the fMRI response amplitude was significantly greater in the low-CPE group compared with the high-CPE or seronegative groups; this finding suggests that treatment effects should be explored in future meta-analytic studies with subject-level data.

Two studies in the meta-analysis included HIV-infected participants with hepatitis, and several studies did not list co-morbidities such as chronic liver or renal disease as exclusionary criteria. Hepatitis C coinfection is found in 25%–30% of HIV-infected individuals and has been associated with reduced FA and increased MD in the WM, including the corpus callosum.

Finally, 10 of the 16 studies enrolled patients with longer infection duration than the subjects enrolled in our comparison study. Although the relationship between HIV infection duration and DTI measures is rarely addressed, infection duration can be negatively associated with callosal FA.

The effects of many of the study characteristics discussed above are difficult to explore with meta-regression because aggregating individual subject variables can result in ecological bias in the resulting parameter estimates. Although it was not possible to explore these biologic effects with the tools of study-level meta-analysis, it is very likely that many of these variables contributed strongly to the high observed between-study heterogeneity, motivating further exploration of potential modulating effects of biologic variables with datasets incorporating subject-level measures.

**Comparison Study Results**

Our study found globally reduced MD and elevated FA in the WM of HIV-infected participants who were naive to antiretroviral therapy. Other studies have reported increased FA values and decreased MD, AD, and RD for multiple corpus callosum regions.
and the centrum semiovale in cART-naive seropositive participants compared with seronegative controls. Because cellular membranes hinder water diffusion, activation of microglia, astrocytes, and perivascular macrophages associated with early CNS HIV infection may have caused reduced MD and increased FA in our seropositive cohort. Because many of the studies in the meta-analysis included patients with longer infection duration than our subjects, the shorter infection duration in our sample might have resulted in different changes in diffusion parameters. Studies reporting higher FA in the seropositive group included participants with shorter disease durations. The earlier phases of HIV infection might be associated with more robust neuroinflammatory changes, causing diffusion restriction effects resulting in higher FA and lower MD. On examining the details of the studies that agreed with our findings, we noted that the authors studied younger samples, many of whom were untreated at the time of imaging, as in our pilot longitudinal study. There is evidence of an age-by–HIV serostatus interaction, evidenced by higher FA and lower MD in younger individuals and lower FA and higher MD in older individuals in the posterior limbs of the internal capsules, cerebral peduncles, and anterior corona radiata. Because most of the studies in the meta-analysis included samples with higher average ages, we believe that this age/serostatus interaction may explain the seeming contradictory results across studies. Unfortunately, we are unable to statistically confirm this explanation, given the study-level data sources used for this meta-analysis. Nevertheless, the biologic interactions among age, serostatus, and WM microstructure is a topic that might be profitably explored in subsequent meta-analyses based on subject-level data.

WM microstructure measures were examined in our seropositive participants at 3 and 6 months after the initiation of cART, demonstrating excellent reliability. We attribute these persistent alterations in WM microstructure, despite the initiation of cART, to the presence of continued activation of microglia and macrophages because this form of continuing inflammation during cART has been documented histologically.

Global temporal stability of DTI measures was observable at the single-subject level, suggesting that the heterogeneity observed in the meta-analysis did not arise because of random temporal fluctuations in the measurement process. It is possible that use of more uniform imaging protocols and data-processing pipelines across studies will improve between-study reproducibility.

CONCLUSIONS

Meta-analysis of DTI results from studies examining the effects of HIV serostatus on WM microstructure revealed high between-study heterogeneity and relatively small changes in measures. Regional variation in callosal WM architecture could contribute to between-study differences if the same callosal regions are not combined for total callosal estimates. In a longitudinal comparison sample, we observed widespread changes related to seropositivity in WM microstructure, with increases in FA and decreases in MD, RD, and AD. Effects of HIV infection on WM microstructure may be age-dependent, related to more prominent neuroinflammatory changes in younger patients. Examination of measures averaged over all brain WM structures during a 6-month span revealed excellent reliability, suggesting that within-subject variation does not substantially contribute to the observed between-study variability. Further work will be required to isolate the sources of variation in WM microstructure estimates in HIV seropositive groups.

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REFERENCES

56. Ragin AB, Wu Y, Storey P, et al. Diffusion tensor imaging of subcor-
75. Alter MJ. Epidemiology of viral hepatitis and HIV co-infection. *J Hepatol* 2006;44(1 suppl):36–9 Medline
Differentiation between Treatment-Induced Necrosis and Recurrent Tumors in Patients with Metastatic Brain Tumors: Comparison among ¹¹C-Methionine-PET, FDG-PET, MR Permeability Imaging, and MRI-ADC—Preliminary Results

N. Tomura, M. Kokubun, T. Saginoya, Y. Mizuno, and Y. Kikuchi

ABSTRACT

BACKGROUND AND PURPOSE: In patients with metastatic brain tumors after gamma knife radiosurgery, the superiority of PET using ¹¹C-methionine for differentiating radiation necrosis and recurrent tumors has been accepted. To evaluate the feasibility of MR permeability imaging, it was compared with PET using ¹¹C-methionine, FDG-PET, and DWI for differentiating radiation necrosis from recurrent tumors.

MATERIALS AND METHODS: The study analyzed 18 lesions from 15 patients with metastatic brain tumors who underwent gamma knife radiosurgery. Ten lesions were identified as recurrent tumors by an operation. In MR permeability imaging, the transfer constant between intra- and extravascular extracellular spaces (/minute), extravascular extracellular space, the transfer constant from the extravascular extracellular space to plasma (/minute), the initial area under the signal intensity–time curve, contrast-enhancement ratio, bolus arrival time (seconds), maximum slope of increase (millimole/second), and fractional plasma volume were calculated. ADC was also acquired. On both PET using ¹¹C-methionine and FDG-PET, the ratio of the maximum standard uptake value of the lesion divided by the maximum standard uptake value of the symmetric site in the contralateral cerebral hemisphere was measured (¹¹C-methionine ratio and FDG ratio, respectively). The receiver operating characteristic curve was used for analysis.

RESULTS: The area under the receiver operating characteristic curve for differentiating radiation necrosis from recurrent tumors was the best for the ¹¹C-methionine ratio (0.90) followed by the contrast-enhancement ratio (0.81), maximum slope of increase (millimole/second) (0.80), the initial area under the signal intensity–time curve (0.78), fractional plasma volume (0.76), bolus arrival time (seconds) (0.76), the transfer constant between intra- and extravascular extracellular spaces (/minute) (0.74), extravascular extracellular space (0.68), minimum ADC (0.60), the transfer constant from the extravascular extracellular space to plasma (/minute) (0.55), and the FDG-ratio (0.53). A significant difference in the ¹¹C-methionine ratio (P < .01), contrast-enhancement ratio (P < .01), maximum slope of increase (millimole/second) (P < .05), and the initial area under the signal intensity–time curve (P < .05) was evident between radiation necrosis and recurrent tumor.

CONCLUSIONS: The present study suggests that PET using ¹¹C-methionine may be superior to MR permeability imaging, ADC, and FDG-PET for differentiating radiation necrosis from recurrent tumors after gamma knife radiosurgery for metastatic brain tumors.

ABBREVIATIONS: BAT = bolus arrival time (seconds); CER = contrast-enhancement ratio; fPV = fractional plasma volume; GK = gamma knife radiosurgery; IAUGC = the initial area under the signal intensity–time curve; Kep = the transfer constant from the extravascular extracellular space to plasma (/minute); \( K^{\text{trans}} \) = the transfer constant between intra- and extravascular extracellular spaces (/minute); MaxSlope = maximum slope of increase (millimole/second); MET = ¹¹C-methionine; Ve = the extravascular extracellular space

Stereotactic radiosurgery such as gamma knife radiosurgery (GK) and CyberKnife (Accuray, Sunnyvale, California) is an effective method for treating intracranial neoplasms.¹,² For metastatic tumors of the brain, stereotactic radiosurgery has generally been the main tool used in therapeutic regimens.³,⁴ Although stereotactic radiosurgery is an effective treatment method, it has a risk of radiation necrosis. Radiation necrosis after stereotactic radiosurgery for metastatic tumors of the brain is more common than previously reported.⁵,⁶ It generally occurs 3–12 months after therapy⁷ and often resembles recurrent tumors on conventional imaging techniques, such as MR imaging,⁸ CT,⁹ and SPECT.¹⁰ Differentiating radiation necrosis and recurrent tumor is extremely important because of the different treatment implications. Histologic examination from a biopsy or resection may aid...
in differentiating these 2 events. However, a noninvasive method is needed for diagnosing whether a contrast-enhanced lesion with surrounding edema on conventional MR imaging is radiation necrosis or a recurrent tumor.

Advanced MR imaging techniques including MR spectroscopy,14 DWI,15 and DTI16 have been used for differentiation of radiation necrosis and recurrent tumors. The CTP technique has also been reported as promising in this field.17 CTP has the advantage of using widely available CT scanners, though x-ray exposure and administration of ionizing contrast material limit the clinical use. In radionuclide studies, SPECT with 201TI-chloride,18 technetium Tc99m-sestamibi,19 123I-alfa-methyl-L-tyrosine,20 O-(2-[18F]-fluoroethyl)-L-tyrosine (FET-PET),21,22 6-[18F]-fluoro-L-dopa (FDOPA),23 and FDG-PET24-26 have been reported to differentiate between radiation necrosis and recurrent tumors. Compared with these studies, the superiority of PET with 11C-methionine (MET) for differentiating radiation necrosis and recurrent tumors has been accepted because of the high sensitivity and specificity.27-31 However, MET-PET is not widely available. Dynamic contrast-enhanced MR imaging with a contrast agent has been used to characterize brain tumors32,33 and stroke.34

MR permeability imaging with dynamic contrast-enhanced–MR imaging based on the Tofts model35 has recently been developed and used for evaluating cerebrovascular diseases,36 brain tumors,37-39 nasopharyngeal carcinomas,40,41 rectal carcinomas,42 and prostate carcinomas.43 The endothelial permeability of vessels in brain tumors can be quantitatively acquired with MR permeability imaging. The vascular microenvironment in tumors can be measured by parameters such as influx transfer constant, reverse transfer constant, and the extravascular extracellular space.44 These parameters may reflect tissue characteristics including vascular density, a damaged blood-brain barrier, vascularity, and neoangiogenesis.44 If the feasibility of MR permeability imaging for differentiating radiation necrosis and recurrent tumors could be demonstrated, this technique may contribute to the management of patients after stereotactic radiosurgery and conventional radiation therapy because MR permeability imaging is widely available. To evaluate the feasibility of MR permeability imaging in the present study, we compared it with MET-PET, FDG-PET, and DWI for differentiating radiation necrosis from recurrent tumor after GK in patients with metastatic brain tumors.

**MATERIALS AND METHODS**

We analyzed 18 lesions from 15 patients (9 men, 6 women; mean age, 63.3 ± 10.9 years) with metastatic brain tumors who underwent GK (Table 1). Each patient provided written informed consent before PET/CT. This retrospective study was approved by the institutional review board at our hospital. Ten lesions were identified as recurrent tumors by an operation after both MR permeability imaging and MET-PET. In these 10 recurrent tumors, MR permeability imaging was performed 6–52 months (average, 19.7 months) after GK. Eight lesions were diagnosed as radiation necrosis because of a lack of change or a decrease in size >4 months after radiosurgery. In these 8 lesions, MR permeability imaging was performed 4–52 months (average, 26.6 months) after GK. MET-PET was performed immediately before FDG-PET on the same day. The protocol has been previously reported.45 After CT, MET was injected, and MET-PET was performed 20 minutes later. FDG was injected 60 minutes after MET-PET. MR permeability imaging and DWI were performed within 1 week before or after PET. Dynamic contrast-enhanced MR imaging was acquired by using gadolinium contrast medium. A 3D fast spoiled gradient-recalled acquisition in the steady-state was applied for dynamic contrast-enhanced MR imaging with a bolus injection of contrast material (total dose, 0.2 mL/kg body weight; dose rate, 3.0 mL/s). Parameters of dynamic contrast-enhanced MR imaging were as follows: TR/TE = minimum (5.7 ms)/minimum (1.3 ms), flip angle = 20°, FOV = 24 cm, matrix = 256 × 160, NEX = 1, number of sections = 16/phase, number of phases = 32, acquisition time = 3 minutes 59 seconds. Dynamic contrast-enhanced data were transferred to a workstation (Advantage Workstation, Version 4.6; GE Healthcare, Milwaukee, Wisconsin) and analyzed with commercially available software (GenIQ; GE Healthcare).

**Table 1: Patient summary**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Disease</th>
<th>Location of Tumor</th>
<th>Duration (mo) from GK to MRP</th>
<th>Necrosis/Recurrence</th>
<th>Radiation Dose by GK</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45</td>
<td>F</td>
<td>Lung ca.</td>
<td>Rt. temporal</td>
<td>24</td>
<td>Necrosis</td>
<td>90%, 22 Gy</td>
</tr>
<tr>
<td>2</td>
<td>64</td>
<td>M</td>
<td>Lung ca.</td>
<td>Lt. cerebellum</td>
<td>18</td>
<td>Recurrence</td>
<td>54%, 22 Gy</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>F</td>
<td>Lung ca.</td>
<td>Lt. occipital</td>
<td>25</td>
<td>Necrosis</td>
<td>70%, 21 Gy</td>
</tr>
<tr>
<td>4</td>
<td>75</td>
<td>M</td>
<td>Lung ca.</td>
<td>Lt. frontal</td>
<td>4</td>
<td>Necrosis</td>
<td>60%, 22 Gy</td>
</tr>
<tr>
<td>5</td>
<td>78</td>
<td>M</td>
<td>Lung ca.</td>
<td>Lt. occipital</td>
<td>14</td>
<td>Necrosis</td>
<td>60%, 22 Gy</td>
</tr>
<tr>
<td>6</td>
<td>64</td>
<td>M</td>
<td>Renal cell ca.</td>
<td>Lt. frontal</td>
<td>34</td>
<td>Necrosis</td>
<td>55%, 20 Gy</td>
</tr>
<tr>
<td>7</td>
<td>56</td>
<td>F</td>
<td>Breast ca.</td>
<td>Midbrain</td>
<td>35</td>
<td>Necrosis</td>
<td>58%, 20 Gy</td>
</tr>
<tr>
<td>8</td>
<td>68</td>
<td>M</td>
<td>Lung ca.</td>
<td>Lt. parietal</td>
<td>52</td>
<td>Necrosis</td>
<td>57%, 20 Gy</td>
</tr>
<tr>
<td>9</td>
<td>76</td>
<td>M</td>
<td>Lung ca.</td>
<td>Lt. occipital</td>
<td>30</td>
<td>Recurrence</td>
<td>65%, 22 Gy</td>
</tr>
<tr>
<td>10</td>
<td>42</td>
<td>F</td>
<td>Breast ca.</td>
<td>Rt. frontal</td>
<td>52</td>
<td>Recurrence</td>
<td>80%, 20 Gy</td>
</tr>
<tr>
<td>11</td>
<td>75</td>
<td>F</td>
<td>Lung ca.</td>
<td>Rt. temporal</td>
<td>6</td>
<td>Recurrence</td>
<td>55%, 22 Gy</td>
</tr>
<tr>
<td>12</td>
<td>60</td>
<td>M</td>
<td>Lung ca.</td>
<td>Lt. frontal</td>
<td>14</td>
<td>Recurrence</td>
<td>52%, 20 Gy</td>
</tr>
<tr>
<td>13</td>
<td>63</td>
<td>M</td>
<td>Lung ca.</td>
<td>Lt. frontal</td>
<td>22</td>
<td>Recurrence</td>
<td>52%, 20 Gy</td>
</tr>
<tr>
<td>14</td>
<td>54</td>
<td>F</td>
<td>Ovarian ca.</td>
<td>Lt. parietal</td>
<td>7</td>
<td>Recurrence</td>
<td>53%, 20 Gy</td>
</tr>
<tr>
<td>15</td>
<td>59</td>
<td>M</td>
<td>Lung ca.</td>
<td>Lt. frontal</td>
<td>16</td>
<td>Recurrence</td>
<td>54%, 32 Gy</td>
</tr>
</tbody>
</table>

Note: —Rt indicates right; Lt, left; ca., carcinoma; MRP, MR permeability imaging.

A prescription dose of 18–32 Gy at 50%–90% isodose.
The transfer constant between intra- and extravascular extracellular space (Ve), the transfer constant from the extravascular extracellular space to plasma (Kep) (1/minute), the initial area under the signal intensity–time curve (IAUGC), the contrast-enhancement ratio (CER), the bolus arrival time (BAT) (seconds), the maximum slope of increase (MaxSlope) (millimole/second), and fractional plasma volume (fPV) were calculated after setting an ROI on the solid portion of the lesion. CER was defined as \( \frac{\text{maximum signal intensity [SI]}}{\text{SI at Baseline}} / \frac{\text{SI at Baseline}}{\text{SI at Baseline}} \). BAT and MaxSlope are shown in Fig 1. ADC (10^{-3} \text{ mm/s}) was also acquired from DWI. On both MET-PET and FDG-PET, the ratio of the maximum standard uptake value of the lesion divided by the maximum standard uptake value of the symmetric site in the contralateral cerebral hemisphere was measured (MET-ratio and FDG-ratio, respectively). For measurement of each data point, ROIs were manually set on the fused images by using the Advantage Workstation. A single ROI was set in a lesion. On the workstation, when an ROI was set on a contrast-enhanced TIWI, its ROI could be set simultaneously in MR permeability images or PET images on the workstation. The ROI was set in the solid portion of the lesion by a neuroradiologist with >35 years of experience.

Receiver operating characteristic analysis was performed to evaluate the utility of those parameters for differentiating radiation necrosis from recurrent tumors. The area under the curve was evaluated for MET-PET, FDG-PET, DWI, and each parameter of MR permeability imaging. Each cutoff value was also acquired by receiver operating characteristic analysis. Each mean value was compared between radiation necrosis and recurrent tumors by using the t test. Statistical analysis was performed with Excel Statistics 2015, Version 1.02 (Social Survey Research Information, Tokyo, Japan).

RESULTS
The minimum, average, and maximum values of each MR imaging parameter were obtained. After the minimum, average, and maximum values were evaluated by receiver operating characteristic analysis, the averages of K\text{trans}, Ve, Kep, IARGC, CER, BAT, MaxSlope, and IPV were better than the minimum and maximum values for each. In ADC, the minimum value was better than the average and maximum values. Figure 2 shows the receiver operating characteristic curve for each parameter. The area under the curve for differentiating radiation necrosis from recurrent tumors was best for the MET ratio (0.90) followed by CER (0.81), MaxSlope (0.80), IARGC (0.78), IPV (0.76), BAT (0.76), K\text{trans} (0.74), Ve (0.68), minimum ADC (0.60), Kep (0.55), and the FDG ratio (0.53) (Table 2). For the MET ratio \( (P < .01), \) CER \( (P < .01) \), MaxSlope \( (P < .05) \), and IARGC \( (P < .05) \), the area under the curve value was significantly better \( (\chi^2 \text{ test}) \) than the area under the curve of 0.5. The cutoff value for the best combination of sensitivity and specificity was 1.42 with the MET ratio, 0.61 with CER, 0.01 with MaxSlope, 0.2 with IARGC, 0.02 with IPV, 44.0 with BAT, 0.05 with K\text{trans}, 0.27 with Ve, 0.73 with the minimum ADC, 0.32 with Kep, and 0.97 with the FDG ratio (Table 2). With the cutoff value, the sensitivity and specificity were 0.90 and 0.75 for the MET ratio, 0.80 and 0.88 for CER, 0.90 and 0.50 for MaxSlope, 0.60 and 1.0 for IARGC, 0.50 and 0.88 for IPV, 0.70 and 0.75 for BAT, 0.70 and 0.67 for K\text{trans}, 0.60 and 0.63 for Ve, 0.60 and 0.25 for minimum ADC, 0.80 and 0.05 for Kep, and 0.40 and 0.50 for the FDG ratio, respectively (Table 2). We observed a significant difference for the MET ratio \( (P < .01), \) CER \( (P < .01) \), MaxSlope \( (P < .05) \), and IARGC \( (P < .05) \) between radiation necrosis (Fig 3) and a recurrent tumor (Fig 4 and Table 3). The Welch t test was applied due to the unequal sample size and variance between the 2 groups.

DISCUSSION
The present study showed that MET-PET was the most promising imaging technique for differentiating radiation necrosis and recurrent metastatic tumors after GK compared with MR permeability imaging, DWI, and FDG-PET. In our literature review, we did not find any previous reports comparing MR permeability imaging with nuclear medicine imaging. For distinguishing treatment-induced necrosis from a recurrent tumor in the brain, the superiority of MET-PET regarding the sensitivity and specificity is widely accepted.\(^{27-31}\) In the present study, both MET-PET and FDG-PET were undertaken on a single day. This technique performing both PETs on a single day has previously been reported.\(^{45-50}\) The interaction between the 2 tracers is considered minimal.

In tumors, MET preferably accumulates due to the high density and activity of amino acid transporters in tumors.\(^{27-31}\) In recurrent tumors, MET can accumulate due to active transport and cell proliferation.\(^{27-31}\) On the other hand, in radiation necrosis, accumulation is presumably due to passive diffusion via blood-brain barrier damage.\(^{27-31}\) The different mechanisms of MET accumulation in the 2 pathologic processes could be a means of distinguishing recurrent tumors from radiation necrosis. MET-PET has preferable sensitivity and specificity for differentiation; however, this technique is not widely available for clinical use. Recently, the usefulness of FET-PET and FDOPA-PET has been reported for differentiating recurrent brain metastatic tumors and radiation injury.\(^{21-23}\) Although high rates of sensitivity and specificity for these techniques have been demonstrated, use of these methods in patients with brain metastases is limited. Further studies regarding their contribution to the management of patients with brain metastases are required.
MR permeability imaging in the present study was performed with dynamic contrast-enhanced MR imaging. DSC MR imaging has also been used for MR perfusion. However, DSC MR imaging has a limitation of susceptibility artifacts due to hemorrhage, calcification, and surgical clips. MR permeability imaging in the present study yielded many parameters, but interpretation of the results of those parameters remains somewhat difficult. Tissue enhancement following administration of a contrast agent generally depends on various factors such as vessel density, vascular permeability, blood flow, and interstitial pressure.\textsuperscript{44,52,53} Although qualitative visual evaluation of the images is possible, quantitative data could improve the results of analysis. The application package for MR permeability used in the present study is commercially available and was an easy tool to use for imaging and quantification of the data. In previous reports\textsuperscript{44,52,53} with a technique similar to that in the present study, $K_{\text{trans}}$, $K_{\text{ep}}$, Ve, and IAUGC were frequently evaluated. In the present study, other parameters including CER, MaxSlope, fPV, and BAT were also evaluated. CER, a relatively simple type of data, was the best for differentiating radiation necrosis and recurrent tumors. MaxSlope, which mainly reflects blood flow, followed CER. Increased vascularity and neovascularity could increase MaxSlope in recurrent tumors. IAUGC, which is nearly equal to blood volume, followed MaxSlope. BAT in recurrent tumors was shorter than in radiation necrosis. BAT can be short due to increased vascularity and/or

- **FIG 2.** Receiver operating characteristic curve of each parameter. A, Receiver operating characteristic curve for the $^{11}$C-methionine ratio, contrast-enhanced ratio, the initial area under the signal intensity–time curve, and MaxSlope. The area under the curve of the MET ratio, CER, IAUGC, and MaxSlope = 0.90, 0.81, 0.80, and 0.78, respectively; B, Receiver operating characteristic curve for the extravascular extracellular space, the transfer constant between intravascular and extravascular extracellular spaces, BAT, and fractional plasma volume. The area under the curve of fPV, BAT, $K_{\text{trans}}$, and Ve = 0.76, 0.76, 0.74, and 0.68, respectively; C, The receiver operating characteristic curve for a minimum apparent diffusion coefficient, the transfer constant from the extravascular extracellular space to plasma, and FDG ratio. The area under the curve of minimum ADC, Kep, and FDG ratio = 0.60, 0.55, and 0.53, respectively.

<table>
<thead>
<tr>
<th>Table 2: Results of each parameter by ROC analysis</th>
<th>AUC ($\chi^2$ test Compared with AUC = 0.5)</th>
<th>AUC, 95% CI</th>
<th>Cutoff Value</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MET ratio</td>
<td>0.90 (P &lt; .01)</td>
<td>0.75–1.05</td>
<td>1.42</td>
<td>0.90 (± 0.026)</td>
<td>0.75 (± 0.082)</td>
</tr>
<tr>
<td>CER av</td>
<td>0.81 (P &lt; .01)</td>
<td>0.58–1.04</td>
<td>0.61</td>
<td>0.80 (± 0.035)</td>
<td>0.88 (± 0.023)</td>
</tr>
<tr>
<td>MaxSlope av</td>
<td>0.80 (P &lt; .05)</td>
<td>0.58–1.02</td>
<td>0.01</td>
<td>0.90 (± 0.014)</td>
<td>0.50 (± 0.098)</td>
</tr>
<tr>
<td>IAUGC av</td>
<td>0.78 (P &lt; .05)</td>
<td>0.55–1.00</td>
<td>0.2</td>
<td>0.60 (± 0.078)</td>
<td>1.0 (0)</td>
</tr>
<tr>
<td>fPV av</td>
<td>0.76</td>
<td>0.53–0.99</td>
<td>0.02</td>
<td>0.50 (± 0.082)</td>
<td>0.88 (± 0.017)</td>
</tr>
<tr>
<td>BAT av</td>
<td>0.76</td>
<td>0.48–1.03</td>
<td>44.0</td>
<td>0.70 (± 0.046)</td>
<td>0.75 (± 0.041)</td>
</tr>
<tr>
<td>$K_{\text{trans}}$ av</td>
<td>0.74</td>
<td>0.49–0.99</td>
<td>0.05</td>
<td>0.70 (± 0.046)</td>
<td>0.67 (± 0.041)</td>
</tr>
<tr>
<td>Ve av</td>
<td>0.68</td>
<td>0.41–0.95</td>
<td>0.27</td>
<td>0.60 (± 0.052)</td>
<td>0.63 (± 0.051)</td>
</tr>
<tr>
<td>ADC min</td>
<td>0.60</td>
<td>0.32–0.88</td>
<td>0.73</td>
<td>0.60 (± 0.039)</td>
<td>0.25 (± 0.061)</td>
</tr>
<tr>
<td>Kep av</td>
<td>0.55</td>
<td>0.26–0.84</td>
<td>0.32</td>
<td>0.80 (± 0.026)</td>
<td>0.50 (± 0.082)</td>
</tr>
<tr>
<td>FDG ratio</td>
<td>0.53</td>
<td>0.23–0.82</td>
<td>0.97</td>
<td>0.40 (± 0.059)</td>
<td>0.50 (± 0.049)</td>
</tr>
</tbody>
</table>

Note: AUC indicates area under the curve; av, average; min, minimum; ROC, receiver operating characteristic.
arteriovenous shunting in the recurrent tumor. When MET-PET is not available, MR permeability imaging including these parameters could possibly replace MET-PET.

As previously reported, IAUGC in recurrent tumors was higher than in radiation necrosis. Although vascular dilation may occur in radiation necrosis, increased neovascularity with dilated vessels can cause increased IAUGC in recurrent tumors. \( K_{\text{trans}} \) has been reported as a feasible parameter for grading gliomas and detecting tumors in the prostate. The present study showed that CER, MaxSlope, and IAUGC were superior to \( K_{\text{trans}} \) for differentiating radiation necrosis and recurrent tumors. This finding may be due to increased vascular permeability in recurrent tumors and in radiation necrosis. In recurrent tumors, newly proliferative tumor vessels in tissue with a damaged blood-brain barrier could play a role in increasing those parameters. Although we found no statistical differences, the mean value of \( K_{\text{trans}} \), Kep, and Ve in recurrent tumors was higher than that in radiation necrosis. This finding also indicated increased permeability in recurrent tumors.

ADC is lower in malignant tumors than in benign tumors in the brain and in other areas. Increased cellularity in malignant tumors causes a decrease in ADC. In the present study, ADC was inferior to most MR permeability imaging parameters. The mean value of minimum ADC in recurrent tumors was not lower than that in radiation necrosis. Some blood components may influence the ADC value in radiation necrosis. Although cellularity was not histologically evaluated, cellularity in recurrent tumors is not necessarily high. Wang et al. also reported that radiation necrosis has significantly lower ADC than malignant gliomas in rats with DTI MR imaging. In their report, the necrotic central zone in radiation necrosis had significantly lower ADC, parallel diffusivity, and perpendicular diffusivity than in the peripheral zone.

The feasibility of FDG-PET for detecting neoplasms and evaluating the treatment response in various organs is well-known, and FDG is the most widely available tracer. The usefulness of FDG-PET for diagnosing radiation necrosis in the brain has been previously reported in the literature. However, the inferiority of FDG-PET was evident compared with each parameter of MR permeability imaging used in the present study. The
The present study indicated that the usefulness of FDG-PET was clearly questionable for differentiating recurrent metastatic tumors of the brain and radiation necrosis. MET is not as readily available as FDG. In Japan, FDG can be used in hospitals without a cyclotron because FDG can be commercially delivered from a medical company. The insurance system covers patients who undergo FDG-PET. The short half-life of $^{11}$C is problematic for MET availability because MET use requires a cyclotron in the hospital. After these difficulties regarding the use of MET are resolved, MET-PET may become more widely available to more patients in the near future.

The present study has several major limitations. The number of subjects was small. Although recurrent tumors were proved by histopathology, radiation necrosis was presumably diagnosed only by our criteria. In a clinical study such as ours, obtaining histologic confirmation is often difficult. The term “stable disease” may be more suitable than “radiation necrosis.” Clinically, radiation necrosis that is increasing in size, which was not observed in the present study, is sometimes experienced. The duration between MR permeability imaging and GK was variable (4–52 months) in each case. This wide range of duration was due to the interval of follow-up MR imaging studies after GK. The follow-up intervals were determined by neurosurgeons who performed GK and managed patients. The intervals of follow-up MR imaging were shorter in patients with recurrent tumors than in those with radiation necrosis. Neurosurgeons requested shorter intervals for follow-up MR imaging in patients with suspected recurrent tumors. ROIs were manually set to measure each parameter. Partial volume averaging within ROIs may influence the value of each parameter. Especially in the region near large vessels, CER and IAUGC may be affected by the partial volume effect.

### Table 3: Mean value of each parameter in radiation necrosis and recurrence

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Radiation Necrosis (mean ± SD)</th>
<th>Recurrence (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MET ratio</td>
<td>1.23 ± 0.21</td>
<td>2.22 ± 0.91*</td>
</tr>
<tr>
<td>CER av</td>
<td>0.49 ± 0.11</td>
<td>1.09 ± 0.56*</td>
</tr>
<tr>
<td>MaxSlope av</td>
<td>0.01 ± 0.002</td>
<td>0.03 ± 0.038*</td>
</tr>
<tr>
<td>IAUGC av</td>
<td>0.07 ± 0.04</td>
<td>0.40 ± 0.52*</td>
</tr>
<tr>
<td>fPV av</td>
<td>0.01 ± 0.01</td>
<td>0.10 ± 0.17</td>
</tr>
<tr>
<td>BAT av</td>
<td>45.32 ± 5.05</td>
<td>41.30 ± 5.23</td>
</tr>
<tr>
<td>$k^{trans}$ av</td>
<td>0.05 ± 0.02</td>
<td>0.28 ± 0.38</td>
</tr>
<tr>
<td>Ve av</td>
<td>0.23 ± 0.11</td>
<td>0.43 ± 0.30</td>
</tr>
<tr>
<td>ADC min</td>
<td>0.59 ± 0.20</td>
<td>0.71 ± 0.31</td>
</tr>
<tr>
<td>Kep av</td>
<td>0.48 ± 0.25</td>
<td>0.54 ± 0.38</td>
</tr>
<tr>
<td>FDG ratio</td>
<td>0.91 ± 0.17</td>
<td>0.97 ± 0.20</td>
</tr>
</tbody>
</table>

* Statistical difference, $P < .01$.

b Statistical difference, $P < .05$.  

---

**FIG 4.** A 42-year-old woman with breast cancer. She underwent GK for a metastatic tumor in the right frontal lobe. Contrast-enhanced T1WI (A) reveals a contrast-enhanced lesion with surrounding edema in the right frontal lobe 59 months after GK (arrows). MR permeability images (B, C, MaxSlope; D, IAUGC) show increased value of each parameter of the lesion (white arrows). MET-PET/CT (E) also shows an increased activity of MET in the lesion (white arrow). A recurrent tumor was demonstrated by an operation.
CONCLUSIONS
The present study suggests that MET-PET may be superior to MR permeability imaging, ADC, and FDG-PET for differentiating radiation necrosis and recurrent tumors after GK for metastatic brain tumors. FDG-PET is questionable for differentiating them. Although MR permeability imaging is not a feasible alternative to MET-PET, MR permeability imaging, especially including CER, MaxSlope, and IAUGC, is feasible for differentiating radiation necrosis and recurrent tumors.

REFERENCES
The Initial Area Under the Curve Derived from Dynamic Contrast-Enhanced MRI Improves Prognosis Prediction in Glioblastoma with Unmethylated MGMT Promoter


ABSTRACT

BACKGROUND AND PURPOSE: Although perfusion and permeability MR parameters have known to have prognostic value, they have reproducibility issues. Our aim was to evaluate whether the initial area under the time-to–signal intensity curve (IAUC) derived from dynamic contrast-enhanced MR imaging can improve prognosis prediction in patients with glioblastoma with known MGMT status.

MATERIALS AND METHODS: We retrospectively examined 88 patients with glioblastoma who underwent preoperative dynamic contrast-enhanced MR imaging. The means of IAUC values at 30 and 60 seconds (IAUC30 mean and IAUC60 mean) were extracted from enhancing tumors. The prognostic values of IAUC parameters for overall survival and progression-free survival were assessed with log-rank tests, according to the MGMT status. Multivariate overall survival and progression-free survival models before and after adding the IAUC parameters as covariates were explored by net reclassification improvement after receiver operating characteristic analysis for 1.5-year overall survival and 1-year progression-free survival and by random survival forest.

RESULTS: High IAUC parameters were associated with worse overall survival and progression-free survival in the unmethylated MGMT group, but not in the methylated group. In the unmethylated MGMT group, 1.5-year overall survival and 1-year progression-free survival prediction improved significantly after adding IAUC parameters (overall survival area under the receiver operating characteristic curve, 0.86; progression-free survival area under the receiver operating characteristic curve, 0.74–0.76) to the model with other prognostic factors (overall survival area under the receiver operating characteristic curve, 0.81; progression-free survival area under the receiver operating characteristic curve, 0.69; \( P < .05 \text{ for all} \) except in the case of IAUC60 mean for 1-year progression-free survival prediction (\( P = .059 \)). Random survival forest models indicated that the IAUC parameters were the second or most important predictors in the unmethylated MGMT group, except in the case of the IAUC60 mean for progression-free survival.

CONCLUSIONS: IAUC can be a useful prognostic imaging biomarker in patients with glioblastoma with known MGMT status, improving prediction of glioblastoma prognosis with the unmethylated MGMT promoter status.

ABBREVIATIONS: AUC = area under the receiver operating characteristic curve; DCE = dynamic contrast-enhanced; EGFR = epidermal growth factor receptor; GBM = glioblastoma; IAUC = initial area under the time-to–signal intensity curve; IDH1 = isocitrate dehydrogenase 1; \( K^{\text{trans}} \) = volume transfer constant; MGMT = \( O^6\)-methylguanine-DNA methyltransferase; nCET = non-contrast-enhanced tumor; OS = overall survival; PFS = progression-free survival; rCBV = relative cerebral blood volume; ROC = receiver operating characteristic

Glioblastoma (GBM) is the most common primary malignant tumor in the adult brain. Although its prognosis remains poor (median survival, \( \sim 14.7 \) months),\(^1\) some patients with GBM show a distinct prognosis and response to chemoradiation. Previous studies have investigated the prognostic factors of GBM, including MR imaging\(^2\)\(^-\)\(^4\) and molecular biomarkers (\( O^6\)-methylguanine-DNA methyltransferase [MGMT] promoter methylation).\(^5\)

Previous studies have shown that high relative cerebral blood volume (rCBV; derived via dynamic susceptibility contrast-enhanced MR imaging) and high volume transfer constant (\( K^{\text{trans}} \); derived via dynamic contrast-enhanced [DCE] MR imaging) are associated with poor survival outcomes.\(^6\)\(^-\)\(^8\) However, rCBV and \( K^{\text{trans}} \) measurements have reproducibility issues related to post-processing techniques, including normalization, model-based calculation, arterial input function, and software.\(^9\)\(^-\)\(^13\) In contrast, the initial area under the time-to–signal intensity curve (IAUC),
derived via DCE MR imaging, is a model-free parameter that does not require an arterial input function or a complicated model-based calculation and is highly reproducible.\textsuperscript{10,14} Because IAUC reflects both tumor perfusion and permeability,\textsuperscript{9,10,15} we hypothesized that IAUC might be useful for predicting the survival outcome in GBM. In this study, we used automatically calculated IAUC parameters to maximize reproducibility.

\textit{MGMT} removes alkyl groups from the alkylation site of temozolomide. Methylation of the \textit{MGMT} promoter inhibits \textit{MGMT} activity and yields a better response to temozolomide and improved prognosis.\textsuperscript{5} Because the \textit{MGMT} status is available after surgery in most patients with GBM, the predictive ability of IAUC for prognosis in patients with GBM with known \textit{MGMT} status is clinically relevant. Here, we aimed to assess whether IAUC can improve prognosis prediction in patients with GBM with known \textit{MGMT} status.

\textbf{MATERIALS AND METHODS}

Our institutional review board approved this retrospective study and waived the requirement for informed consent.

\textbf{Study Population}

We reviewed the records of 101 consecutive patients who underwent preoperative DCE MR imaging for newly diagnosed GBM from October 2010 to July 2014. The enrollment process is shown in On-line Fig 1. The inclusion criteria were pathologically confirmed GBM, no prior biopsy or treatment, and available \textit{MGMT} promoter methylation status. The exclusion criteria were previous brain biopsy or treatments (\(n=6\)), unavailable \textit{MGMT} status (\(n=3\)), and inadequate DCE image quality, leading to processing errors (\(n=4\)). Thus, 88 patients were enrolled.

\textbf{Imaging}

A 3T MR imaging unit (Achieva; Philips Healthcare, Best, the Netherlands) and an 8-channel sensitivity encoding head coil were used for preoperative MR imaging. The protocol included T1-weighted turbo spin-echo images with inversion recovery (TR, 2000 ms; TE, 10 ms; TI, 1000 ms; FOV, 240 mm; section thickness, 5 mm; matrix, 256 \(\times\) 256), T2-weighted turbo spin-echo (TR, 3000 ms; TE, 80 ms; FOV, 240 mm; section thickness, 5 mm; matrix, 256 \(\times\) 256), and T2-weighted fluid-attenuated inversion recovery (TR, 10,000 ms; TE, 125 ms; TI, 2500 ms; FOV, 240 mm; section thickness, 5 mm; matrix, 256 \(\times\) 256) images. 3D T1-weighted turbo field echo images (TR, 9.8 ms; TE, 4.6 ms; FOV, 240 mm; section thickness, 1 mm; matrix, 224 \(\times\) 224) were acquired after the injection of gadolinium-based contrast (0.1 mL/kg of gadobutrol, Gadovist; Bayer Schering Pharma, Berlin, Germany). For DCE-MR imaging, 60 dynamic phases of DCE T1-weighted images were acquired with the following parameters: TR, 6.3 ms; TE, 3.1 ms; FOV, 240 mm; matrix, 192 \(\times\) 192; section thickness, 3 mm; flip angle, 15°. After we acquired the fifth phase, gadolinium-based contrast (0.1 mL/kg of gadobutrol) was injected (rate, 3 mL/s). The total acquisition time for DCE-MR imaging was 6 minutes 18 seconds and the temporal resolution was approximately 6 seconds.

\textbf{Image Postprocessing and Analysis}

The ROIs were drawn by the consensus of 2 neuroradiologists (Y.S.C. and S.-K.L., with 4 and 20 years of experience in neuroradiology, respectively) who were blinded to the \textit{MGMT} status and other clinical information, using a semiautomatic signal-intensity-threshold method to include the entire enhanced portion of the tumors on postcontrast T1-weighted images, while avoiding necrotic or cystic portions.

IAUC values were acquired by integrating the area under the time-to-signal-intensity curve, from 0 to 30 seconds (IAUC30) and 0 to 60 seconds (IAUC60) after contrast agent arrival on the basis of previous studies.\textsuperscript{10} IAUC values were automatically calculated without any user-dependent input, to maximize interrater reliability, through automatic determination of the time of contrast agent arrival for each pixel; the time of contrast agent arrival was defined as the initial time at which a signal increase of \(>5\%\) of the maximum signal increase was observed during \(>2\) serial phases. The combination of this automatic calculation of IAUC and semiautomatic ROI segmentation of enhancing tumor yields almost perfect reproducibility.\textsuperscript{16} The IAUC values were normalized to the maximum signal increase. A detailed description of the image processing is provided in the On-line Appendix. The mean values of IAUC30 (IAUC30\_mean) and IAUC60 (IAUC60\_mean) were extracted from the enhanced tumors. Images were analyzed with Medical Image Processing, Analysis, and Visualization (Version 7.0; National Institutes of Health, Bethesda, Maryland) and R software, Version 3.0.2 (R Foundation, http://www.r-project.org/).

\textbf{MGMT and Other Prognostic Parameters}

\textit{MGMT} promoter methylation status was evaluated with a methylation-specific polymerase chain reaction, which was retrospectively recorded from pathologic reports. Because IAUC may be related to other genetic profiles, including isocitrate dehydrogenase 1 (\textit{IDH1}) mutation status, epidermal growth factor receptor (\textit{EGFR}) expression, and the presence of 1p/19q codeletion, the data regarding these profiles were also recorded as described in the On-line Appendix. The presence of oligodendroglial components was also recorded because the presence of these components is related to better prognosis.\textsuperscript{17} Furthermore, we followed the following clinical factors: age, sex, Karnofsky performance status, extent of resection, and postoperative treatment, along with conventional MR imaging findings. The extent of resection was categorized as total, subtotal (\(<100\%\) but \(\geq 75\%\) of gross tumor removal), or partial (\(<75\%\) of gross tumor removal) resection/biopsy based on the intraoperative impressions of the surgeons (J.H.C., S.-G.K., and E.H.K., with 20, 16, and 10 years of experience in neurosurgery, respectively) and postoperative MR imaging. Postoperative treatment was categorized as concurrent chemoradiation with temozolomide, radiation therapy only, temozolomide-based chemotherapy only, and no postoperative treatment.

Conventional MR imaging findings included volume of enhanced tumor, degree of edema, presence of non-contrast-enhanced tumor (nCET), presence of deep white-matter invasión, and eloquent brain involvement, which are associated with prognosis.\textsuperscript{2,3} Conventional MR imaging findings were de-
Statistical Analysis

Overall survival (OS) duration was defined as the time from MR imaging–based diagnosis to death or the final follow-up in living cases. Progression-free survival (PFS) duration was defined as the time from MR imaging–based diagnosis to tumor progression, recurrence, death, or the final follow-up in cases in which no tumor progression or death was noted, according to the Response Assessment in Neuro-Oncology19 as described elsewhere.4,8

Univariate survival analyses for OS and PFS of the entire cohort were performed with Kaplan-Meier estimates and the log-rank test; the analyses included IAUC30mean, IAUC60mean, MGMT status, the presence of an oligodendrogial component, clinical factors (age, sex, Karnofsky performance status, extent of tumor resection, and postoperative treatment), and conventional MR imaging findings (enhanced tumor volume, edema, nCET, eloquent brain involvement, and deep white-matter invasion). Subgroup survival analyses of the methylated and unmethylated MGMT groups were performed with the IAUC parameters. If the variables were continuous or had >3 categories, they were dichotomized by the optimal cutoff values for OS and PFS that were calculated by using the “cutp” function of the “survMisc” R package, as defined by Contal and O’Quigley.20 This method determines the optimal cutoff value yielding the most significant prognostic differences between the 2 groups based on test scores from the Cox regression model.20

The multivariate models were established with the significant factors of univariate analyses for OS and PFS in the unmethylated MGMT promoter group because the IAUC parameters were prognostic for the unmethylated MGMT group only, as shown later. In the multivariate models, all the variables that were continuous or had >3 categories were dichotomized, as in the univariate analyses. The multivariate models for OS and PFS were established from other prognostic factors only (model 0), and IAUC30mean and IAUC60mean were subsequently added as covariate parameters (IAUC30mean in model 1 and IAUC60mean in model 2). These multivariate models before (OS and PFS model 0) and after (OS and PFS models 1 and 2) adding IAUC parameters were explored and compared using 2 methods: 1) The diagnostic accuracies for 1.5-year OS and 1-year PFS prediction were assessed by receiver operative characteristic (ROC) analysis. Then, the reclassification improvement on adding the IAUC parameters was assessed using net reclassification improvement, as described by Pencina et al.21 2) The random survival forest method was used to determine the variable importance of the IAUC parameters in prognosis prediction. The forests consisted of 50,000 trees, having a minimum of 3 samples in a terminal node. The IAUC parameters and other prognostic factors were ranked by the relative importance scores, and the C-indices of the random survival forest models were calculated. Representative trees were constructed with the variables that showed the highest importance scores.22,23

RESULTS

The clinical characteristics of the patients according to the MGMT status are summarized in On-line Table 1. None of the clinical characteristics, except for median OS and PFS, showed a significant difference between the methylated and unmethylated MGMT groups. The median OS and PFS were 442 days and 272 days, respectively, in the unmethylated MGMT group, whereas they were 790 days and 657 days, respectively, in the methylated MGMT group (log-rank test, \( P = .014 \) and .003 for OS and PFS, respectively). The other genetic characteristics of patients are summarized in On-line Table 2.

Univariate Survival Analyses

The results of the univariate analyses for OS and PFS in the entire cohort are summarized in On-line Table 3. The IAUC parameters were not significant predictors of OS and PFS in the entire cohort, though high IAUC parameters tended to be associated with poor OS (\( P = .090 \) for IAUC30mean, \( P = .072 \) for IAUC60mean). Unmethylated MGMT, 66 years of age or older, less than total resection, postoperative treatment other than concurrent chemoradiation with temozolomide, and enhanced tumor volume of \( \geq 30.2 \) cm\(^3\) were associated with poor OS (\( P < .05 \) for all). Similarly, unmethylated MGMT, 70 years of age or older, less than total resection, postoperative treatment other than concurrent chemoradiation with temozolomide, and enhanced tumor volume of \( \geq 30.2 \) cm\(^3\) were associated with poor PFS (\( P < .05 \) for all). Eloquent brain involvement was associated with poor OS (\( P = .033 \)), but not with PFS. Sex, Karnofsky performance status, edema, nCET, and deep white-matter invasion were not associated with OS or PFS.

The results of the subgroup univariate analyses of the IAUC parameters in the methylated and unmethylated MGMT groups are summarized in Table 1 and Fig 1. High IAUC parameters were significant predictors of poor OS (\( P = .008 \) for IAUC30mean, \( P = .015 \) for IAUC60mean) and poor PFS (\( P = .010 \) for IAUC30mean, \( P = .015 \) for IAUC60mean) in the unmethylated MGMT group, but not in the methylated MGMT group. Therefore, we established multivariate models for the unmethylated MGMT group alone. Representative cases of GBMs with unmethylated MGMT promoter status are shown in Figs 2 and 3.
ROC Analyses and Net Reclassification Improvement for Predicting 1.5-Year OS and 1-Year PFS

The results of the ROC analyses with the multivariate models for 1.5-year OS and 1-year PFS in the unmethylated and methylated MGMT subgroups are summarized in Table 2. Among the 51 patients in the unmethylated MGMT group, 8 were excluded from the 1.5-year OS analysis and 1 was excluded from the 1-year PFS analysis because the follow-up duration was insufficient. Both OS and PFS model 0 included age, extent of resection, postoperative treatment, and enhanced tumor volume as covariates; eloquent brain involvement was included as a covariate in the OS model 0 only, according to the results of the univariate analyses. When the IAUC30\text{mean} or IAUC60\text{mean} were added in the OS model 0 and PFS model 0 as covariates, the diagnostic accuracies improved for 1.5-year OS prediction (OS models 1 and 2 area under the receiver operating characteristic curve [AUC], 0.86) and 1-year PFS prediction (PFS model 1 AUC, 0.76; PFS model 2 AUC, 0.74), compared with model 0 (OS model 0 AUC, 0.81; PFS model 0 AUC, 0.69). Reclassification improvement by adding IAUC parameters was statistically significant, as assessed by net reclassification improvement (P < .005 for OS models 1 and 2; P < .020 with PFS model 1), except in the case of PFS model 2 with IAUC60\text{mean}, which showed borderline significance (P = .059).

Contribution of IAUC Parameters in the Multivariate Model of Random Survival Forest

Random survival forests for OS showed that IAUC parameters were the second most important variable, following the volume of TABLE 1: Univariate analysis of IAUC histogram parameters as predictors of OS and PFS in the unmethylated and methylated MGMT subgroups.

<table>
<thead>
<tr>
<th>Survival/Parameters</th>
<th>Unmethylated MGMT (n = 51)</th>
<th>Methylated MGMT (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cutoff Value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>OS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IAUC30\text{mean}</td>
<td>≥10.9</td>
<td>3.04 (1.28–7.21)</td>
</tr>
<tr>
<td>IAUC60\text{mean}</td>
<td>≥28.4</td>
<td>3.48 (2.20–10.14)</td>
</tr>
<tr>
<td>PFS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IAUC30\text{mean}</td>
<td>≥10.9</td>
<td>2.60 (1.23–5.50)</td>
</tr>
<tr>
<td>IAUC60\text{mean}</td>
<td>≥32.6</td>
<td>2.15 (1.14–4.05)</td>
</tr>
</tbody>
</table>

Note: —HR indicates hazard ratio.

\( ^{a} \) Calculated from the log-rank test.

FIG 1. Kaplan-Meier curves of overall survival (A–C) and progression-free survival (D–F) with IAUC30\text{mean} in the unmethylated MGMT (A and D, n = 51) and methylated MGMT groups (B and E, n = 31) and the entire cohort (C and F, n = 88). IAUC30\text{mean}, stratified OS (log-rank test, P = .008) and PFS (log-rank test, P = .010) only in the unmethylated MGMT group, but not in the methylated MGMT group (log-rank test, P = .429 for OS, P = .238 for PFS).
enhancing tumor as the top variable and followed by postoperative treatment as the third most important variable. The variable importance of random survival forests is shown in On-line Figs 2 and 3. The relative importance was 41% for IAUC30mean in OS model 1 and 57% for IAUC60mean in OS model 2, assuming that the relative importance of volume of enhancing tumor was 100%.

Generation of a signal tree from this forest using the top 2 predictors (ie, volume of enhancing tumor and IAUC parameters) resulted in volume of enhancing tumor as the primary split and IAUC parameters as the secondary split for a group with a low volume of enhancing tumor (Fig 4). This splitting caused a significant difference in survival between the groups (P < .001 for trees with IAUC30mean and IAUC60mean, log-rank test), with a difference in mean survival of 354 days and 388 days between the high volume of enhancing tumors versus low volume of enhancing tumors with low IAUC30mean and IAUC60mean, respectively. The C-indices were higher after the IAUC parameters were added in OS models 1 and 2 (C-index = 0.67), compared with OS model 0 (C-index = 0.61).

Random survival forests for PFS showed that IAUC30mean in PFS model 1 was the most important variable, followed by extent of resection and volume of enhancing tumor as the second and third most important variables, respectively, whereas in PFS model 2, IAUC60mean was the third most important variable, following the extent of resection and volume of enhancing tumor as the first and second most important variables, respectively. The relative importance was 100% for IAUC30mean, and 94% for extent of resection in PFS model 1. Generation of a single tree with

Table 2: Reclassification improvement by adding IAUC parameters for predicting 1.5-year OS (n = 43) and 1-year PFS (n = 50) in the unmethylated MGMT group

<table>
<thead>
<tr>
<th>Survival Time/Models</th>
<th>AUC (95% CI)</th>
<th>NRI (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5-year OS (n = 43)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 0 (ref)</td>
<td>0.81 (0.65–0.96)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Model 1</td>
<td>0.86 (0.74–0.98)</td>
<td>0.95 (0.61–1.29)</td>
<td>.005</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.86 (0.72–0.99)</td>
<td>0.81 (0.47–1.15)</td>
<td>.018</td>
</tr>
<tr>
<td>1-year PFS (n = 50)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 0 (ref)</td>
<td>0.69 (0.54–0.84)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Model 1</td>
<td>0.76 (0.62–0.90)</td>
<td>0.69 (0.39–0.98)</td>
<td>.020</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.74 (0.58–0.89)</td>
<td>0.56 (0.26–0.85)</td>
<td>.059</td>
</tr>
</tbody>
</table>

Note: —NRI indicates net reclassification improvement; ref, reference.

* Calculated from category-less NRI.

FIG 2. A 52-year-old male patient with glioblastoma with unmethylated MGMT promoter status, whose overall survival time was 477 days. TI-weighted images (A), IAUC30 parameter map of the enhancing tumor (B), the relative frequency histogram of IAUC30 (C), and the time to the mean signal-intensity curve of the enhancing tumor (D). The volume of enhancing tumor was 8.4 cm³, and the IAUC30mean was 5.4.

FIG 3. A 59-year-old female patient with glioblastoma with unmethylated MGMT promoter status, whose overall survival time was 250 days. TI-weighted image (A), IAUC30 parameter map of the enhancing tumor (B), the relative frequency histogram of IAUC30 (C), and the time to the mean signal-intensity curve of the enhancing tumor (D). The volume of the enhancing tumor was 7.4 cm³, and the IAUC30mean was 16.1.
Furthermore, IAUC values were paradoxically higher in the methylated group compared with that of the PFS model without IAUC. Despite the limitation of IAUC regarding the lack of a clear biologic association, IAUC values are correlated with $K_{trans}$ and rCBV. However, we hypothesized that IAUC would be useful for prognosis prediction because it reflects both perfusion and permeability, which are complementarily associated with prognosis. Although previous studies have reported that model-free parameters may be useful for differentiation of radiation necrosis and tumor, the prognostic value of IAUC in GBM remains unclear. Moreover, to establish the practical role of an imaging biomarker, one must elucidate whether that imaging biomarker has prognostic value after other prognostic factors are considered in the usual clinical settings. We found that IAUC parameters have prognostic value even after clinical factors and conventional MR imaging findings are considered in the unmethylated MGMT group. Therefore, IAUC represents a useful imaging biomarker that has practicality and high reproducibility. Nevertheless, considering that IAUC$_{60\text{mean}}$ did not achieve the same improvement in PFS prediction as IAUC$_{30\text{mean}}$, the optimal time point of IAUC needs to be determined in future investigations.

The association between high IAUC values and poor prognosis in the unmethylated group is consistent with findings in previous studies, which have reported the association between high rCBV and $K_{trans}$ values and poor prognosis. However, in our study, the IAUC values were not prognostic when applied to the methylated MGMT group or the entire GBM cohort, and IAUC$_{60\text{mean}}$ did not achieve the same improvement in PFS prediction as IAUC$_{30\text{mean}}$. The optimal time point of IAUC needs to be determined in future investigations.

In this study, we found that higher IAUC values were predictors of poor OS and PFS in the unmethylated MGMT group and that IAUC parameters improved prognosis prediction of the unmethylated MGMT group, when added to other prognostic factors. Furthermore, IAUC values were paradoxically higher in the methylated MGMT group than in the unmethylated group.

$rCBV$ and $K_{trans}$ values are indicators of tumor perfusion and permeability, respectively, and high values are predictors of worse prognosis. However, the variability of rCBV ranges from 24% to 67%, depending on the normalization method or software used for postprocessing. Similarly, $K_{trans}$ can vary according to the model selection, arterial input function, software, and prebolus T1 measurement. In contrast, IAUC is a model-free parameter that does not depend on model selection and arterial input function and is highly reproducible. Whether model-free parameters show high reproducibility and performance, compared with model-based parameters, was debated recently.

**FIG 4.** Kaplan-Meier curves depicting survival classification after random survival forest ranking of prognostic factors in glioblastomas with unmethylated MGMT promoter status ($n = 5$). Representative trees with IAUC$_{30\text{mean}}$ (A) and IAUC$_{60\text{mean}}$ (B) for OS caused the volume of enhancing tumor to be the primary split and then the extent of resection to split the subgroup with high IAUC$_{30\text{mean}}$. Subsequently (log-rank test, $P < .001$). C, A representative tree with IAUC$_{30\text{mean}}$ for PFS caused the IAUC$_{30\text{mean}}$ to be the primary split and then the extent of resection to split the subgroup with high IAUC$_{30\text{mean}}$. Subsequently (log-rank test, $P < .002$).

**DISCUSSION**

In this study, we found that higher IAUC values were predictors of poor OS and PFS in the unmethylated MGMT group and that IAUC parameters improved prognosis prediction of the unmethylated MGMT group, when added to other prognostic factors. Furthermore, IAUC values were paradoxically higher in the methylated MGMT group than in the unmethylated group.
higher in GBM cases with unmethylated MGMT than in those with methylated MGMT. In contrast, another study reported that \( K^{trans} \) values were higher in GBMs with methylated MGMT, a finding discordant with the previously reported association between high \( K^{trans} \) values and poor prognosis, and the authors hypothesized that high permeability of the methylated MGMT group allowed better penetration of temozolomide, yielding better response and prognosis.

Although the underlying mechanism is unclear, our results may reflect IAUC values being more affected by permeability difference than perfusion difference between the methylated and unmethylated MGMT groups. Subsequently, a combination of these paradoxically high IAUC values of the methylated MGMT group and the effect of methylated MGMT as a good prognostic factor might have counteracted the association between high IAUC values and poor prognosis. This possibility is 1 explanation for our result that the IAUC values were not prognostic in the methylated MGMT group or the entire cohort. Similarly, a previous study reported that low \( K^{trans} \) values were associated with poor prognosis in GBM, which is contradictory to the results of other studies on the association between high \( K^{trans} \) values and poor prognosis. These conflicting results might be attributable to the complicated relationship among tumor permeability, MGMT status, and prognosis, as observed in our study. Future investigation with a larger cohort is necessary to analyze the relationship among tumor permeability, MGMT status, and prognosis. Given that the IAUC values have prognostic value only in the unmethylated MGMT group, the MGMT status should be known before IAUC may be considered a useful imaging biomarker. However, because the MGMT status is clinically available in most patients with GBM, in our opinion, this requirement does not mitigate the practicality of IAUC.

This study has several limitations, apart from its retrospective design. First, the IAUC parameters were not directly compared with rCBV and \( K^{trans} \). Thus, the superiority of IAUC regarding its model-free parameter may have limited reproducibility. However, because the MGMT status is clinically available in most patients with GBM, in our opinion, this requirement does not mitigate the practicality of IAUC.

**CONCLUSIONS**

Our study demonstrated that IAUC could be a useful prognostic imaging biomarker in patients with GBM with known MGMT status, improving the prognosis prediction of GBM with unmethylated MGMT promoter status. We propose that this complementary role of IAUC and MGMT status should be considered in future investigations.

**REFERENCES**

Retrospective Validation of a Computer-Assisted Quantification Model of Intracerebral Hemorrhage Volume on Accuracy, Precision, and Acquisition Time, Compared with Standard ABC/2 Manual Volume Calculation


ABSTRACT

BACKGROUND AND PURPOSE: Intracerebral hemorrhage accounts for 6.5%–19.6% of all acute strokes. Initial intracerebral hemorrhage volume and expansion are both independent predictors of clinical outcomes and mortality. Therefore, a rapid, unbiased, and precise measurement of intracerebral hemorrhage volume is a key component of clinical management. The most commonly used method, ABC/2, results in overestimation. We developed an interactive segmentation program, SegTool, using a novel graphic processing unit, level set algorithm. Until now, the speed, bias, and precision of SegTool had not been validated.

MATERIALS AND METHODS: In a single stroke academic center, 2 vascular neurologists and 2 neuroradiologists independently performed a test-retest experiment that involved repeat measurements of static, unchanging intracerebral hemorrhage volumes on CT from 76 intracerebral hemorrhage cases. Measurements were made with SegTool and ABC/2. True intracerebral hemorrhage volumes were estimated from a consensus of repeat manual tracings by 2 operators. These data allowed us to estimate measurement bias, precision, and speed.

RESULTS: The measurements with SegTool were not significantly different from the true intracerebral hemorrhage volumes, while ABC/2 overestimated volume by 45%. The interrater measurement variability with SegTool was 50% less than that with ABC/2. The average measurement times for ABC/2 and SegTool were 35.7 and 44.6 seconds, respectively.

CONCLUSIONS: SegTool appears to have attributes superior to ABC/2 in terms of accuracy and interrater reliability with a 9-second delay in measurement time (on average); hence, it could be useful in clinical trials and practice.

ABBREVIATIONS: ICH = intracerebral hemorrhage; LS = level set; MDC = 95% minimum detectable change

Mortality from intracerebral hemorrhage (ICH) is between 31% and 34% at 7 days and 53% and 59% at 1 year.1 Initial ICH volume and rate of growth are independent predictors of clinical outcome and mortality.2 Attenuation of growth is an important treatment strategy.2 Consequently, a rapid, unbiased, and precise measurement of ICH volume is an important component of clinical management.

CT is sensitive for identifying ICH and is commonly used for clinical management.3 The most common method to measure ICH volume is the simplified ellipsoid formula (ABC/2),4 “where A is the greatest hemorrhage diameter by CT, B is the diameter 90° to A, and C is the approximate number of CT sections with hemorrhage multiplied by the section thickness.”5 Use of this formula often results in large volume-estimation errors, particularly for large or irregularly shaped objects.4,6

There is particular interest in semiautomatic computer models that can offer fast, low-bias, and precise lesion volume measurements.7 Among computer-based models, level set (LS) algorithms8 have become widely used to determine lesion, organ, and bone volumes in recent years.9-11 LS algorithms grow a “seed” placed within the ROI. Several parameters, including the rate of growth and curvature of the segmented surface, are controlled by local image properties and can also be adjusted by the reader.12 LS algorithms are robust and flexible and prevent growth of the seed across weak, incidental connections into areas outside the lesion.13

For example, Cates et al14 demonstrated, in a study of 9 me-
ningioma or low-grade glioma MR images, that LS volume measurements produce results that are similar to those from hand tracings. Colliot et al\textsuperscript{15} found that measurement bias was low when they used LSs to measure cortical dysplasia lesions on MR imaging in 18 patients. Similarly, Saba et al\textsuperscript{16} obtained a low bias with LSs to measure carotid artery wall thickness on MR images of 10 patients; the LS volumes were compared with volumes calculated with manual tracings in both studies.

However, LS algorithms require an enormous number of computations and long execution times on central processing units. To address this issue, we previously developed a novel LS algorithm that leverages the massive parallelism of commodity graphic processing units.\textsuperscript{13} This algorithm is 14 times faster than the fastest previously reported parallel algorithm and hundreds of times faster than serial algorithms on current central processing units. The algorithm had low bias and variability when segmenting tissues in a realistic brain phantom, an anatomically accurate 3D simulation of the human brain.\textsuperscript{13} Dang et al\textsuperscript{17} reported that its speed, bias, and precision in measuring meningioma volume were superior to the modified McDonald criteria and manual outlining on 25 contrast-enhanced MR imaging examinations. To our knowledge, the speed, bias, and precision of LS algorithms have not been previously tested with a large sample size of ICH and multiple clinician readers, the objective of this study.

In summary, growth in ICH volume is often used to inform treatment decisions in clinical practice. For example, Dowlatshahi et al\textsuperscript{18} reported that hematoma expansion of 33% or 12.5 mL was highly predictive of poor outcome. As described above, the ABC/2 method can be used to estimate hematoma volume. However, it has poor accuracy, which limits its clinical utility. Manual outlining by an expert can provide accurate volume measurements. However, the associated time penalty limits its clinical utility. Thus, there is an unmet clinical need for simple, rapid, and accurate measurement of ICH volume. Characterizing, validating, and integrating such a tool into clinical workflows would allow clinicians to provide more precise and personalized care.

\section*{MATERIALS AND METHODS}
After institutional review board approval, images for this study were obtained from an existing data base of hemorrhagic stroke cases presenting to Mayo Clinic Hospital in Arizona between January 2007 and January 2013. Seventy-six consecutive cases with CT imaging available showing intraparenchymal hematomas were selected. Exclusion criteria included extraparenchymal hemorrhage and/or intraventricular hematoma. Six cases were randomly withheld from the experimental dataset and used for training purposes.

Four operators, 2 neuroradiologists and 2 vascular neurologists, collected measurements in this study. ABC/2 measurements were acquired with OsiriX Imaging Software (http://www.osirix-viewer.com). LS measurements were acquired with SegTool, a custom-developed in-house program that runs on Windows 7 (Microsoft, Redmond, Washington) computers equipped with graphic processing units (CUDA; Nvidia, San Jose, California). During the measurements, SegTool ran on a stand-alone computer and was not integrated into the PACS workflow. All the operators had experience with the ABC/2 method but no prior knowledge of SegTool. The 70 evaluation cases were each measured twice by 4 operators using both methods, for a total of 1120 measurements (70 cases \times 4 operators \times 2 methods \times 2 repeats). One of the neuroradiologists and one of the neuroradiologists also manually outlined lesions with OsiriX (70 cases \times 2 operators \times 2 repeats) to estimate true lesion volumes (described below).

Repeat measurements of all cases in random order occurred after a minimum 2-week delay to limit learning effects. To minimize the bias from the results of SegTool, we conducted the measurements in the following order: Manual tracings were performed first, followed by ABC/2, and finally SegTool. An additional SegTool correction process was introduced after initial data analysis. Figure 1A reviews the workflow for both the ABC/2 and SegTool measurement processes.

\section*{ABC/2 Method}
The operator identified the axial sections with the largest lesion extent and then measured the 2 longest orthogonal diameters of the lesion with the OsiriX ROI Length Tool (Fig 1B). The lesion volume was estimated as

\begin{equation}
\text{Lesion Volume} = A \times B \times C / 2,
\end{equation}

where $A$ and $B$ are the length of the 2 diameters and $C$ is section thickness multiplied by the number of sections where the lesion was visible.

\section*{Level Set Method}
The operator drew $\geq 1$ green stroke in the ICH and $\geq 1$ red stroke in the surrounding tissue that they did not want to include (surrounding brain parenchyma in our experiments). Strokes were placed on 2D axial sections (Figs 1C and 2A). The operator then clicked a “Play” button to initiate object growth. Growth occurred in real-time and could be visualized in 2 or 3 dimensions interactively (Fig 2B, D). The algorithm naturally handles the simultaneous growth, merging, and separation of multiple distinctly seeded regions.

The surface propagation was guided by a K-nearest neighbor statistical model of the intensity values provided by the seed points and a curvature parameter between 0 and 1 that determined the surface stiffness. In all cases, the curvature parameter was initialized to 0.25. During or following region growth, the operator could adjust a slider to manipulate the curvature parameter. Higher values encouraged smoother, smaller volumes. Lower values encouraged larger, more irregular volumes. The effects of changes in the curvature parameter on the segmented volume occurred and were displayed in real-time.

The user had the ability to then review the segmentation in 2D or 3D by rotating the CT scan volume (Fig 2D). After the user accepted the results, SegTool calculated and recorded the ICH volume, measurement time, and binary mask (segmentation) of the ICH.

A common issue in LS segmentation is “leakage.” Artificial connections between blood and bone (both bright on CT) can be caused by partial volume effects between hemorrhage and skull (due, in part, to the large section thickness of clinical image examinations). These can be corrected by either increasing the LS surface stiffness (causing the leak to retract back into the segmented region) or removing the leaked regions with editing tools.

An informal review of the SegTool volume measurements was
Performing a review of all ICHs, step by step, it was found that several had a single volume measurement that was more than double the median volume. Closer inspection of these saved segmented regions revealed that large leaks had occurred (Fig 3).

It was then discovered that the default transparency level of the segmented region was such that operators found it difficult to detect leaks into bone (Fig 3A). Consequently, all operators performed a review of their SegTool 3D measurements with the suggested workflow that reduced the transparency of the green region until it was opaque (Fig 3B). Readers were permitted to correct any segmentation by either editing or starting over. Readers recorded and compared both the initial and “after review” SegTool measurements using ABC/2.

**True ICH Volume Estimation**

The true ICH volume was estimated from manual tracings. One neurologist and 1 neuroradiologist operator each independently manually traced the lesion on each axial section in which it was apparent with the ROI Pencil Tool of OsiriX (Fig 1D). OsiriX was used to calculate the area in each section, and the lesion volume was calculated as

\[
\text{Lesion Volume} = \text{Section Thickness} \times \text{Summation of Lesion Areas of All Sections.}
\]
Statistical Analysis

We used methodology recommended by the Quantitative Imaging Biomarker Alliance\(^\text{19}\) to assess the uncertainty in volume measurement. In particular, we used a disaggregate approach to express uncertainty in terms of bias and precision. They defined "bias" as "the difference between the average (expected value) of measurements made on the same object and its true value." They defined "precision" as "the closeness of agreement between measured quantity values obtained by replicate measurements on the same or similar experimental units under specified conditions."

Precision is related to the variability in volume measurement. There are several ways it can be described numerically. Here, we chose to express precision as a clinically relevant threshold: the 95% minimum detectable change (MDC).\(^\text{19}\) Magnitude changes in volume \(\leq\) MDC can be explained by variability in the measurement process alone with 95% confidence. Therefore, magnitude changes in volume > MDC can be ascribed to lesion growth (or shrinkage) with a type II error rate of 5%.

We used a 2-way random-effects analysis of variance as previously described\(^\text{20,21}\) to estimate between- and within-operator variability for both measurement methods. These values were then used to calculate the between- and within-operator MDC for each method. The measurement bias of each method was determined by comparing the mean measured ICH volume with the estimated true ICH volume. The measurement time of ABC/2 was determined by timing the readers as they measured the volumes. The measurement time of SegTool in seconds was recorded directly by the program.

RESULTS

Summary statistics for our experiments are presented in the Table. ABC/2 produced larger volume estimates than SegTool. SegTool measurements, after review, were smaller, on average, than the initial SegTool measurements. Operators modified 140 (of 560) SegTool measurements during the review process.

![Image](image_url)

**FIG 3.** The level set algorithm may leak. An axial (A) and 3D view (B) of 1 segmented ICH lesion (enclosed in a red ellipse) along with level set leakage outside the lesion. Leakage was caused by partial volume effects between hemorrhage and skull (due, in part, to the large section thickness of the clinical imaging examinations). This can be corrected by either increasing the level set surface stiffness or removing the leaked regions with editing tools. However, when the transparency of the segmented (green) region was high (as it was by default), operators found it difficult to detect leaks. Consequently, we asked all operators to perform a blinded review of their level set segmentations. They performed this by interactively reducing the transparency of the green region until it was opaque and then viewing their segmentation in 3D (B). If, for any reason, they were not satisfied with the labeled region, they were asked to re-segment the lesion. In the text, we describe several enhancements to the tool that could be made to help operators detect leaks before saving the final segmented region.

Each true volume was estimated from 4 manual tracings by the 2 operators. Any voxel selected in at least 3 of the 4 manual tracings was labeled a "true" lesion voxel and was used to estimate the true lesion volume.

**DISCUSSION**

True lesion volumes are required to determine bias. These are often unknown in clinical experiments. A compromise is to estimate the true volume of each lesion with a consensus of expert segmentations in medical images. In our experiments, we assumed that true ICH voxels were those that were selected in at least 3 out of 4 manual outlinings by experts (2 experts \(\times\) 2 repeated measurements each). Other schemes are also possible.\(^\text{19}\) Several studies have reported that baseline ICH volume is highly predictive of 30-day morbidity and mortality.\(^\text{22,23}\) It is also well-acknowledged that ABC/2 tends to overestimate lesion volumes.\(^\text{24,25}\) In our study, ABC/2 overestimated ICH volume by 45%, on average. While the mean SegTool measurements were

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**Summary statistics for our experiments**

<table>
<thead>
<tr>
<th></th>
<th>ABC/2 (Initial)</th>
<th>SegTool (Initial)</th>
<th>SegTool (after Review)</th>
<th>SegTool (Revisions)</th>
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<tr>
<td>No.</td>
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<td>Mean (SD)</td>
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<td>27.47</td>
<td>0.40</td>
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</tbody>
</table>

* All values are in milliliters, except No. that is dimensionless. The values in the SegTool (revisions) column indicate the change after operators reviewed their initial measurements. Negative values mean that the after-review value was smaller than the initial value.
not significantly different from the estimated true ICH volumes, the low measurement bias of SegTool could be important for future clinical trials that rely on baseline ICH volume for patient stratification.

There was no significant difference in the within-operator MDC between ABC/2 and SegTool (after review to check for leaks). However, SegTool had between-operator MDC that was approximately 50% lower (better) than ABC/2. This is important because in many clinical scenarios, it is difficult to ensure that a single individual performs all volume measurements.

A recent study by Dowlatshahi et al. reported that hematoma expansion of 33% or 12.5 mL was highly predictive of poor outcome. The between-operator MDC of ABC/2 in our study was 13.94 mL. Consequently, an expansion of 12.5 mL measured this way can be explained by measurement variability alone (with 95% confidence) and may not correspond to true hematoma growth. SegTool, on the other hand, had a between-operator MDC of 9.51 mL. An expansion of 12.5 mL measured this way is too large to be explained by measurement variability alone. Consequently, it may be ascribed to ICH growth.

A number of previous studies have compared ABC/2 with computer-assisted method for measuring ICH volume. For example, Divani et al. compared ABC/2 with planimetric measurements made with Medical Image Processing, Analysis, and Visualization (National Institutes of Health, Bethesda, Maryland) and with computer-assisted segmentation with Analyze software (AnalyzeDirect, Overland Park, Kansas) and Voxar 3D (Barco NV, Kortrijk, Belgium). Their study focused on determining measurement bias. Measurements were made from a silicone phantom and from simulated lesions implanted in cadaver brains. A variety of CT protocols were used. They found that ABC/2 produced large overestimations of lesion volume. They did not report measurement precision or time.

Freeman et al. compared ABC/2 with Analyze in a series of 8

![Graph showing measurement bias, precision, and time for ICH volume measurement.](image)

**FIG 4.** The bias (A), precision (B), and time (C) for ICH volume measurement. Measurements made using the ABC/2 method are shown in red. Those made using SegTool are shown purple (initial) or blue (after review). A, Bias: the dashed (purple) line indicates perfect agreement between measured and true volumes. Each true volume was determined from 4 manual tracings placed by experts (details in the text). The solid markers indicate the mean measured volume determined from 8 measurements (4 operators × 2 measurements/operator). The error bars indicate the 95% confidence interval for the mean measured volume. The solid lines show a linear regression fit through all measurements for each method. The shaded zone around each solid line indicates the 95% confidence interval for the slope of the line. Each line is labeled with its equation, the $R^2$ value from the linear regression, and the coefficient of determination describing goodness of fit ($1.0$ equals a perfect fit). B, Precision: lower values are better. Changes in ICH volume less than the indicated value can be explained by measurement variability alone, with 95% confidence. The values in the “Between Operator” group are all statistically significantly different ($P < 0.02$). The “SegTool (initial)” value in the “Within Operators” group is significantly different than the other values ($P < 0.001$), which are not significantly different from each other ($P = 0.8$). C, Time: each bar indicates the mean value from 560 measurements (70 ICH lesions × 4 operators × 2 repeated measurements). The SegTool time is based on the initial measurements. The error bars indicate the standard error of the mean. On average, SegTool required an extra 8.9 seconds to measure ICH volume. This difference is statistically significantly different from 0 ($P < 0.0001$).
patients with ICH treated with warfarin. They used the Analyze measurements to estimate true lesion volumes. These were then used to estimate the measurement bias of ABC/2. They concluded that ABC/2 has a small measurement bias for small lesions but can produce large errors (both over- and underestimation of true volume) for large or complex lesions. They did not exhaustively examine measurement time but reported that the most accurate method of measuring lesion volume with Analyze required 20–30 minutes per study, after a steep learning curve. They did not report measurement precision.

Xu et al.24 compared ABC/2 with computer-assisted measurements made with an intensity-threshold algorithm in 3D Slicer (http://www.slicer.org) in 294 CT examinations. Two physicians each made a single measurement of each lesion with each method. They used the Slicer measurements to estimate true lesion volumes. These were then used to estimate the measurement bias of ABC/2. They also divided the lesions into groups based on size and shape and compared the 2 measurement methods between groups. They concluded that ABC/2 overestimated lesion volumes and that these errors increased with lesion volume and more complex shape. They reported that the average time required to measure lesion volume with 3D Slicer was 96 seconds. They did not report measurement precision or ABC/2 measurement times.

Kosior et al.7 compared ABC/2 with computer-assisted measurements made using custom-developed software (Quantomo) that used an intensity-threshold algorithm available as part of the Insight Segmentation and Registration Toolkit (National Institutes of Health, Bethesda, Maryland). The study of Kosior et al was focused on evaluating measurement precision. As in our study, they used a test-retest experiment and a 2-way random-effects ANOVA to determine the MDC for each method. They also had 4 operators each perform 2 repeat measures using each measurement method. They reported the within-operator MDCs for ABC/2 and Quantomo as 15.7 and 5.3 mL, respectively (versus our values of 7.47 and 7.37 mL for ABC/2 and SegTool [after review], respectively). Their reported between-operator MDCs for ABC/2 and Quantomo were 37.0 and 8.1 mL, respectively (versus our results of 13.94 and 9.51 mL, respectively). There were several differences between their methods and ours. These include the following: 5 days between repeated measures (versus 2 weeks in our study) and measurement of 30 CT scans (versus 70 in our study). It is also likely that their CT protocol was more consistent among patients than ours because their patients were recruited from a clinical trial, whereas ours were recruited from our general patient population during several years. Finally, they did not report measurement bias or times.

One of the weaknesses of our study was the need to have operators review their initial SegTool measurements. This review was performed in a blinded fashion—operators were not provided with any information on which studies may have had leaks. They were free to redo or edit any, all, or none of their prior measurements. In total, 140 of the initial 560 segmentations were revised. The median result was to reduce the lesion volume by 0.01 mL. The mean effect was to reduce lesion volume by 2.2 mL. The impact on measurement precision was to reduce between-operator MDC from 11.93 to 9.51 mL and to reduce the within-operator MDC from 9.93 to 7.37 mL.

We could make several modifications to SegTool to increase the visibility of LS leaks and/or reduce their likelihood. By default, the segmented region was highly translucent. This made LS growth into brightly saturated bone very difficult to see. Simply increasing the default opacity of the segmented region would address this limitation. We could also preprocess the image volumes to strip skulls. Several open-source algorithms are available to perform this task; however, this would cause delays in interpretation.

CONCLUSIONS

SegTool measurements took 9 seconds longer to complete on average. However, the SegTool measurements were not significantly different from the true ICH volumes, while ABC/2 overestimated ICH volume by 45%. The between-operator measurement variability with SegTool was 50% less than that with ABC/2. SegTool was capable of detecting clinically important differences in ICH volume, whereas the ABC/2 was not. Consequently, SegTool could be useful in clinical trials and clinical practice when intervention and prognostication rely on accurate baseline ICH volume or detecting changes in serial ICH volumetric measurements.

References: Bart M. Demaerschalk—UNRELATED: Other: Co-Editor-in-Chief of Neurologist.

REFERENCES


Transcranial Duplex Sonography Predicts Outcome following an Intracerebral Hemorrhage


ABSTRACT

BACKGROUND AND PURPOSE: Several radiologic features such as hematoma volume are related to poor outcome following an intracerebral hemorrhage and can be measured with transcranial duplex sonography. We sought to determine the prognostic value of transcranial duplex sonography in patients with intracerebral hemorrhage.

MATERIALS AND METHODS: We conducted a prospective study of patients diagnosed with spontaneous intracerebral hemorrhage. Transcranial duplex sonography examinations were performed within 2 hours of baseline CT, and we recorded the following variables: hematoma volume, midline shift, third ventricle and lateral ventricle diameters, and the pulsatility index in both MCAs. We correlated these data with the CT scans and assessed the prognostic value of the transcranial duplex sonography measurements. We assessed early neurologic deterioration during hospitalization and mortality at 1-month follow-up.

RESULTS: We included 35 patients with a mean age of 72.2 ± 12.8 years. Median baseline hematoma volume was 9.85 mL (interquartile range, 2.74–68.29 mL). We found good agreement and excellent correlation between transcranial duplex sonography and CT when measuring hematoma volume ($r = 0.791; P < .001$) and midline shift ($r = 0.827; P < .001$). The logistic regression analysis with transcranial duplex sonography measurements showed that hematoma volume was an independent predictor of early neurologic deterioration (OR, 1.078; 95% CI, 1.023–1.135) and mortality (OR, 1.089; 95% CI, 1.020–1.160). A second regression analysis with CT variables also demonstrated that hematoma volume was associated with early neurologic deterioration and mortality. When we compared the rating operation curves of both models, their predictive power was similar.

CONCLUSIONS: Transcranial duplex sonography showed an excellent correlation with CT in assessing hematoma volume and midline shift in patients with intracerebral hemorrhage. Hematoma volume measured with transcranial duplex sonography was an independent predictor of poor outcome.

ABBREVIATIONS: END = early neurologic deterioration; HV = hematoma volume; ICH = intracerebral hemorrhage; IQR = interquartile range; LV = lateral ventricle; MLS = midline shift; IIIV = third ventricle; TDS = transcranial duplex sonography

Spontaneous intracerebral hemorrhage (ICH) is a major cause of morbidity and mortality, with half of the events related to case fatality occurring within the first 48 hours. Thus, identifying variables that contribute to early neurologic deterioration (END) and mortality is of enormous importance. An early estimation of the prognosis is crucial for deciding on a treatment plan. Several neuroimaging prognostic factors include hematoma volume (HV), hematoma enlargement, midline shift (MLS), and intraventricular hemorrhage, and CT is the technique most frequently used to assess them. However, in the early stages, it can be difficult to monitor these radiologic features with repeat CT due to the clinical and/or hemodynamic state of the patient and the risk of radiation overexposure.

Transcranial duplex sonography (TDS) is a noninvasive technique that provides simultaneous 2D imaging of brain parenchyma and hemodynamic information from the main cerebral arteries. The role of TDS is well-established in the assessment of ischemic stroke, but its usefulness in acute ICH has been reported in only a few studies.

Visualization of acute ICH with TDS is feasible: The ICH can be identified as a hyperechoic mass. Additionally, TDS allows...
We conducted a prospective observational study of consecutive adult patients admitted to our center with the diagnosis of spontaneous ICH during a 1-year period (2012–2013). Patients were included when the time from the onset of symptoms to admission CT was <24 hours and the TDS examination was performed within 2 hours of baseline CT. We excluded patients with primary intraventricular hemorrhage, infratentorial ICH, and secondary ICH related to fibrinolysis, trauma, central venous thrombosis, arteriovenous malformations, or aneurysms. During hospitalization, patients received treatment in accordance with the guidelines of the Spanish Society of Neurology. All patients or their representatives gave written consent to participate in the study.

The following clinical data were collected from all patients at admission: 1) demographics (age and sex); 2) relevant medical history, including hypertension, diabetes, hypercholesterolemia, stroke, coronary artery disease, liver disease, and alcohol abuse; 3) previous treatments; 4) time from the onset of symptoms to admission; 5) admission blood pressure and blood glucose level; 6) NIHSS score and Glasgow Coma Scale score; and 7) results of blood tests including hematocrit level, hemoglobin level, white cell count, platelet count, electrolytes, glomerular filtration rate, liver function, and a basic hemostatic study (international normalized ratio and activated partial thromboplastin time).

**Neurosonographic Methods**

A single experienced examiner (P.C.-R.) was trained in a Neurosonology Laboratory by R.D.-M. and J.M.-F. for 6 months before study initiation and was certified in Neurosonology by the Spanish Society of Neurology. The TDS examinations were performed with a CX50 Ultrasound (Philips Healthcare, Best, the Netherlands) with a sectorial probe with a 2- to 5-MHz range. For the explorations, the probe was set up at 5 MHz and placed on the contralateral temporal bone window with a penetration depth of 14–16 cm. The transducer was skewed approximately $10^\circ$ upward to visualize the contralateral skull bone, and from there, insonation planes were adapted according to the hematoma location. Image brightness, contrast, and time-gain compensation were adjusted to get the best image. ICH was identified as a hyperechoic mass. The examiner was blinded to the CT findings, and he or she was informed only of the side of the ICH (left or right).

**RESULTS**

During the study period, we screened 59 patients: Five were excluded due to the absence of a temporal bone window, 2 died...
before the TDS examination could be performed, 15 were excluded because the TDS examination was not available within 2 hours of the baseline CT or the patient underwent surgical evacuation before TDS could be performed, and eventually 2 patients were excluded because the ICH was not identified despite presentation of a reasonable temporal bone window. We finally included 35 patients with a mean age of 72.2 ± 12.8 years; 23 (65.7%) were men. In 25 (71.4%) patients, the time from the onset of symptoms to baseline CT was <6 hours. Clinical and radiologic characteristics of the patients are detailed in Table 1. The median baseline NIHSS score was 11 (interquartile range [IQR], 3.5–19), and prior antithrombotic therapy was observed in 10 (28.6%) patients: Six (17.1%) were receiving aspirin and 4 (11.4%) were taking warfarin before admission.

There were 16 (45.7%) lobar (6 frontal, 6 parietal, 2 temporal, and 2 occipital) and 19 (54.3%) deep ICHs. The median HV was 9.85 mL (IQR, 2.74–68.29 mL) assessed with CT and 14.46 mL (IQR, 4.96–39.42 mL) as determined by TDS. As described in the “Materials and Methods,” all patients underwent a TDS examination within 2 hours of the baseline CT. We found an excellent correlation between the baseline TDS examination and the CT when measuring the HV (r = 0.791, P < .001) and, separately, the longitudinal (r = 0.711, P < .001), axial (r = 0.768, P < .001), and coronal diameters (r = 0.754, P < .001) (Fig 2). We repeated the same analysis dividing the population by ICH location, and the correlation remained excellent in both groups (r = 0.792, P < .001 for the lobar ICH and r = 0.805, P < .001 for the deep ICH).

### Table 1: Clinical and radiologic characteristics of the patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men [No.] (%)</td>
<td>23 (65.7)</td>
</tr>
<tr>
<td>Age (mean) [SD] (yr)</td>
<td>72.2 (12.8)</td>
</tr>
<tr>
<td>Hypertension [No.] (%)</td>
<td>17 (48.6)</td>
</tr>
<tr>
<td>Diabetes mellitus [No.] (%)</td>
<td>5 (14.3)</td>
</tr>
<tr>
<td>Dyslipidemia [No.] (%)</td>
<td>10 (28.6)</td>
</tr>
<tr>
<td>Previous ischemic stroke [No.] (%)</td>
<td>4 (11.4)</td>
</tr>
<tr>
<td>Previous ICH [No.] (%)</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Coronary artery disease [No.] (%)</td>
<td>3 (8.6)</td>
</tr>
<tr>
<td>Atrial fibrillation [No.] (%)</td>
<td>4 (11.4)</td>
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<tr>
<td>Glomerular filtration rate &lt;30 mL/min [No.] (%)</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Alcohol abuse (&gt;80 g/day) [No.] (%)</td>
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</tr>
<tr>
<td>Smoking [No.] (%)</td>
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<tr>
<td>Liver disease [No.] (%)</td>
<td>1 (2.9)</td>
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<tr>
<td>Prior antiplatelet therapy [No.] (%)</td>
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<tr>
<td>Previous use of oral anticoagulants [No.] (%)</td>
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<tr>
<td>Previous use of atorvastatin [No.] (%)</td>
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<tr>
<td>NIHSS score at admission (median) (IQR)</td>
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<tr>
<td>GCS at admission (median) (IQR)</td>
<td>15 (13–15)</td>
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<tr>
<td>Systolic blood pressure [mean] (SD) (mm Hg)</td>
<td>1681 (52.8)</td>
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<tr>
<td>Blood glucose level [mean] (SD) (mg/dL)</td>
<td>137.8 (47.5)</td>
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<tr>
<td>Platelet count/mm³ [mean] (SD)</td>
<td>220,469 (75,971)</td>
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<tr>
<td>Lobar ICH [No.] (%)</td>
<td>16 (45.7)</td>
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<tr>
<td>IVH [No.] (%)</td>
<td>10 (28.6)</td>
</tr>
<tr>
<td>HV [mL] (median) (IQR)</td>
<td>9.85 (2.74–68.29)</td>
</tr>
</tbody>
</table>

Note: —GCS indicates Glasgow Coma Scale; IVH, intraventricular hemorrhage.
We also observed an excellent correlation when analyzing the IIIV diameter ($r = 0.678, P < .001$) and the MLS ($r = 0.827, P < .001$). Conversely, CT and TDS showed no correlation when measuring the LV diameter ($r = 0.196, P = .327$).

For further comparison between techniques, we conducted a 1-sample $t$ test contrast of the difference between the measurements obtained by CT and TDS. There were no significant differences when contrasting HV measurements (mean difference $= -0.077; P = .624$) and MLS (mean difference $= 0.086; P = .134$). Conversely, despite showing a good correlation, the 2 techniques presented significant differences when measuring IIIV diameter (mean difference $= 0.132; P = .001$). We also constructed Bland-Altman plots with the HV and the MLS measurements (Fig 3). Most interesting, despite finding good agreement between techniques, we detected a systematic bias between both techniques when measuring HV: TDS tended to overestimate the volumes of smaller ICHs and, conversely, to underestimate volumes in larger ICHs.

During hospitalization, 9 (25.7%) patients presented with END during the first 3 days. Table 2 provides details of the patients presenting with and without END. Remarkably, prior antiplatelet therapy ($P = .017$) was more frequently reported in patients presenting with END. Additionally, baseline HV measured with CT ($P = .002$), baseline HV measured with TDS ($P = .001$), baseline MLS assessed with CT ($P = .018$), and baseline MLS calculated with TDS ($P = .007$) showed an association with the probability of END. In the first logistic regression analysis with CT variables, only baseline HV showed an independent associa-
with TDS (baseline HV measured with CT (P = 0.001), baseline HV measured with TDS (P < .001), baseline MLS assessed with CT (P = .001), and baseline MLS calculated with TDS (P = .001) showed an association with the risk of mortality. In addition, the pulsatility index from the ipsilateral MCA also showed an association with mortality risk (P = .033). Finally, lobar localization (P = .018), baseline NIHSS scores (P < .001), and Glasgow Coma Scale scores (P = .007) were variables also found to be related to the risk of mortality. In the first logistic regression model with CT variables, only baseline HV showed an independent association with mortality (OR, 1.064; 95% CI, 1.017–1.112). Most interesting, in the logistic regression model with the TDS variables, we once again found that baseline HV (OR, 1.089; 95% CI, 1.020–1.160) was the only variable included in the final model. The receiver operating characteristic curves of both models showed that the best threshold to predict mortality at 1-month follow-up was an HV of 47.62 mL as assessed with CT (85.7% sensitivity and 85.7% specificity) and an HV of 30.63 mL as measured with TDS (88.9% sensitivity and 80% specificity). When we compared the receiver operating characteristic curves of both models, the predictive power was similar between them, and no significant differences were observed when contrasting the 2 areas under the curve (On-line Fig 2).

At the 1-month follow-up, 7 (20%) patients had died. Variables associated with mortality are shown in Table 3. Remarkably, baseline HV measured with CT (P < .001), baseline HV measured with TDS (P < .001), baseline MLS assessed with CT (P = .001), and baseline MLS calculated with TDS (P = .001) showed an association with the risk of mortality. In addition, the pulsatility index from the ipsilateral MCA also showed an association with mortality risk (P = .033). Finally, lobar localization (P = .018), baseline NIHSS scores (P < .001), and Glasgow Coma Scale scores (P = .007) were variables also found to be related to the risk of mortality. In the first logistic regression model with CT variables, only baseline HV showed an independent association with mortality (OR, 1.064; 95% CI, 1.017–1.112). Most interesting, in the logistic regression model with the TDS variables, we once again found that baseline HV (OR, 1.089; 95% CI, 1.020–1.160) was the only variable included in the final model. The receiver operating characteristic curves of both models showed that the best threshold to predict mortality at 1-month follow-up was an HV of 47.62 mL as assessed with CT (85.7% sensitivity and 85.7% specificity) and an HV of 30.63 mL as measured with TDS (88.9% sensitivity and 80% specificity). Again, as shown in On-line Fig 2, the predictive power of both models was similar, and no significant differences were observed when contrasting both areas under the curve.
DISCUSSION
We aimed to determine the prognostic value of TDS in a prospective cohort of patients presenting with spontaneous ICH. Our study confirms previously reported data concerning the strong correlation between TDS and CT and adds new information regarding the prognostic value of this technique in patients with ICH.

ICH is a devastating condition, and several radiologic features may predict poor outcome. Currently, the widespread availability of CT allows a rapid and reliable assessment of these variables. However, ICH is a dynamic process, and it can be difficult to monitor complications with repeat CT scans due to the clinical status of the patient. This issue led to interest in TDS, which may represent a viable, noninvasive alternative to CT and can be easily performed at the bedside.

Some previous studies have reported a good correlation between TDS and CT in measuring HV and other intracranial structures.\(^1\)\(^-\)\(^3\) In accordance with these studies, we found an excellent correlation between CT and TDS when measuring HV and its longitudinal, axial, and coronal diameters, as well as MLS and the IIIV diameter. Conversely, we were unable to demonstrate a good correlation when measuring the LV diameter. Our results disagree with findings in previous studies that reported a good correlation.\(^14\)\(^-\)\(^15\) A possible explanation for this discrepancy may be the difficulty in visualizing the real margins of the LV when skewing the transducer upward from the IIIV, which results in considerable variability in the measures.

In addition to the correlation analysis, our study presents new information regarding the agreement between both techniques. We found good agreement when measuring HV and MLS, but the IIIV measurements presented a significant difference between CT and TDS. In addition, we observed a systematic bias when assessing HV: TDS tended to overestimate the volumes of smaller ICHs and, contrariwise, to underestimate volumes in larger ICHs. Thus, TDS may be a useful complementary diagnostic tool but may not substitute for CT as the criterion standard technique to assess ICH characteristics.

In addition to the morphologic information, TDS allows assessment of some hemodynamic parameters, such as the pulsatility index, which has been related to increased intracranial pressure. Remarkably, in the univariate analysis, we found that the pulsatility index from the ipsilateral MCA was associated with the risk of mortality. Our results are in accordance with a previous study that assessed the prognostic value of the pulsatility index in an ICH,\(^16\)\(^-\)\(^18\) though that study used transtranscranial Doppler and found a significant association between mortality and the pulsatility index from the contralateral MCA.

Baseline HV has been recognized as a major determinant of outcome in patients with acute ICH.\(^9\) Remarkably, we found that HV measured with TDS was an independent predictor of END and mortality. The predictive power of the logistic regression model with TDS variables was similar to that of the same model with CT measurements. Therefore, it is prudent to conclude that TDS may be regarded as a potential tool for the noninvasive monitoring of these patients.

We must be aware of the limitations of TDS, including examiner dependency, susceptibility to an insufficient temporal bone window, low spatial resolution, and possible imaging artifacts. Additionally, some specific limitations occur when assessing ICH, including the loss of echogenicity of the blood with time and the difficulty in evaluating the hematoma in some locations, for example in the infratentorial structures. These drawbacks designate TDS as a complementary diagnostic tool; CT remains the most reliable examination in acute ICH. Nevertheless, a TDS examination following the baseline CT may allow neurologists to monitor the HV at the bedside, regardless of the clinical status of the patient, and to avoid constant transfers to the CT room.

Our study has several limitations, including the small sample size, the limited follow-up of the patients, and the absence of a follow-up TDS examination, which prevented us from assessing hematoma expansion. In addition, a single examiner performed the TDS examinations; thus, we were not able to assess interrater reliability. Finally, we excluded patients who died before a TDS could be performed or who underwent surgical evacuation, which may represent a selection bias.

CONCLUSIONS
TDS showed an excellent correlation with CT in assessing HV, MLS, and IIIV diameters in an acute ICH. HV measured with TDS was an independent predictor of poor outcome with a predictive power similar to that of CT. Further studies are warranted to continue testing TDS as a complementary technique for monitoring ICH and to establish whether this monitoring may improve clinical outcomes.

ACKNOWLEDGMENT
We acknowledge Carly Calvert for English grammar revision.


REFERENCES
8. TuhLin S, Horowitz DR, Sacher M, et al. Volume of ventricular blood is
ABSTRACT

BACKGROUND AND PURPOSE: Branch atheromatous disease is a stroke subtype considered a risk factor for early neurologic deterioration. Meanwhile, crossed cerebellar diaschisis is thought to be influenced by the degree and location of supratentorial perfusion abnormalities and is associated with the clinical outcome in the case of an ischemic stroke. In this article, our aim was to clarify the utility of using a whole-brain 3D pulsed continuous arterial spin-labeling method as an imaging biomarker for predicting neurologic severity in branch atheromatous disease.

MATERIALS AND METHODS: Twenty-three patients with branch atheromatous disease in the lenticulostriate artery territory were enrolled. All patients underwent MR imaging, including DWI, 3D-TOF-MRA, and 3D-arterial spin-labeling. We measured the asymmetry index of CBF in the affected area (branch atheromatous disease), the asymmetry index of the contralateral cerebellar hemisphere (crossed cerebellar diaschisis), and the DWI infarct volume in the lenticulostriate artery territory. We also compared each parameter with the initial NIHSS score with the Pearson correlation coefficient.

RESULTS: Among the 23 patients, we found no correlation between NIHSS score and the asymmetry index of CBF in the affected area (branch atheromatous disease) \((r = -0.027, P = .724)\), whereas the asymmetry index of the contralateral cerebellar hemisphere (crossed cerebellar diaschisis) and DWI infarct volumes were significantly correlated with NIHSS score \((r = 0.515, P = .012; r = 0.664, P = .001, respectively)\).

CONCLUSIONS: In patients with branch atheromatous disease, 3D-arterial spin-labeling can detect crossed cerebellar diaschisis, which is correlated with the degree of neurologic severity.

ABBREVIATIONS: \(AICCD\) = asymmetry index of the affected area (branch atheromatous disease); \(ALCCD\) = asymmetry index of the contralateral cerebellar hemisphere (crossed cerebellar diaschisis); \(ASL\) = arterial spin-labeling; \(BAD\) = branch atheromatous disease; \(CCD\) = crossed cerebellar diaschisis; \(END\) = early neurologic deterioration; \(LSA\) = lenticulostriate artery; \(ref\) = reference

Intracranial branch atheromatous disease (BAD) is a stroke subtype that was first described in 1989.\(^1\) BAD was originally determined on the basis of pathologic findings of occlusion or stenosis at the origin of a deep penetrating artery due to the presence of a microatheroma or a junctional plaque.\(^2,3\) Representative vascular territories of BAD include the lenticulostriate artery (LSA), the pontine paramedian artery, and sometimes the anterior choroidal artery.\(^4,5\) Previous studies have mentioned that BAD is strongly associated with early neurologic deterioration (END), and some patients with BAD may experience a worsening of neurologic deficits despite intensive medical treatment, resulting in a worse functional outcome.\(^6-10\) Although few pathologic studies for BAD have been reported, some articles have investigated its neuroradiologic characteristics, with MR imaging in particular.\(^7-10\)

Arterial spin-labeling (ASL) is a noninvasive MR perfusion imaging technique that uses magnetically labeled blood as an intrinsic tracer.\(^11-13\) ASL permits a quantitative measurement of cerebral perfusion and repetitive acquisitions with independent labeling because it requires neither an injection of a contrast medium nor radiation exposure.\(^11-13\) 3D-ASL is considered an advanced method for ASL and uses pulsed continuous arterial spin-labeling with a volumetric spiral fast spin-echo readout, which enables the acquisition of high signal-to-noise ratio and quantitative whole-brain perfusion images.\(^13,14\)
Previous articles have suggested that 3D-ASL is useful for evaluating cerebral ischemia.\textsuperscript{12,15} To the best of our knowledge, no report has used ASL imaging findings to assess BAD, and a few articles have examined the neuroradiologic features of BAD that are related to END.\textsuperscript{6-8} In addition, some studies using \textsuperscript{15}O-positron-emission tomography and perfusion CT imaging have indicated that crossed cerebellar diaschisis (CCD) occurrence is influenced by the degree and location of the supratentorial perfusion abnormalities and is associated with the clinical outcome.\textsuperscript{16,17} Therefore, we hypothesized that perfusion abnormalities detected with 3D-ASL, including CCD, might be correlated with the degree of neurologic deterioration despite the small lesions found with BAD. The aim of our study is to clarify the utility of whole-brain 3D-ASL as an imaging biomarker for predicting the neurologic severity in BAD.

**MATERIALS AND METHODS**

**Patients**

This retrospective study analyzed data obtained from patients with acute cerebral infarctions who were admitted to our institution between October 2012 and November 2016. Patients were eligible if they met the following criteria: The NIHSS score on admission was obtained by stroke physicians; MR imaging, including 3D-ASL, DWI, and 3D-TOF-MRA, was performed; subtypes of intracranial BAD in the LSA region defined as a lesion of $\geq 15$ mm in diameter and visible on $\geq 3$ sections were observed on DWI;\textsuperscript{2} there was no occlusion or severe stenosis ($\geq 50\%$) in the horizontal segment of the MCA on the MRA; and cardioembolism and large-artery atherosclerosis based on clinical features and other examinations, such as the pattern of symptom onset, resting electrocardiography, continuous electrocardiographic monitoring, transthoracic echocardiography, transthoracic echocardiography, and carotid ultrasonography, were excluded.\textsuperscript{18} Our institutional review board approved this study and waived the need for written informed consent because of its retrospective design.

**Imaging Examinations**

All MR imaging examinations were performed with a 3T MR imaging system (Discovery MR750w; GE Healthcare, Milwaukee, Wisconsin). For 3D-ASL, DWI, and MRA, the scanning parameters were the following: 3D-ASL: TR, 4554 ms; TE, 10.7 ms; FOV, 24 cm; matrix, 512 $\times$ 512; section thickness, 4.0 mm; postlabel delay, 1525 ms; acquisition time, 1 minute 31 seconds; DWI: TR, 7000 ms; TE, 10.7 ms; FOV, 21 cm; matrix, 128 $\times$ 128; section thickness, 5.0 mm; maximum b factor, 1000 mm$^2$/s; acquisition time, 56 seconds; MRA: TR, 20 ms; TE, 3.4 ms; FOV, 20 cm; matrix, 384 $\times$ 224; section thickness, 1.0 mm; acquisition time, 4 minutes 36 seconds.

**Image Analysis**

3D-ASL maps were registered to DWIs by linear transformations (translation and rotation) by using SPM8 (https://www.fil.ion.ucl.ac.uk/spm/software/spm8). BAD lesions in the section of the largest infarcted area of the LSA territory were outlined semiautomatically to measure the regional CBF (millilitter/100 mL/min) on 3D-ASL (ASL-BAD) according to the consensus of 2 neuroradiologists (Y.S. and A.K., with 13 and 5 years of experience in diagnostic neuroradiology, respectively). ROIs with an elliptic shape were also marked on the contralateral corona radiata from the BAD lesions (ASL-BAD$_{reference}$) and in the bilateral cerebellar hemispheres in the section of the middle cerebellar peduncles and pons (ASL-CCD and ASL-CCD$_{ref}$) (Fig 1). The asymmetry index of the 3D-ASL based on the affected lesion was obtained as follows: asymmetry index of the affected area (branch atherosomatous disease, AI$_{BAD}$) or asymmetry index of the contralateral cerebellar hemisphere (crossed cerebellar diaschisis, AI$_{CCD}$) = (ASL-BAD$_{ref}$ or -CCD$_{ref}$ – ASL-BAD or -CCD)/(ASL-BAD$_{ref}$ or -CCD$_{ref}$ + ASL-BAD or -CCD) $\times$ 100 (%). DWI infarct volume measurements of BAD were performed with a semiautomated commercially available image-analysis program (AnalyzePro; AnalyzeDirect, Overland Park, Kansas).

**Statistical Analysis**

Linear regression analyses and Pearson correlation coefficients were used to compare the admission NIHSS score with each asymmetry index and DWI infarct volume. Each correlation was analyzed by using SPSS software (Version 23.0; IBM, Armonk, New York). $P < .05$ was statistically significant.

**RESULTS**

Twenty-three patients met our study criteria. Seventeen (73.9\%) patients were men, and 10 (43.5\%) lesions involved the left hemisphere. The mean patient age was 69.3 $\pm$ 13.3 years. The mean interval between symptom onset and MR imaging examination...
was 40.6 ± 37.6 hours. The median admission NIHSS score was 3 (interquartile range, 2.5–5). The mean \(A_{\text{BAD}}\) and \(A_{\text{CCD}}\) were 12.0% ± 14.5% and 10.5% ± 12.1%, respectively, and the mean DWI infarct volume was 2.50 ± 1.72 mL.

No significant correlation was found between NIHSS and \(A_{\text{BAD}}\) \((r = 0.027, P = 0.724)\). In contrast, we found a significant correlation between NIHSS and both \(A_{\text{BAD}}\) \((r = 0.515; P = 0.012, \text{Fig } 2\text{A})\) and DWI infarct volume \((r = 0.664, P = 0.001, \text{Fig } 2\text{C})\). A demonstrable case is shown in \text{Fig 3}.

**DISCUSSION**

Our results showed that the CCD on 3D-ASL and DWI infarct volume are strongly correlated with the degree of neurologic severity in patients with BAD-related infarcts. END can often occur in patients with BAD, and early management based on an accurate diagnosis is therefore needed in a clinical setting. These findings on 3D-ASL and DWI may represent important imaging biomarkers for predicting neurologic severity in the early stages of BAD.

Intracranial BAD was first described in 1989 as a new entity of atheromatous infarctions. The pathogenesis of BAD is considered an occlusion or stenosis at the origin of a deep penetrating artery due to the presence of a microatheroma or large parent artery plaque. Although the term BAD was originally presented on the basis of pathologic findings, few pathologic studies have been performed so far. In contrast, many neuroimaging studies of BAD have been performed, particularly with MR imaging. DWI shows comma-shaped restricted diffusion that extends to the basal surface of the parent artery in patients with BAD, and noninvasive vessel imaging methods such as CTA or MRA usually reveal no or mild stenosis of the parent artery.

Furthermore, BAD-related infarcts are considered predictive factors for END or progressive motor deficits. Yamamoto et al proposed that the severity of the neurologic status on admission (eg, initial NIHSS score) and preceding transient ischemic attacks could be predictors of END for LSA-type BAD. Meanwhile, a few reports have described the association between END and imaging findings of BAD. A previous study on BAD suggested that DWI findings associated with poor outcomes include a larger lesion size in a direction perpendicular to the axial section. This suggestion is compatible with our results in which the DWI infarct volume of BAD showed a favorable correlation with the initial NIHSS. Thus, an initial DWI may play an important role in estimating the neurologic severity of BAD-related infarcts.

3D-ASL is widely used as a noninvasive and repeatable whole-brain perfusion imaging method in clinical settings. 3D-ASL enables acquisition of both the relative CBF near the affected lesions, including those associated with ischemia, tumors, or trauma, and the perfusion changes due to remote effects such as CCD. CCD is a matched depression of blood flow and met-
tabolism in the cerebellar hemisphere contralateral to a focal, supratentorial lesion and is a well-recognized phenomenon following cerebral infarctions.26 Previous articles have also indicated that asymmetry indices for CCD in 3D-ASL were well-correlated with those of SPECT.25 To the best of our knowledge, no reports have shown a relationship between 3D-ASL findings for BAD and neurologic status. In the present study, the CCD for BAD in 3D-ASL was much better correlated with the initial NIHSS score than the regional CBF of the 3D-ASL in the affected LSA region. Because the severity of neurologic status on admission is considered to be closely associated with the END in patients with BAD,21 the degree of initial CCD on 3D-ASL, as well as initial DWI infarct volume, may be predictors of END for LSA-type BAD.

CCDs may demonstrate good correlations with the initial NIHSS score due to the localization of LSA-type BAD, which usually affects the pyramidal tract of the corona radiata or the internal capsule so that secondary degenerative changes along the corticospinal tract may easily occur. According to a previous report with MR tractography, the degree of pyramidal tract involvement within the LSA territory infarction is strongly related to the severity of the stroke and functional recovery.27 Further studies with larger sample sizes are warranted to validate the relationship between CCD detected by 3D-ASL and the neurologic outcome, including follow-up by NIHSS.

Our study has several limitations. First, we examined the luminal patency with MRA and did not directly evaluate the parent artery wall. As previously mentioned, the pathogenesis of BAD is associated with proximal stenosis or occlusion of a penetrating artery due to a microatheroma or large parent artery plaque; and routine imaging techniques, such as MRA, are unable to visualize small vessel changes. However, recent studies showed that black-blood high-resolution MR imaging enables an evaluation of the intracranial artery vessel morphology, including the presence of plaques involving parent arteries.28 This capability could allow direct exploration of atheromatous small vessels and parent vessel lesions that cause BAD. Second, the interval from symptom onset to initial MR imaging examination varied widely among patients in this retrospective study. Finally, we only enrolled patients with LSA-type BAD. Patients with BAD involving other vascular territories, including the paramedian pontine artery, were not included because of the small sample size. A further prospective study that includes all types of BAD should be performed.

CONCLUSIONS

In patients with LSA-type BAD, the CCD detected by 3D-ASL and DWI infarct volume was correlated with the severity of the neurologic status. Because the initial NIHSS score of BAD is considered a predictor of END and both 3D-ASL and DWI are noninvasive, repeatable, feasible sequences, they could be useful as radiologic imaging biomarkers for predicting the neurologic outcome in patients with BAD.

REFERENCES

5. Arboix A, Blanco-Rojas L, Martí-Vilalta JL. Advancements in understanding the mechanisms of symptomatic lacunar ischemic stroke:

FIG 3. A 72-year-old man with a right BAD-related infarction. The admission NIHSS score was 5, and MR imaging was performed 24 hours after onset. A–D, DWIs show high signal intensity from the posterior putamen to the corona radiata (white arrows). E, MRA reveals no stenosis or occlusion in the right MCA. H, The 3D-ASL shows hypoperfusion signal intensity in the right corona radiata, corresponding to the infarcted area (white dotted arrow). F and G, Hypoperfusion intensity in the left cerebellum (white arrowheads) can be observed, which indicates crossed cerebellar diaschisis due to the remote effect of the BAD-related infarction.
Temporal and Spatial Variances in Arterial Spin-Labeling Are Inversely Related to Large-Artery Blood Velocity

A.D. Robertson, G. Matta, V.S. Basile, S.E. Black, C.K. Macgowan, J.A. Detre, and B.J. MacIntosh

ABSTRACT

BACKGROUND AND PURPOSE: The relationship between extracranial large-artery characteristics and arterial spin-labeling (ASL) MR imaging may influence the quality of ASL images for older adults with and without vascular pathology. We hypothesized that extracranial arterial blood velocity can explain between-person differences in arterial spin-labeling data systematically across clinical populations.

MATERIALS AND METHODS: We performed consecutive pseudocontinuous arterial spin-labeling (PCASL) and phase-contrast (PC) imaging on 82 individuals (20–88 years of age, 50% women), including healthy young adults, healthy older adults, and older adults with cerebral small vessel disease or chronic stroke infarcts. We examined associations between extracranial phase-contrast hemodynamics and intracranial arterial spin-labeling characteristics, which were defined by labeling efficiency, temporal signal-to-noise ratio, and spatial coefficient of variation.

RESULTS: Large-artery blood velocity was inversely associated with labeling efficiency (P = .007), temporal SNR (P < .001), and spatial coefficient of variation (P = .05) of arterial spin-labeling, after accounting for age, sex, and group. Correction for labeling efficiency on an individual basis led to additional group differences in GM-CBF compared to correction using a constant labeling efficiency.

CONCLUSIONS: Between-subject arterial spin-labeling variance was partially explained by extracranial velocity but not cross-sectional area. Choosing arterial spin-labeling timing parameters with on-line knowledge of blood velocity may improve CBF quantification.

ABBREVIATIONS: ASL = arterial spin-labeling; CoV = coefficient of variation; PC = phase contrast; WMH = white matter hyperintensities

Quantitative CBF is a valuable measure to track pathophysiologic changes in cerebrovascular function and brain metabolism. Two noninvasive MR imaging–based techniques, which capture distinct hemodynamic features, are arterial spin-labeling (ASL) and phase-contrast (PC) imaging. ASL measures regional CBF with tissue-level precision, using magnetized arterial blood water as an endogenous tracer. PC imaging, by comparison, quantifies whole-brain CBF with a bipolar gradient to induce phase shifts proportional to blood velocity within the carotid and vertebral arteries. Among the factors that influence ASL, CBF quantification is most sensitive to labeling efficiency and the equilibrium magnetization of arterial blood. In practice, labeling efficiency is assumed constant (eg, 0.85). Field inhomogeneity and nonlinear effects of blood velocity, however, contribute individual variability. Studies that have empirically estimated labeling efficiency by normalizing pseudocontinuous ASL-based whole-brain CBF to that measured with PC imaging report individual labeling efficiencies ranging from 0.7 to 1.1. Recent work in a large middle-aged cohort, however, has questioned the validity of this normalization method due to substan-

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ADULT BRAIN

tial variability within individual measurements.\(^\text{11}\) Rather than incorporating PC-based CBF as a normalization factor, corresponding knowledge of PC-based metrics, such as blood velocity, may be beneficial for planning ASL protocols because many labeling and acquisition parameters are timing-based.

Simulated and empiric ASL data suggest that labeling efficiency is highest for blood velocities of \(\sim 10\) cm/s.\(^\text{8}\) These studies reflect hemodynamics in healthy adults, leaving questions regarding the reliability of ASL in patients with vascular pathology. Aging, cerebrovascular risk factors, and stroke status are associated with larger cross-sectional areas and slower, more pulsatile blood velocity within the large arteries.\(^\text{12,13}\) Such changes occurring in proximity to the ASL labeling plane may confound CBF quantification in these clinical cohorts. For instance, age is associated with a decreased signal-to-noise ratio, due, in part, to increased variance between individual control-tag difference images.\(^\text{14}\) Arterial transit time is another velocity-sensitive hemodynamic characteristic associated with aging\(^\text{15}\) and the presence of white matter hyperintensities (WMH).\(^\text{16}\) Prolonged transit time is visualized by localized regions of hyperintense ASL signal, contributing to greater spatial variance in whole-brain CBF.\(^\text{17}\) To expand our understanding of the relationship between large-artery characteristics and CBF estimates, we compared ASL and PC in individuals across a range of age and vascular pathology. We hypothesized that large-artery blood velocity would be inversely related to labeling efficiency, temporal SNR, and spatial variance in ASL.

**MATERIALS AND METHODS**

**Participants and Protocol**

Participants were recruited into 4 groups: 1) healthy young adults (younger than 40 years); 2) healthy older adults (50 years or older); 3) older adults with WMH of presumed vascular origin; and 4) older adults with chronic stroke infarcts (\(\geq 3\) months post-stroke). Exclusion criteria included the presence of dementia, a genetic predisposition to WMH, and extracranial arterial occlusion.

Participants underwent a single MR imaging scan. The SUNYbrook Research Institute’s research ethics board approved this study, and all participants provided written informed consent.

**MR Imaging Acquisition**

We completed neuroimaging with a 3T MR imaging system (Achieva; Philips Healthcare, Best, the Netherlands) with a body coil transmitter and an 8-channel head coil receiver. Structural imaging included high-resolution T1 (\(\text{TR}/\text{TE} = 9.5/2.3\) ms, flip angle = 8\(^\circ\), voxel dimensions = 0.9 \(\times\) 0.7 \(\times\) 1.2 mm\(^3\), FOV = 240 \(\times\) 191 \(\times\) 168 mm\(^3\)) and FLAIR (\(\text{TR}/\text{TE}/\text{TI} = 9000/125/2800\) ms, flip angle = 90\(^\circ\), voxel dimensions = 0.4 \(\times\) 0.4 \(\times\) 3 mm\(^3\), FOV = 240 \(\times\) 240 \(\times\) 156 mm\(^3\)) acquisitions. Two 2D acquisitions independently quantified CBF: PC to measure large-artery blood flow and ASL to measure tissue-level CBF. The PC acquisition captured a single 5-mm section perpendicular to the extracranial internal carotid artery, with cardiac synchronization (finger pulse gating, single cardiac phase [acquisition delay = 250 ms, acquisition window = 500 ms], \(\text{TR}/\text{TE} = 20/9.1\) ms, flip angle = 15\(^\circ\), maximum velocity encoding = 100 cm/s, voxel dimensions = 0.5 \(\times\) 0.5 mm\(^2\), FOV = 150 \(\times\) 150 mm\(^2\)). Pseudocontinuous labeling for the ASL scan used a train of radiofrequency pulses (duration = 0.5 ms, flip angle = 18\(^\circ\), interpulse pause = 0.5 ms) with a balanced gradient scheme for 1650 ms and occurred at a position identical to that of the PC acquisition. Thirty control and tag ASL volume pairs were acquired by single-shot echo-planar imaging (\(\text{TR}/\text{TE} = 4000/9.6\) ms, flip angle = 90\(^\circ\), in-plane resolution = 3 \(\times\) 3 mm\(^3\), FOV = 192 \(\times\) 192 mm\(^2\), section thickness = 5 mm, number of sections = 18 [no gap], postlabel delay = 1600 ms at the first section and ascending for subsequent sections).

We did not select background suppression to maximize the detectability of deleterious individual-difference images that were spurious due to head motion. A proton density-weighted reference volume was acquired to estimate the equilibrium magnetization and extract a receiver coil sensitivity profile (\(\text{TR} = 10\) seconds, but otherwise identical to ASL parameters). We prioritized the frontal cortices and subcortical tissue when setting the ASL FOV, leaving inconsistent coverage of the cerebellum and the most superior cerebrum. PC and ASL scan durations were 1.5 and 4.5 minutes, respectively. The 2 acquisitions were run sequentially, and the order was varied between participants.

**MR Imaging Processing**

Images were processed with the FMRIB Software Library (FSL; www.fmrib.ox.ac.uk/fsl). Brain extraction\(^\text{18}\) and segmentation\(^\text{19}\) tools isolated GM and WM from the T1WI. Brain mass was estimated on the basis of tissue densities of 1.03 g/mL for GM and 1.04 g/mL for WM.\(^\text{20}\) In-house software,\(^\text{21}\) combined with manual editing, segmented WMH from the FLAIR image. Stroke lesions were identified by CSF segmentation from the T1WI, manual editing, and confirmation against the FLAIR image. WMH and infarct volumes were normalized to an intracranial capacity of 1300 mL. Older adults with a normalized hyperintensity burden of \(\geq 10\) mL across periventricular and deep brain regions were assigned to the WMH group.

Internal carotid and vertebral artery masks were isolated from the PC magnitude image by using FSL segmentation software and manual editing. Interrater reliability of this method was excellent (Cronbach \(\alpha >0.99\) for the internal carotid artery and \(>0.95\) for the vertebral artery between 1 experienced and 2 novice raters). These masks represent the cross-sectional area of each artery, and they were overlaid onto the PC phase image to compute mean blood velocity. Arterial blood flow is the product of area and mean velocity, and PC-CBF was calculated as the sum of flow through all 4 arteries, normalized to brain mass. Peak blood velocity was taken as the highest velocity signal from a voxel in the center of the vessel lumen.

ASL-CBF was calculated from the mean of the control-tag difference images. To maximize image quality, we systematically removed individual-difference images with high relative head motion before CBF calculation, as previously described.\(^\text{14}\) The remaining difference images underwent in-plane spatial smoothing by using a Gaussian kernel of 5-mm full width at half maximum, section-by-section adjustment for incremental postlabel delay, and calibration to absolute CBF units with a proton density-weighted image.\(^\text{1}\) The T1 relaxation time for arterial blood is 3.2 minutes across periventricular and deep brain regions assigned to the WMH group.

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cular artifacts are suggestive of prolonged arterial transit time, CBF calculations over the whole brain should remain valid in the absence of crushing gradients.3

We calculated 4 ASL variables to compare against extracranial hemodynamics: 1) GM-CBF, 2) individual labeling efficiency equal to the ratio between ASL-based and PC-based whole-brain CBF, 3) temporal SNR equal to the ratio between the mean and the SD of the individual-difference images, and 4) spatial coefficient of variation (CoV) equal to the ratio between the SD and mean of the GM-CBF image. A GM mask without any overlapping stroke lesion was created for the calculation of GM-CBF, temporal SNR, and spatial CoV. GM-CBF was subsequently corrected for labeling efficiency in 2 ways: 1) with a constant of 0.85, and 2) with the calculated labeling efficiency.

**Statistical Analysis**

CBF, mean blood velocity, and cross-sectional area were compared between groups by ANOVA. We assessed the associations of mean blood velocity and cross-sectional area with GM-CBF, individual labeling efficiency, temporal SNR, and spatial CoV by linear regressions, adjusting for age, sex, and group. To account for between-vessel differences in area and velocity, we calculated flow-weighted measures in which the influence of each artery on the pooled variables was proportional to the contribution of that vessel to whole-brain CBF. Differences between whole-brain ASL-CBF and PC-CBF were characterized in a paired analysis by ratio and mean difference. Finally, we compared GM-CBF with ASL-CBF and PC-CBF accounted for a significant proportion of the between-group variability was observed in older adults with vascular pathology (Fig 1, lower panel).

**RESULTS**

Large-artery characteristics and whole-brain hemodynamics from 82 participants (n = 15 young, 22 healthy older, 15 with WMH, and 30 with stroke) are reported in Table 1. In WMH, the normalized hyperintensity volume range varied from 10.9 to 52.2 mL. Stroke participants were 3–65 months postevent with cortical, subcortical, and subcortentorial infarcts. The normalized infarct volume ranged from 0.03 to 98.2 mL. Group differences in velocity, but not cross-sectional area, were observed (Fig 1). Although the fraction of whole-brain CBF contributed by each extracranial artery was similar across groups, greater within-group variability was observed in older adults with vascular pathology (Fig 1, lower panel).

**Labeling Efficiency**

PC-CBF accounted for a significant proportion of the between-person variance in ASL-CBF ($r^2 = 0.40, P < .001$), though technique differences were evident. Intermodality analyses suggested that ASL-CBF was systematically lower than PC-CBF ($t = −2.6, P = .01$), and this difference was greater in WMH than in stroke or healthy older adults groups (Table 2). The ASL-CBF to PC-CBF ratio (ie, individual labeling efficiency) ranged from 0.48 to 1.60 across our entire sample. A group effect was observed ($F = 4.3, P = .008$), with the ratio being lower in WMH than in stroke and healthy older adults groups (Table 2). The ASL-CBF to PC-CBF ratio (ie, individual labeling efficiency) ranged from 0.48 to 1.60 across our entire sample. A group effect was observed ($F = 4.3, P = .008$), with the ratio being lower in WMH than in stroke and

Temporal and Spatial Variance

Temporal SNR and spatial CoV were associated with mean blood velocity in bivariate linear regression (Fig 2), though no difference between young and healthy older adults was noted, but both groups exhibited less spatial CoV than WMH and stroke groups ($P_{\text{Bonferroni}} < .05$). Both temporal SNR and spatial CoV were associated with mean blood velocity in bivariate analysis (Fig 2) and remained significant after adjusting for age, sex, and group (Table 3). The spread of spatial CoV increased with decreasing velocity, particularly below 10 cm/s. Calculated label efficiency was directly related to temporal SNR ($r^2 = 0.07, P = .017$), but not spatial CoV ($r^2 = 0.02, P = .16$).

GM-CBF

GM-CBF was directly correlated with mean blood velocity (Fig 2 and Table 3). A group-by-method interaction ($F = 4.6, P = .005$) indicated that additional group differences in GM-CBF were observed when using a PC-based correction for labeling efficiency compared with the constant 0.85 correction (Fig 3). When we used the constant correction across all participants, GM-CBF was lower in the WMH and stroke groups than in young adults and lower in the WMH group than in healthy older adults. Correction for PC-based labeling efficiency identified additional differences between the healthy young and old groups and between the healthy old and stroke groups.

**DISCUSSION**

The accuracy of regional CBF maps—an important consideration for the clinical uptake of ASL imaging—depends on multiple parameters in the scanning protocol. In this study, we compared PC and ASL MR imaging in adults with and without vascular-related pathology to assess how large-artery characteristics relate to ASL signal. The regression results demonstrated an inverse relationship between labeling efficiency and arterial blood velocity, which is consistent with previous work. However, label efficiency variance was high for low velocities; thus, we are unable to provide empiric support for the theorized inverted U-shaped profile. Notably, features of ASL variance, namely temporal SNR and spatial CoV, were independently associated with mean blood velocity but not cross-sectional area in regression analyses. Reduced temporal SNR at a low velocity contributed to the increased variance of labeling efficiency within this range. These results reaffirm that hemodynamics at the labeling plane are an important consideration for CBF quantification in ASL, especially in older adults with cerebrovascular disease.

Previous work estimated ASL labeling efficiency based on PC, though the validity of this method has recently come under scrutiny. Our current findings contrast with ASL simulations that posited a direct association between velocity and labeling efficiency below peak velocities of 20 cm/s. Whereas the previous findings were under the assumption of constant flow profiles, our PC implementation averaged velocities over the cardiac cycle; consequently, the velocity estimates more closely reflect data from Aslan et al., who found an inverse association between velocity and labeling efficiency above 10 cm/s. ASL signal intensity and transit delays have been shown to vary as a function of the cardiac cycle, so dissimilar relationships between mean and peak veloc-

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**Table 2: Comparison of MRI methods for whole-brain CBF estimation**

<table>
<thead>
<tr>
<th>No.</th>
<th>ASL-PC (ratio)</th>
<th>ASL-PC Difference (mL/100 g/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young</td>
<td>15 0.91 ± 0.20</td>
<td>−4.9 ± 9.8</td>
</tr>
<tr>
<td>Old</td>
<td>22 1.00 ± 0.18</td>
<td>−0.6 ± 7.0</td>
</tr>
<tr>
<td>WMH</td>
<td>15 0.80 ± 0.20</td>
<td>−9.2 ± 9.4</td>
</tr>
<tr>
<td>Stroke</td>
<td>30 1.01 ± 0.23</td>
<td>0.5 ± 7.9</td>
</tr>
<tr>
<td>All</td>
<td>82 0.95 ± 0.22</td>
<td>−2.6 ± 9.0</td>
</tr>
</tbody>
</table>

---

* Data are mean ± SD.

† Group differences compared with WMH at $P_{\text{Bonferroni}} < .05$.

FIG 2. The association of mean blood velocity with GM-CBF (panel 1), ASL-to-PC ratio for whole-brain CBF (panel 2), ASL temporal SNR (panel 3), and CBF spatial CoV (panel 4). Velocity is shown as a weighted mean of all 4 extracranial vessels relative to their contribution to total CBF. GM-CBF is uncorrected for labeling efficiency. Age, sex, and group-adjusted linear models are reported in Table 3.

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healthy older adults. Labeling efficiency was unrelated to mean blood velocity in bivariate linear regression (Fig 2), though labeling efficiency and peak blood velocity showed a modest correlation ($r^2 = 0.05, P = .043$). Furthermore, an inverse association between labeling efficiency and mean velocity was observed in a regression model that adjusted for age, sex, group status, and cross-sectional area (Table 3). This multivariate model was altered when peak velocity replaced mean velocity.

**Temporal and Spatial Variance**

Group differences in the temporal SNR within gray matter were also observed (young: 2.05 ± 0.33 versus old: 1.79 ± 0.43 versus WMH: 1.23 ± 0.44 versus stroke: 1.42 ± 0.42; $F = 13.4, P < .001$). No difference between young and healthy older adults was noted, but both groups had greater SNR than WMH and stroke groups ($P_{\text{Bonferroni}} = 0.010$). Group differences in spatial CoV within gray matter were also observed (young: 0.31 ± 0.04 versus old: 0.36 ± 0.07 versus WMH: 0.49 ± 0.15 versus stroke: 0.48 ± 0.16; $F = 8.80, P < .001$). Again, no difference between young and healthy older adults was noted, but both groups exhibited less spatial CoV than WMH and stroke groups ($P_{\text{Bonferroni}} < .05$). Both temporal SNR and spatial CoV were associated with mean blood velocity in bivariate analysis (Fig 2) and remained significant after adjusting for age, sex, and group (Table 3). The spread of spatial CoV increased with decreasing velocity, particularly below 10 cm/s. Calculated label efficiency was directly related to temporal SNR ($r^2 = 0.07, P = .017$), but not spatial CoV ($r^2 = 0.02, P = .16$).
Table 3: Linear regression parameters for the association of extracranial mean blood velocity and cross-sectional area with ASL characteristics

<table>
<thead>
<tr>
<th>Model</th>
<th>Independent Variables</th>
<th>$\beta$</th>
<th>95% CI</th>
<th>T-Statistic</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GM-CBF</td>
<td>Area (cm$^2$)</td>
<td>46.5</td>
<td>(8.2–84.7)</td>
<td>2.03</td>
<td>.046</td>
</tr>
<tr>
<td>Adjusted $R^2 = 0.43$</td>
<td>Velocity (cm/s)</td>
<td>1.5</td>
<td>(0.8–2.3)</td>
<td>3.42</td>
<td>.001</td>
</tr>
<tr>
<td>ASL-CBF-PC-CBF</td>
<td>Area (cm$^2$)</td>
<td>−0.79</td>
<td>(−1.58–0.01)</td>
<td>−1.65</td>
<td>.103</td>
</tr>
<tr>
<td>Adjusted $R^2 = 0.21$</td>
<td>Velocity (cm/s)</td>
<td>−0.02</td>
<td>(−0.04–0.01)</td>
<td>−2.78</td>
<td>.007</td>
</tr>
<tr>
<td>GM-temporal SNR</td>
<td>Area (cm$^2$)</td>
<td>1.78</td>
<td>(0.24–3.32)</td>
<td>1.93</td>
<td>.058</td>
</tr>
<tr>
<td>Adjusted $R^2 = 0.47$</td>
<td>Velocity (cm/s)</td>
<td>0.07</td>
<td>(0.04–0.10)</td>
<td>3.99</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>GM-spatial CoV</td>
<td>Area (cm$^2$)</td>
<td>−0.11</td>
<td>(−0.61–0.39)</td>
<td>−0.36</td>
<td>.720</td>
</tr>
<tr>
<td>Adjusted $R^2 = 0.31$</td>
<td>Velocity (cm/s)</td>
<td>−0.01</td>
<td>(−0.02–0.00)</td>
<td>−2.01</td>
<td>.048</td>
</tr>
</tbody>
</table>

*All models were adjusted for age, sex, and group. GM-CBF is uncorrected for labeling efficiency.

FIG 3. GM-CBF between groups calculated with 2 labeling efficiency estimates. White bars incorporate a constant labeling efficiency (ie, 0.85), and gray bars incorporate individual labeling efficiency based on the ASL-to-PC ratio for whole-brain CBF. Post hoc group comparisons are indicated at $P_{	ext{corr}} < .05$ for differences from the young group (asterisk) and differences from old group (dagger) within the same calibration technique.

A large proportion of the variance remains unexplained in this study. In several cases, the calculated labeling efficiency exceeded 1.0, which is an implausible finding. We implemented gated cardiac PC-MRI to capture velocity data at a single phase in the cardiac cycle on the basis of a 500-ms acquisition window that was optimized for a range of R-R intervals centered at 1000 ms. Heart rate variability could shift this acquisition window to favor the diastolic phase of the cardiac cycle, which would influence the PC-CBF calculation and contribute to a higher ratio between ASL-CBF and PC-CBF. Vessel segmentation and partial volume errors related to vertebral artery tortuosity and smaller arterial caliber may have reduced PC-CBF accuracy. Another consideration is the ASL volume coverage. Whereas PC-CBF reflects whole-brain flow, the ASL FOV did not encapsulate the entire captured as hyperintense signal, contributing to greater heterogeneity within the perfusion-weighted image. Indeed, a recent ASL study in hypertensive older adults demonstrated a direct relationship between single postlabel delay spatial CoV and arterial transit time. To combat this, longer postlabel delays are recommended for imaging older adults to allow signal to reach the tissue before acquisition, albeit at a cost of lower signal intensity. We observed that slower velocity was related to greater spatial CoV of the perfusion-weighted image, which is consistent with greater macrovascular signal at the time of acquisition. Real-time monitoring of blood velocity before ASL planning may help mitigate these indices of ASL variance in 2 ways: First, acquiring additional tag and control volumes in individuals with low velocity would improve signal-to-noise ratio. Second, prescribing postlabel delay based on arterial blood velocity may help to distinguish aspects of arterial transit time that separate slower flow velocity from collateral or tortuous pathways.

The GM-CBF values observed here are consistent with those in other studies involving younger adults, healthy older adults, and individuals with chronic stroke. Older adults with WMH, however, exhibited lower GM-CBF than previously reported. Calibration of the GM-CBF to individual labeling efficiency on the basis of PC altered the sensitivity to distinguish clinical groups. With PC-based calibration, we noted GM-CBF differences between healthy young and older adults and between healthy older adults and those with stroke, which were not apparent with a constant labeling efficiency for all participants. Longitudinal relaxation time was held constant across all groups in our estimation of CBF with ASL. Age- and sex-dependent variability in blood T1 may have partially contributed to group differences in global ASL signal. The change in group differences following calibration to PC-CBF, which is independent of blood T1 effects, may be partially due to correction for group differences in longitudinal relaxation. Nevertheless, these results raise important questions about the consideration of labeling efficiency and the design of ASL protocols for CBF quantification in clinical cohorts with altered large-artery velocity profiles.
brain for all participants. Anatomic variability in the circle of Wil- lis (ie, distal to PC imaging) may also contribute to a mismatch between upstream and downstream flow measurements.34

These discrepancies may have contributed to a portion of the unexplained variance between ASL-CBF and PC-CBF and em- phasize the need for caution when comparing ASL-CBF directly with PC-CBF.11 Of note, our ASL protocol did not incorporate background suppression or involve 3D acquisition, which are now consensus guidelines for clinical ASL.3 Two main reasons for these preferences were the following: 1) Study development pre- dated the consensus article, and 2) a parallel objective of the data acquisition was to address deleterious head motion, which is more easily approached with multiple 2D sections as opposed to 3D readouts. Recently, a sequence that measures artery-specific label efficiency, thereby improving ASL-CBF accuracy, has been pro- posed and validated.35 Comparison of PC-CBF with ASL-CBF using this calibration method may facilitate investigation into the impact of age- and disease-related increases in hemodynamic pul- satility on ASL after controlling for effects on label efficiency.

CONCLUSIONS

The current study compared characteristics from ASL- and PC- based cerebral perfusion imaging in adults with and without vas- cular disease. Mean blood velocity through the ASL labeling plane was inversely related to labeling efficiency, as well as ASL temporal and spatial variance. These associations suggest that velocity im- pacts ASL at both the labeling and acquisition stages. ASL plan- ning based on real-time velocity monitoring (eg, number of control/tag pairs, postlabel delay) may help optimize the signal-to-noise ratio and minimize the effect of arterial transit time on CBF maps.

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Disclosures: Sandra E. Black—UNRELATED: Consultancy: Novartis, Merck, Pfizer, Eli Lilly, Comments: ad hoc consulting, Grants/Grants Pending: Hoffmann-La Roche, Eli Lilly, Pfizer, Lundbeck, Transition Therapeutics, GE Healthcare, Aventan Sciences, Cognoptix, Biogen, Canadian Institutes of Health Research, National Institutes of Health, Heart and Stroke Foundation of Canada, Alzheimer’s Drug Discovery Foun- dation, Brain Canada, Ontario Brain Institute, Fondation Leducq, Weston Foundation, Canadian Partnership for Stroke Recovery, Comments: contract grants and grants from government agencies paid to the institution*; Payment for Lectures Including Service on Speakers Bureau: Mediscare, Biogen, Comments: lecture presented at the Alzheimer’s Association International Conference, 2016, Toronto, John A. Detre—UNRELATED: Board Membership: International Society for Magnetic Reso- nance in Medicine, Comments: board member, 2011–2014, Consultancy: Child Health and Development Institute, Ironwood Pharmaceuticals, National Institutes of Health, Wellcome Trust, Comments: I have been a paid consultant on neuroimaging for the Child Health and Development Institute (nonprofit Huntington dis- ease research entity, Ironwood Pharmaceuticals company); I review grants for National Institutes of Health and the Wellcome Trust (UK) and have received honoria for that work; Employment: University of Pennsylvania: Grants/Grants Pending: National Institutes of Health, Comments: I am a co-investigator on numerous National Institutes of Health grants that are funded or pending*; Payment for Lectures Including Service on Speakers Bureau: Stanford Univer- sity, Moss Rehabilitation Research Institute, Korean Society for Magnetic Reso- nance in Medicine, Stock/Stock Options: Blackfynn, Comments: I am eligible for stock in Blackfynn, a Pennsylvania startup company in exchange for consulting, but I have not exercised this option. *Money paid to the institution.

REFERENCES

23. Zhang Y, Brady M, Smith S. Segmentation of brain MR images through a hidden Markov random field model and the expectation-


Head-to-Head Visual Comparison between Brain Perfusion SPECT and Arterial Spin-Labeling MRI with Different Postlabeling Delays in Alzheimer Disease


ABSTRACT

BACKGROUND AND PURPOSE: Arterial spin-labeling MR imaging has been recently developed as a noninvasive technique with magnetically labeled arterial blood water as an endogenous contrast medium for the evaluation of CBF. Our aim was to compare arterial spin-labeling MR imaging and SPECT in the visual assessment of CBF in patients with Alzheimer disease.

MATERIALS AND METHODS: In 33 patients with Alzheimer disease or mild cognitive impairment due to Alzheimer disease, CBF images were obtained by using both arterial spin-labeling–MR imaging with a postlabeling delay of 1.5 seconds and 2.5 seconds (PLD1.5 and PLD2.5, respectively) and brain perfusion SPECT. Twenty-two brain regions were visually assessed, and the diagnostic confidence of Alzheimer disease was recorded.

RESULTS: Among all arterial spin-labeling images, 84.9% of PLD1.5 and 9% of PLD2.5 images showed the typical pattern of advanced Alzheimer disease (ie, decreased CBF in the bilateral parietal, temporal, and frontal lobes). PLD1.5, PLD2.5, and SPECT imaging resulted in obviously different visual assessments. PLD1.5 showed a broad decrease in CBF, which could have been due to an early perfusion. In contrast, PLD2.5 did not appear to be influenced by an early perfusion but showed fewer pathologic findings than SPECT.

CONCLUSIONS: The distinctions observed by us should be carefully considered in the visual assessments of Alzheimer disease. Further studies are required to define the patterns of change in arterial spin-labeling–MR imaging associated with Alzheimer disease.

ABBREVIATIONS: AD = Alzheimer disease; ASL = arterial spin-labeling; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; PLD = postlabeling delay; PLD1.5 = postlabeling delay of 1.5 seconds; PLD2.5 = postlabeling delay of 2.5 seconds

For the imaging diagnosis of Alzheimer disease (AD), CBF is typically evaluated with brain perfusion SPECT.1,2 MR imaging is also commonly performed, chiefly for the evaluation of atrophy and ischemic changes in the brain. Obtaining these images simultaneously would be significantly beneficial to both patients and caregivers. Arterial spin-labeling (ASL) MR imaging has been recently developed as a noninvasive technique with magnetically labeled arterial blood water as an endogenous contrast medium for the evaluation of CBF.3-6 Several studies have reported interesting perfusion comparisons between patients with various forms of dementia and demographically matched healthy controls. Both AD and mild cognitive impairment (MCI) have been associated with hypoperfusion in the middle occipital areas, medial temporal lobe, and especially the parietal lobe.7 Similar hypoperfusion has been reported in the posterior cingulate and precuneus, in addition to frontal and parietal regions.8,9 ASL-MR imaging is a potentially useful tool for the differential diagnosis of dementia.10,11 However, most studies have performed voxelwise or ROI analyses to detect abnormal findings in patients with AD compared with healthy patients or those with other forms of dementia. To date, only a few studies of AD have focused on visual assessment with ASL-MR imaging, mainly because of the lack of established criteria for using ASL-MR imaging to diagnose AD.

Pseudocontinuous ASL, the most common form of ASL, is a distinct form of pulsed and continuous labeling and is recommended for clinical imaging by the International Society for Magnetic Resonance in Medicine Workshop on Perfusion Imaging.12 For ASL imaging, arterial water in the neck is labeled with a radiofrequency pulse and the brain is imaged after a fixed time interval, which is termed the postlabeling delay (PLD) and is the key parameter of ASL imaging. However, the optimal PLD for the
evaluation of patients with dementia is unknown. Many previous studies of AD have used a PLD of 1.5 seconds (PLD_{1.5}), while others have used 2.0 seconds. The International Society for Magnetic Resonance in Medicine Workshop recommends 2.0 seconds for adult clinical patients, but a longer PLD might be appropriate for elderly patients due to their relatively slow blood flow. In the present study, we performed a clinical visual assessment to compare the CBF images obtained by using ASL-MR imaging or brain perfusion SPECT in patients with AD. PLDs of 1.5 and 2.5 seconds (PLD_{2.5}) were used for ASL-MR imaging.

**MATERIALS AND METHODS**

We recruited 33 patients who underwent brain MR imaging and SPECT for the diagnosis of AD or MCI due to AD between September 2015 and June 2016. Patients with AD met the criteria of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer Disease and Related Disorders Association for probable AD. Patients were excluded from the study if they had a significant history of psychiatric or neurologic disorders other than AD, including stroke, head injury, epilepsy, psychiatric disorders, alcohol abuse, and other serious medical conditions. All patients underwent MR imaging, SPECT, and standard dementia screening, which included a medical history and Mini-Mental State Examination (MMSE) and neuropsychological testing. SPECT and MR imaging were performed ≤1 month apart. The local institutional review board approved the study, and all subjects provided written informed consent.

**MR Imaging**

MR imaging was performed with a 3T MR imaging system (Discovery 750w; GE Healthcare, Milwaukee, Wisconsin) and a 12-channel head coil. Structural imaging for anatomic information was performed with a sagittal 3D T1-weighted sequence (TR = 6.6 ms, TE = 2 ms, flip angle = 14°, matrix = 256 × 256, 170 sections, voxel size = 1.0 × 0.9 × 0.9 mm³, FOV = 23 × 23 cm) with an acquisition time of 6 minutes.

A whole-brain pseudocontinuous ASL 3D perfusion sequence was acquired (3D fast spin-echo acquisition with background suppression). The imaging protocol with PLD_{1.5} was TR = 4641 ms, TE = 10.7 ms, flip angle = 36, FOV = 23 × 23 cm, voxel size = 2 × 2 × 4 mm³, labeling duration = 1.5 seconds, NEX = 1, and an acquisition time of 1 minute 33 seconds. The imaging protocol with PLD_{2.5} was TR = 5336 ms, TE = 10.7 ms, and NEX = 2. All other parameters were the same, and the acquisition time was 2 minutes 51 seconds.

**Brain Perfusion SPECT**

The SPECT scans began 15 minutes after the intravenous injection of 148 MBq of iodine 123 N-isopropyl-p-iodoamphetamine (^{123}I-IMP) (Nihon Mediphysics, Hyogo, Japan) and were performed for 30 minutes by using a SPECT/CT scanner (Symbia T6; Siemens, Erlangen, Germany). The SPECT scans were acquired by using low-medium-energy general purpose collimation, a 128 × 128 matrix of 3.3-mm pixel size, and 300 s/rotation in a continuous-rotation mode. SPECT reconstruction was performed with a Butterworth filter for filtered back-projection with a cutoff = 0.35/cm and an order of 8. A uniform attenuation correction was performed by using the Chang method, with μ = 0.11.

**Visual Assessment**

Two board-certified radiologists who are also nuclear medicine physicians with >10 years of experience in reading MR imaging and SPECT brain images and 2 years of experience reading ASL-MR imaging independently reviewed the images obtained in the present investigation without the clinical information of the patient. SPECT and ASL-MR imaging were shown with a section thickness of 6.6 and 6.4 mm, respectively. We used the scoring sheet shown in Fig 1 to assess 22 brain regions. The regions were located at the levels of the vertex, lateral ventricle, basal ganglia, and cerebellum. The raters scored each region by using a 4-point scale, where 0 is a normal CBF, 1 is a mild decrease, 2 is a moderate decrease, and 3 is a severe decrease.

**FIG 1.** The regions used for scoring brain images. We evaluated 22 regions located at the levels of the vertex, lateral ventricle, basal ganglia, and cerebellum. The raters scored each region with a 4-point scale, where 0 is a normal CBF, 1 is a mild decrease, 2 is a moderate decrease, and 3 is a severe decrease.

| Table 1: Demographic and neuropsychological summary of the participants* |
|----------------|------------------|
|                | AD               | MCI due to AD |
| Age (yr)       | 77.1 (7.7)       | 78.2 (5.6)    |
| No. of patients| 14               | 19            |
| Sex (M/F)      | 3:11             | 8:11          |
| MMSE score     | 16.9 (3.0)       | 25.2 (2.6)    |

* Data are presented as mean (±SD).

b There was a significant difference in the MMSE score (P < .01) between AD and patients with AD-induced MCI.

gray-scale and in color-scale fused with T1-weighted images. SPECT images were displayed in color.

**Statistical Analysis**

The interrater variability was assessed for the diagnostic confidence of AD by using the $\kappa$ statistic. The diagnostic confidence was evaluated with not only the 2-point scale but also positive (3 and 4) or negative (0–2) scores for AD diagnosis. The total scores for SPECT, PLD$_{1.5}$, and PLD$_{2.5}$ from each rater were analyzed by using a Friedman test. Data were analyzed in Excel (Microsoft, Redmond, Washington) and JMP12 (SAS, Cary, North Carolina). A $P < .01$ was statistically significant.

**RESULTS**

**Demographic Findings**

Patient demographics are shown in Table 1, including age, the male-to-female ratio, and MMSE scores. There was no difference in age, but a significant difference in MMSE ($P < .01$) was observed between patients with AD and those with AD-induced MCI.

**Visual Assessment**

Table 2 shows the results of the visual assessment as the percentage of patients diagnosed with AD (score of 3 or 4) for each rater. The agreement concerning the percentage of patients with an AD diagnosis between the 2 raters is also shown. These results are presented for 3 groups: namely, the total population, the AD group (MMSE $\leq 21$), and the AD-induced MCI group (MMSE $> 21$). Both raters observed that for the total population, the AD group, and the AD-induced MCI group, PLD$_{1.5}$ imaging had the highest positive rate for AD diagnosis, while PLD$_{2.5}$ imaging had the lowest. Moreover, the positive rate for AD diagnosis was higher for the AD group than for the MCI group (Table 2). The Friedman analysis of variance test revealed a significant difference in total scores among all 3 imaging modalities ($P < .01$), and the Wilcoxon test revealed a significant difference between the 2 groups in the assessment of PLD$_{1.5}$, PLD$_{2.5}$, and SPECT images ($P < .01$) (Fig 2). There were no significant differences between the AD and AD-induced MCI groups in the total score for 3 imaging modalities. The interrater agreements were low for both the 5-point or 2-alternative scoring of AD (Table 3).

**Case Presentations**

Case 1 was an 86-year-old woman with AD. Her MMSE score was 14. The ASL-MR imaging and SPECT images for this patient are shown in Fig 3. Case 2 was an 83-year-old woman with AD. Her MMSE score was 19. The images for this patient are shown in Fig 4. Case 3 was a 73-year-old woman with MCI due to AD. Her MMSE score was 23. The images for this patient are shown in Fig 5.

**DISCUSSION**

We clearly observed differences in the visual assessments of PLD$_{1.5}$, PLD$_{2.5}$, and SPECT images. The total scores of the 2 raters were highest for the PLD$_{1.5}$ images; this finding suggests a large decrease in CBF. Indeed, these scores were diminished or ambiguous in PLD$_{2.5}$ images. SPECT findings were of intermediate severity compared with those for the PLD$_{1.5}$ and PLD$_{2.5}$ images. These findings appeared to have a profound effect on the diagnostic confidence of AD—that is, for both raters, the positive rate for AD diagnosis was very high (approximately 90%) with a high agreement rate for PLD$_{1.5}$ images, while the diagnostic confidence of AD was low for PLD$_{2.5}$ images with a low agreement rate. In addition, SPECT images were associated with a moderately high diagnostic confidence and agreement rate. The positive rate of AD diagnosis for the SPECT images in the present investigation was consistent with that of previous studies.\(^1,2\)

In the present study, the PLD$_{1.5}$ images often showed marked

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**Table 2: The results of visual assessments for the diagnosis of AD**

<table>
<thead>
<tr>
<th></th>
<th>Overall Positive Rate (%)</th>
<th>Positive Rate in AD (%)</th>
<th>Positive Rate in MCI (%)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>PLD$_{1.5}$</td>
<td>PLD$_{2.5}$</td>
<td>SPECT</td>
</tr>
<tr>
<td>Rater 1</td>
<td>87.9</td>
<td>9.1</td>
<td>69.7</td>
</tr>
<tr>
<td>Rater 2</td>
<td>97.0</td>
<td>12.1</td>
<td>90.1</td>
</tr>
<tr>
<td>Agreement</td>
<td>84.8</td>
<td>3.0</td>
<td>66.7</td>
</tr>
</tbody>
</table>

**Table 3: Interrater agreement**

<table>
<thead>
<tr>
<th></th>
<th>5-Point Scoring</th>
<th>Positive or Negative for AD Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLD$_{1.5}$</td>
<td>0.033</td>
<td>0.3694</td>
</tr>
<tr>
<td>PLD$_{2.5}$</td>
<td>0.141</td>
<td>0.203</td>
</tr>
<tr>
<td>SPECT</td>
<td>0.010</td>
<td>0.195</td>
</tr>
</tbody>
</table>
bilateral decreases in signal intensity in the frontal and temporo-parietal lobes, even for patients with AD-induced MCI, but these findings were mostly not present in the PLD2.5 images (case 3, Fig 3). A previous study using PLD1.5 for patients with cerebrovascular disease reported a low ASL signal with surrounding cortical areas showing a high signal intensity in the middle cerebral artery–anterior cerebral artery and middle cerebral artery–posterior cerebral artery borderzones. This phenomenon was termed the “borderzone sign”. Another recent study evaluated the performance of PLD1.5 compared with SPECT in patients with AD and reported that PLD1.5 images frequently showed the borderzone sign. Our results suggest the presence of the borderzone sign for PLD1.5, but not PLD2.5. The presence of the borderzone sign in ASL-MR images with a short PLD, but not in those with a long PLD, could have been due to an early perfusion adjacent to the main cerebral arteries. In fact, our PLD2.5 images did not frequently show such a broad decrease in CBF, and neither did the SPECT images.

In the present study, the PLD2.5 images frequently showed only minor pathologic findings with a low image contrast. Generally, a long PLD decreases the signal-to-noise ratio because of T1 relaxation. Thus, we doubled the number of excitations for

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**FIG 3.** An 86-year-old woman with AD. The patient had an MMSE score of 14. Axial images of T2-weighted MR imaging (A), ASL-MR imaging with PLD1.5 in a color-scale fused with T1-weighted MR imaging (B), ASL-MR imaging with PLD2.5 in a color-scale fused with T1-weighted MR imaging (C), and brain perfusion SPECT at the level of the parietal lobe, corona radiata, basal ganglia, and cerebellum (D). Both raters indicated a score of 4 (definitely AD) for PLD1.5 and SPECT and 1 (probably not AD) for PLD2.5.
PLD₂.₅ compared with PLD₁.₅; however, a greater number of excitations or the modification of some other parameter might be necessary to improve image contrast and quality.

A previous study comparing PET using FDG and ASL-MR imaging using PLD₁.₅ in patients with AD reported that both methods showed similar regional abnormalities and have comparable diagnostic accuracy in AD. The PLD₁.₅ images of this previous study were different from ours, which did not show decreased CBF in the frontal lobes. The findings of this previous study also contradict those in another study that reported decreased CBF in the frontal lobes of patients with AD. Another study performed multidelay multiparametric ASL for patients with stroke; however, their PLD₁.₅ images did not show decreased CBF in the frontal lobes but resembled those of PLD₂.₅ images. Such conflicting results between these studies may be due to scanner differences, parameters other than PLD, or other experimental differences.

There is a strong link between brain metabolism and CBF. Thus, SPECT images have been generally interpreted in a manner similar to that of FDG-PET. However, as our results show, ASL-MR images can change depending on the PLD and show

**FIG 4.** An 83-year-old woman with AD. The patient had an MMSE score of 19. Axial images of T₂-weighted MR imaging (A), fused T₁-weighted and PLD₁.₅ ASL-MR imaging (B), fused T₁-weighted and PLD₂.₅ ASL-MR imaging (C), and brain perfusion SPECT (D). Both raters indicated a score of 4 for PLD₁.₅ and 2 (undetermined) for PLD₂.₅. One rater indicated a score of 3 (probably AD) and another rater indicated a score of 4 for SPECT.
significantly different findings from SPECT. The use of FDG criteria for ASL-MR imaging diagnosis of AD increases the risk of over- or underdiagnosis. Further studies will be needed to establish the optimal conditions for ASL-MR imaging in the diagnosis of AD and to define the dynamic temporal patterns of ASL-MR images associated with the development of AD.

Regarding the differentiation of AD and AD-induced MCI, we did not observe significant differences in total scores of the 3 modalities between the AD and AD-induced MCI groups. The positive rates for AD diagnosis for the AD group were slightly higher than those for the AD-induced MCI group; however, the differences were small. Further studies are required to clarify the usefulness of ASL for the discrimination of AD and AD-induced MCI.

The interrater agreements were low in the present study, even for the 2-alternative scoring method. The participants in our study had relatively high MMSE scores. Only 1 participant had an MMSE score of <10, and 5 of the participants had scores of <15, which could have resulted in a low interrater agreement.

The present study has several limitations. First, the sample size was small; a larger sample would produce more reliable results. Second, we did not perform MR angiography due to tight time constraints.

**FIG 5.** A 73-year-old woman with MCI. The patient had an MMSE score of 23. Axial images of T2-weighted MR imaging (A), fused T1-weighted and PLD\textsubscript{1.5} ASL-MR imaging (B), fused T1-weighted and PLD\textsubscript{2.5} ASL-MR imaging (C), and brain perfusion SPECT (D). Both raters scored 4 for PLD\textsubscript{1.5}. However, 1 rater indicated a score of 1 (probably not AD) for PLD\textsubscript{2.5} and 2 for SPECT, while another rater indicated a score of 0 (definitely not AD) for PLD\textsubscript{2.5}, and 1 for SPECT.
constraints. Third, no images of cognitively healthy participants were used as controls; thus, we could not evaluate the accuracy of the visual-based diagnosis. Finally, an optimal PLD could not be determined in the present study. These limitations should be considered for future research.

CONCLUSIONS

Significant differences in visual assessments were observed for PLD$_{1.5}$, PLD$_{2.5}$, and SPECT images. PLD$_{1.5}$ images showed a robust decrease in CBF, which could have been due to an early perfusion. In contrast, PLD$_{2.5}$ did not appear to be influenced by an early perfusion but showed fewer pathologic findings than SPECT. Visual assessment of AD should be performed with attention to these distinctions. Further studies are required to define the dynamic temporal ASL-MR imaging pattern associated with AD.

ACKNOWLEDGMENTS

We thank Mr. Yuki Koyo for his assistance with data collection and analyses, Dr. Ayako Hino for reading images, and Mr. Naoki Hirata for his advice on the processing of ASL-MR imaging.

REFERENCES

CT Angiography ASPECTS Predicts Outcome Much Better Than Noncontrast CT in Patients with Stroke Treated Endovascularly


ABSTRACT

BACKGROUND AND PURPOSE: Noncontrast CT ASPECTS has been investigated as a predictor of outcome in patients with acute ischemic stroke. Our purpose was to investigate whether CTA source images are a better predictor of clinical and radiologic outcomes than NCCT ASPECTS in candidates for endovascular stroke therapy.

MATERIALS AND METHODS: CT scans of patients (n = 124) were independently evaluated by 2 readers for baseline NCCT and CTA source image ASPECTS and for follow-up ASPECTS. An mRS of ≤2 at 3 months was considered a favorable outcome. Receiver operating characteristic curve analysis was used to assess the ability of NCCT and CTA source image ASPECTS to identify patients with favorable outcomes. A stepwise multiple regression analysis was performed to find independent predictors of outcome.

RESULTS: Baseline CTA source image ASPECTS correlated better than NCCT ASPECTS with follow-up ASPECTS (r = 0.76 versus r = 0.51; P for comparison of the 2 coefficients < .001). Receiver operating characteristic curve analysis showed that baseline CTA source image ASPECTS compared with NCCT ASPECTS can better identify patients with favorable outcome (CTA source image area under the curve = 0.83; 95% CI, 0.76–0.91; NCCT area under the curve = 0.67; 95% CI, 0.58–0.77; P < .001). Finally, the stepwise regression analysis showed that lower age, good recanalization, lower time to recanalization, and good baseline CTA source image ASPECTS, not NCCT ASPECTS, were independent predictors of favorable outcome.

CONCLUSIONS: CTA source image ASPECTS predicts outcome better than NCCT ASPECTS; this finding suggests CTA rather than NCCT as a main step in the decision-making process for patients with acute ischemic stroke.

ABBREVIATIONS: CTA-SI = CTA source images; ET = endovascular stroke therapy

The Alberta Stroke Program Early CT Score merges the ability of quantifying and describing the topography of brain tissue damage produced by acute ischemic stroke in a semiquantitative way.\(^1\) ASPECTS on noncontrast CT is widely used for the assessment of early ischemic changes, and its prognostic value has already been established,\(^3\) though with poor NCCT sensitivity.\(^3\) Recent randomized controlled trials on endovascular stroke therapy (ET) have been based on strict inclusion criteria, leading to treatment of only those patients with high CT ASPECTS indicating smaller infarct burden.\(^4\-^6\)

Many attempts have been made to understand which patients are likely to undergo futile reperfusion.\(^7\) For instance, it has been recently demonstrated that patients with poor collaterals and longer time to reperfusion do not achieve good outcomes after ET.\(^8\) Thus, a careful patient selection for ET should be desirable and should be based on a multimodal neuroimaging approach in addition to onset time and stroke severity. Although not as commonly available as NCCT in the acute ischemic stroke setting, CT angiography is useful for confirmation of vessel occlusion in candidates for ET, and hypodensity on CTA source images (CTA-SI) has been shown to reliably correlate with ischemic lesion volume on diffusion-weighted imaging\(^9\) and final infarct size.\(^10\) The superiority of CTA-SI on NCCT in the detection of infarcted areas has been demonstrated for readers of all levels of experience.\(^11\) Few data exist on the value of CTA-SI ASPECTS in patients un-
derning ET for acute ischemic stroke,\textsuperscript{12,13} and this lack of data may explain why only ASPECTS NCCT is currently considered in the guidelines for eligibility for ET. Our purpose was to investigate whether CTA-SI ASPECTS correlate better than NCCT ASPECTS with clinical and radiologic outcome measures in patients with acute ischemic stroke undergoing ET.

\textbf{MATERIALS AND METHODS}

A retrospective analysis of patients identified from a prospective registry at a comprehensive stroke center (University Hospital of Tor Vergata, Rome, Italy) was performed. Patients with anterior circulation acute ischemic stroke secondary to intracranial proximal arterial occlusion (M1 MCA, M2 MCA, distal internal carotid artery, and proximal ICA plus intracranial proximal arterial occlusion) admitted within 6 hours of symptom onset were included. Due to the study period (between 2009 and 2015) before the publication of recent endovascular stroke trials,\textsuperscript{4-6} no exclusion criteria other than the time from symptom onset were adopted. Patients presenting within 4.5 hours of symptom onset were treated with intravenous thrombolysis, which was continued in the angiographic suite during the endovascular procedure. Patients presenting beyond the time window for intravenous thrombolysis, or with major contraindications to intravenous thrombolysis (ie, warfarin therapy with an international normalized ratio of 1.7, recent major surgery, or a history of hemorrhage/hematoma) underwent stand-alone thrombectomy. Demographics, vascular risk factors, and baseline and 24-hour NIHSS scores were reported. The modified Rankin Scale was adopted for outcome analysis, and an mRS of \( \leq 2 \) at 3 months was considered a favorable outcome. The study was approved by the Tor Vergata Policlinic Ethical Committee, and informed consent was obtained from all patients or their relatives.

\textbf{Image Acquisition}

The NCCT and CTA were acquired with a standardized protocol. Axial CT was performed on a multissection scanner (Light Speed VCT; GE Healthcare, Milwaukee, Wisconsin) by using 120 kV and 170 mAs with a 5-mm section thickness. Continuous axial sections parallel to the orbitomeatal line were obtained from the skull base to the vertex. CTA was performed with a 64–detector row scanner. Acquisitions were obtained after single-bolus intravenous contrast injection of 90–120 mL of nonionic contrast media into an antecubital vein at 3–5 mL/s. Imaging was autotrig- gered by the appearance of contrast media in the ascending aorta. Standard coverage included the area from the arch to the vertex. Source images were reconstructed at a 1.25-mm thickness in the axial planes at half-thickness intervals. NCCT or DWI was performed between 1 and 7 days after stroke onset and used for follow-up ASPECTS.

\textbf{Image Processing}

NCCT, CTA-SI, and MR imaging (DWI sequences and apparent diffusion coefficient map) scans were independently screened for ASPECTS by 1 neuroradiologist (M.S.) and 1 stroke neurologist (G.K.) who were blinded to the patients’ symptoms but aware of acute nonlacunar stroke. The readers performed their evaluation at different time periods to make their assessment blinded as much as possible. Adequate window and optimal level settings were adopted to maximize the contrast produced by attenuation differences between normal and ischemic tissue. Our ASPECTS reading includes evaluation of all axial sections (www.aspectsinstroke.com), and as in previous studies, we excluded isolated cortical swelling from the score.\textsuperscript{14} In case of a discrepancy between readers, a third neuroradiologist (R.G.) was involved to achieve a consensus. The interrater reliability was 0.71 for NCCT and 0.75 for CTA-SI, indicating a good interrater agreement for both methods.

\textbf{Statistical Analysis}

The analysis was performed by using STATATA/IC, Version 13 (StataCorp, College Station, Texas) and GraphPad Prism software, Version 6.00 (GraphPad Software, San Diego, California). Continuous variables are summarized as mean \( \pm SD \) or median with interquartile range. Categoric variables are expressed as percentages. To determine differences between the 2 groups, we used a Student \( t \)-test or Mann-Whitney \( U \)-test for continuous variables. Interrater agreement was estimated with the \( \kappa \) statistic. Comparison of frequencies among ASPECTS groups was performed with the Fisher exact test after dichotomization into poor and good ASPECTS. Univariate associations between baseline and follow-up ASPECTS were investigated with the Spearman \( \rho \) analysis, with confidence limits calculated by means of the Fisher \( z \)-transformation. Bubble plots were used to graphically display correlation analyses, and the area of the bubble has to be read as proportional to the number of observations at each point. A nonparametric receiver operating characteristic curve analysis and the area under the curve were used to assess the ability of NCCT and CTA-SI ASPECTS to identify patients with favorable outcomes (mRS \( \leq 2 \)).

We then calculated the statistical significance of the difference between the area under the curves using the method of DeLong.\textsuperscript{15} For both NCCT and CTA-SI ASPECTS, a receiver operating characteristic curve was used to identify the best cutoff point with which to maximize the sensitivity and specificity for discriminating patients with favorable outcomes. A backward and forward stepwise logistic regression analysis was finally performed to determine the independent predictors of good outcome (mRS \( \leq 2 \)), including NCCT and CTA-SI ASPECTS as well as all other variables with a significant association in univariate analysis, to weigh for potentially confounding factors. Odds ratios with standard errors and 95% confidence intervals were provided. A \( P \) value < .05 was considered statistically significant.

\textbf{RESULTS}

Of 167 patients with anterior circulation stroke, 124 had complete CT, CTA, and clinical data and were included in the analysis. Baseline characteristics are summarized in Table 1. Single-artery occlusion (ICA, anterior cerebral artery, and middle cerebral artery) was diagnosed in 55.6%, whereas tandem lesions occurred in 44.3% of patients. Correlation analysis showed that baseline CTA-SI ASPECTS correlated better with follow-up ASPECTS \(( r = 0.76; 95\% CI, 0.67–0.83; P < .001)\) than baseline NCCT ASPECTS \(( r = 0.51; 95\% CI, 0.36–0.63; P < .001; P \) for comparison
of the 2 coefficients < .001) (Fig 1). Furthermore, the ability to identify patients with good outcome (mRS ≤ 2), revealed by receiver operating characteristic curve analysis, was significantly higher for CTA-SI ASPECTS with respect to NCCT ASPECTS (CTA-SI area under the curve, 0.83; 95% CI, 0.76–0.91; NCCT area under the curve, 0.67; 95% CI, 0.58–0.77; P < .001). According to each receiver operating characteristic curve, we determined cutoff values (Table 2), on the basis of which we defined a good CTA-SI ASPECTS as ≥5 and a good NCCT ASPECTS as ≥8. Most interesting, a median baseline NCCT ASPECTS of 9 resulted from a recent meta-analysis of 5 endovascular stroke trials. No statistical difference was found in onset-to-imaging acquisition time between good and poor ASPECTS groups (good CTA-SI, 135 ± 56 minutes versus poor CTA-SI, 137 ± 52 minutes; P > .05; good NCCT, 129 ± 54 minutes versus poor NCCT, 131 ± 54 minutes; P > .05).

Factors predicting favorable outcome (mRS ≤ 2, n = 48) in univariate analysis were both good NCCT ASPECTS and good CTA-SI ASPECTS, as well as age, baseline NIHSS, time to recanalization, and good recanalization (TICI ≥ 2b) (Table 3). To find the best outcome predictors, we finally constructed backward and forward stepwise regression analyses, including all variables significantly associated with favorable outcome in the univariate analysis. Both the backward and forward procedures showed that good CTA-SI ASPECTS, age, good recanalization, and time to recanalization remained independent predictors of good clinical outcome, indicating CTA-SI ASPECTS as a better predictor of functional outcome than NCCT ASPECTS (Table 4).

**DISCUSSION**

ET seems a safe and effective adjuvant treatment strategy for patients with acute ischemic stroke secondary to large intracranial vessel occlusion in the anterior circulation, and many attempts have been made in the recent past to better select those patients who can reliably benefit from ET. One such effort has been in recent randomized endovascular stroke trials that included only patients with small infarct size as defined by an ASPECTS of 6–7 on NCCT. Among these trials, the Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands (MR CLEAN) was the only one to include patients on the basis of time from symptom onset and confirmation of occlusion on neuroimaging. Nevertheless, a recent meta-analysis of these trials showed a median baseline CT ASPECTS of 9. Consequently, from all these trials, we have learned that ET works, but we do not know yet whether this kind of reperfusion therapy would be safe and effective in patients with lower ASPECTS.

Regarding these findings, a recent subgroup analysis from the MR CLEAN data showed that patients with NCCT ASPECTS of 5–7, not only those with NCCT ASPECTS of 8–10, may also benefit from ET. This study could not provide further information on patients with NCCT ASPECTS of 0–4 because of a paucity of data. Therefore, there are not thorough data concerning the effects of ET in patients with larger infarct burdens, and we only know that those with lower ASPECTS could be unsuitable for ET but cannot be excluded from treatment. A recent study of 249 patients showed a rate of good outcome of 5% in the CT ASPECTS group of 0–4 and of 38.5% in the CT ASPECTS group of 5–8, suggesting a chance for ET in patients

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**Table 1: Patient characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>68 ± 13.2</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>52.4%</td>
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<tr>
<td>Hypertension</td>
<td>79.8%</td>
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<tr>
<td>Diabetes</td>
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<tr>
<td>Atrial fibrillation</td>
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<tr>
<td>Smoking</td>
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<tr>
<td>Intravenous thrombolysis</td>
<td>60.4%</td>
</tr>
<tr>
<td>Baseline NIHSS</td>
<td>19 (IQR, 16–21)</td>
</tr>
<tr>
<td>NCCT ASPECTS</td>
<td>8 (IQR, 7–10)</td>
</tr>
<tr>
<td>CTA-SI ASPECTS</td>
<td>4 (IQR, 2–6)</td>
</tr>
<tr>
<td>Follow-up ASPECTS</td>
<td>3 (IQR, 1–5)</td>
</tr>
</tbody>
</table>

Note: —IQR indicates interquartile range.

**Table 2: ROC curve analysis—CTA-SI ASPECTS and NCCT ASPECTS cutoff values indicating patients with good clinical outcomes**

<table>
<thead>
<tr>
<th></th>
<th>AUC (95% CI)</th>
<th>Best Cutoff Value</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Correct Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTA-SI ASPECTS</td>
<td>0.83 (0.76–0.91)</td>
<td>5</td>
<td>60.42%</td>
<td>88.16%</td>
<td>77.42%</td>
</tr>
<tr>
<td>NCCT ASPECTS</td>
<td>0.67 (0.58–0.77)</td>
<td>8</td>
<td>64.58%</td>
<td>61.84%</td>
<td>62.90%</td>
</tr>
</tbody>
</table>

Note: —AUC indicates area under curve; ROC, receiver operating characteristic.
with larger infarct burden. Further scientific effort is warranted to identify any markers that could better predict outcome and give useful information for the decision-making process.

Thus, CTA can depict the area of ischemia (though not necessarily infarcted) much better than NCCT, especially when analyzing parenchymal CTA-SI. Hypodensity on CTA-SI provides greater demarcation between normal and abnormal tissue, and this finding could be explained by the ability of CTA to detect alterations in cerebral blood volume, as opposed to cytotoxic edema on NCCT, with a threshold insufficient to produce NCCT changes. In a small previous study, CTA-SI was shown to be more sensitive in the early detection of irreversible ischemia and dependence at 3 months. NCCT ASPECTS can better identify patients with functional impairment compared with baseline CTA-SI ASPECTS. In line with this finding, good reperfusion has been repeatedly demonstrated to improve the rate of good outcome irrespective of ASPECTS.

Table 3: Univariate analysis—variables associated with good clinical outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>mRS 0–2 (n = 48)</th>
<th>mRS 3–6 (n = 76)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>63.3 ± 15.3</td>
<td>70.3 ± 11.0</td>
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<td>Sex (male)</td>
<td>52%</td>
<td>52%</td>
<td>1.0</td>
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<tr>
<td>Baseline NIHSS</td>
<td>17.6 ± 3.1 (IQR: 11–23)</td>
<td>19.3 ± 3.5 (IQR: 9–25)</td>
<td>.009</td>
</tr>
<tr>
<td>Good NCCT ASPECTS</td>
<td>81.2%</td>
<td>50%</td>
<td>.001</td>
</tr>
<tr>
<td>Good CTA-SI ASPECTS</td>
<td>79.2%</td>
<td>26.3%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Onset to recanalization (min)</td>
<td>291.9 ± 86.3 (IQR: 140–635)</td>
<td>322.5 ± 70.3 (IQR: 155–505)</td>
<td>.03</td>
</tr>
<tr>
<td>Hypertension</td>
<td>70.8%</td>
<td>85.5%</td>
<td>.07</td>
</tr>
<tr>
<td>Diabetes</td>
<td>14.6%</td>
<td>17.3%</td>
<td>.80</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>33.3%</td>
<td>31.6%</td>
<td>.84</td>
</tr>
<tr>
<td>Smoking</td>
<td>18.7%</td>
<td>19.7%</td>
<td>1.0</td>
</tr>
<tr>
<td>Intravenous thrombolysis</td>
<td>93.7%</td>
<td>90.8%</td>
<td>.74</td>
</tr>
<tr>
<td>sICH</td>
<td>23.4%</td>
<td>14.7%</td>
<td>.23</td>
</tr>
<tr>
<td>TICI 2b–3</td>
<td>79.2%</td>
<td>56.6%</td>
<td>.01</td>
</tr>
</tbody>
</table>

Note: sICH indicates symptomatic intracranial hemorrhage.

Table 4: Multivariable regression model—best predictors of good clinical outcome

<table>
<thead>
<tr>
<th>OR</th>
<th>SE</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good CTA-SI ASPECTS</td>
<td>15.61</td>
<td>8.24</td>
<td>5.54–43.97</td>
</tr>
<tr>
<td>Age</td>
<td>0.95</td>
<td>0.02</td>
<td>0.91–0.99</td>
</tr>
<tr>
<td>TICI 2b–3</td>
<td>3.12</td>
<td>1.70</td>
<td>1.07–9.09</td>
</tr>
<tr>
<td>Onset to recanalization (min)</td>
<td>0.99</td>
<td>0.01</td>
<td>0.98–0.99</td>
</tr>
</tbody>
</table>

Note: SE indicates standard error.

ACKNOWLEDGMENTS

We thank all stroke neurologists of the Comprehensive Stroke Center at the University of Tor Vergata (Angela Giordano, MD, Vittoria Carla D’Agostino, PhD, Barbara Rizzato, PhD, Simone Napolitano, MD, Domenico Samà, PhD) and interventional radiologists of the Department of Diagnostic Imaging at the University of Tor Vergata (Daniel Konda, MD, Enrico Pampana, MD) for data collection.

REFERENCES

8. Sallustio F, Motta C, Pizzuto S, et al. CT angiography-based collat-
eral flow and time to reperfusion are strong predictors of outcome in endovascular treatment of patients with stroke. J Neurointerv Surg 2016 Sep 23. [Epub ahead of print] CrossRef Medline
State of Practice: Endovascular Treatment of Acute Aneurysmal SAH in Germany

H. Janssen, A. Berlis, J. Lutz, N. Thon, and H. Brückmann

ABSTRACT

BACKGROUND AND PURPOSE: Acute aneurysmal SAH is a severe disease that requires prompt treatment. Endovascular coiling and neurosurgical clipping are established treatment options. Our intention was to determine the state of current practice in acute aneurysmal SAH treatment in Germany, with emphasis on logistic and temporal aspects.

MATERIALS AND METHODS: We interviewed 74 German university and nonuniversity hospitals with an anonymous questionnaire comprising 15 questions concerning the practice of treatment and diagnostics of acute aneurysmal SAH at their respective institutions. The response rate was 74% among all institutions (55/74); among university hospitals, 77%; and among nonuniversity hospitals, 72%.

RESULTS: The majority of all aneurysms were treated endovascularly (66% of acute aneurysmal SAH, 66% of unruptured aneurysms). Treatment on weekends was provided by 100% of endovascular and 96% of neurosurgical facilities. Average patients with acute aneurysmal SAH were not treated during the night (98%). Seventy percent of endovascular and 78% of neurosurgical treatments were not started later than 8:00 PM. Fifty-three percent of hospitals would not start a same-day diagnostic angiography in acute aneurysmal SAH if treatment was scheduled for the following day. Eighty-two percent of all centers performed DSA after clipping to evaluate the treatment results.

CONCLUSIONS: Our survey gives a detailed summary of the current practice of endovascular treatment and related topics in acute aneurysmal SAH in Germany and also reveals considerable changes in practice in comparison with older data.

ABBREVIATIONS: AASAH = acute aneurysmal SAH; ICH = intracranial hemorrhage

Acute aneurysmal SAH (AASAH) is a severe condition. The incidence worldwide is approximately 9 per 100,000 per year, but there are regional differences.1 In Germany, the incidence is reported to be between 5.9 and 10—13 per 100,000.1,7 While up to 12% of patients die before getting to the hospital,1 therapeutic occlusion of the causative aneurysm is one of the most important treatment goals.4,5 However, because SAH is a complex disease, many other factors also influence clinical outcome.6 When the aneurysm is left untreated, the mortality rate is >60% within 1 year.7 The major reason is the high risk of rebleeding after the initial rupture. This risk is time-dependent—up to 15% within the first hours and approximately 4% on the first day and then declining to 1%–2% per day for the first month.8–10 Therefore, the timing of the obliterating therapy needs to be adapted to this course of the disease. The German Association of the Scientific Medical Societies recommends, in their SAH guidelines, obliteratoring aneurysm treatment within 72 hours.9 The European Stroke Organization recommends the same 72-hour time window but states that the therapy should be performed as early as possible.11 The American Heart Association and the American Stroke Association, in the latest update of their guidelines, postulate treatment as early as feasible without further specification.12 According to the quality record by the largest German health insurance provider, Allgemeine Ortskrankenkasse (AOK), 7213 aneurysms were treated in 2008 in Germany.13,14 To our knowledge, no published data are available that describe current clinical practice in Germany concerning the timing and availability of therapy in AASAH. Therefore, a nationwide cross-sectional survey was conducted.

MATERIALS AND METHODS

We compiled a questionnaire comprising 15 questions concerning the treatment of AASAH. All questionnaires were designed to
be administered in an anonymous fashion, and no identification of the participating hospital could be inferred. Self-addressed prepaid envelopes were enclosed.

All questions were designed to obtain the current state at the participating institution. Thirteen questions were multiple-choice, and 2 questions were open-ended. Questions concerning neurosurgical services were also surveyed through the addressed neurointerventionalist. Patient data were sought on a population level; no individual patient data were required.

Forty-three nonuniversity neuroendovascular departments in Germany were identified through the membership roster of the German Professional Organization of Neuroradiologists. Beyond these, we sent the questionnaire to all 31 German university departments of neuroradiology. The questionnaires were sent in June 2014 and were addressed to the head of department/neurosurgery divisions of the participating hospital. While question 5 asked for the total number of aneurysms treated per year, on average, at the institution, with patients presenting with and without AASAH in total and by endovascular services, respectively. Question 4 asked about neurosurgical clipping as a treatment option at the institution. The overall response rate was 74% through 55 completed questionnaires.

The response rate of university hospitals was 77% (24/31) and of nonuniversity hospitals, 72% (31/43).

The group of participating nonuniversity hospitals consisted of 22 maximum care hospitals and 9 specialist/other hospitals. In 4/9 of specialist hospitals, endovascular treatment but no neurosurgical clipping was available. In the remaining institutions, both options were routinely performed. The sum of all reported aneurysms treated neurosurgically and endovascularly per year by the participating hospitals in the survey was 6335.

The median number of treated aneurysms per year in total (AASAH + unruptured) was 100 per hospital (range, 30–420). Patients with AASAH compose, on average, 53% of all patients. The median number of treated patients with SAH in all hospitals was 60 (range, 15–150) (Table 1).

In the group of specialist hospitals, 1 center reported 420 aneurysm treatments per year, while the other 8 hospitals in this group only had 30–70 aneurysm treatments in total.

Sixty-six percent of all aneurysm treatments (SAH and unruptured, respectively; $P < .001$) were treated endovascularly. At university hospitals, the rate was 62%; at maximum care hospitals, 71%; and in specialist hospitals, 86%. Corrected for the 4 institutions that did not provide aneurysm clipping, the rate was 84% in specialist hospitals (Tables 2 and 3).

Quartiles for the total number of aneurysm treatments and endovascular treatments according to hospital type are provided in Table 4.

Questions 5 and 6 dealt with the process flow at the participating hospital. While question 5 asked for the total number of neurointerventionists at the institution, question 6 asked for the decision-making process in SAH aneurysm treatment concerning the decider of the treatment strategy. The multiple-

### RESULTS

#### Characterization of Participating Hospitals

Question 1 asked for the type of hospital, with choices among university hospital, maximum care hospital, or specialist hospital/other. A maximum care hospital provides all medical specializations for other reasons. Therefore, the category "specialist hospital/other" was introduced in the questionnaire. Questions 2 and 3 were the only open-ended questions in the questionnaire and asked for the number of aneurysms treated per year, on average, at the institution, with patients presenting with and without AASAH in total and by endovascular services, respectively. Question 4 asked about neurosurgical clipping as a treatment option at the institution.

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---

### Table 1: Distribution of all aneurysms

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Unruptured (%)</th>
<th>SAH (%)</th>
<th>Unruptured (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>University hospital</td>
<td>147.2</td>
<td>160</td>
<td>250</td>
<td>35</td>
</tr>
<tr>
<td>Maximum care hospital</td>
<td>94.8</td>
<td>80</td>
<td>400</td>
<td>30</td>
</tr>
<tr>
<td>Specialist hospital</td>
<td>89.6</td>
<td>38</td>
<td>420</td>
<td>30</td>
</tr>
<tr>
<td>All</td>
<td>117.3</td>
<td>100</td>
<td>53</td>
<td>47</td>
</tr>
</tbody>
</table>

**Note:**—Max indicates maximum; Min, minimum.

### Table 2: Distribution of aneurysms presenting with SAH (AASAH)

<table>
<thead>
<tr>
<th></th>
<th>All SAH</th>
<th>Endovascularly Treated SAH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Median</td>
</tr>
<tr>
<td>University hospital</td>
<td>87.0</td>
<td>80</td>
</tr>
<tr>
<td>Maximum care hospital</td>
<td>45.3</td>
<td>50</td>
</tr>
<tr>
<td>Specialist hospital</td>
<td>30.6</td>
<td>26</td>
</tr>
<tr>
<td>All</td>
<td>61.6</td>
<td>60</td>
</tr>
</tbody>
</table>

**Note:**—Max indicates maximum; Min, minimum.

### Table 3: Distribution of unruptured aneurysms

<table>
<thead>
<tr>
<th></th>
<th>All Unruptured</th>
<th>Endovascularly Treated Unruptured</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Median</td>
</tr>
<tr>
<td>University hospital</td>
<td>60.2</td>
<td>60</td>
</tr>
<tr>
<td>Maximum care hospital</td>
<td>49.5</td>
<td>30</td>
</tr>
<tr>
<td>Specialist hospital</td>
<td>59.0</td>
<td>18</td>
</tr>
<tr>
<td>All</td>
<td>55.7</td>
<td>62</td>
</tr>
</tbody>
</table>

**Note:**—Max indicates maximum; Min, minimum.
choice options were either a decision by the neurointerventional- 
ist or neurosurgeon alone or by a conjoint interdisciplinary decision.

In 85% of all hospitals, the mode of treatment was routinely 
decided by a consensus of both neurointerventionists and neu- 
surgeons. In 9% and 5% of hospitals, treatment decisions were 
made alone either by the neurointerventionists or the neurosur-
gons, respectively. Differences were seen between types of hospi-
tals: An interdisciplinary treatment consideration was preferred 
by 88% of the university hospitals. In the remaining 12%, the 
choice options were either a decision by the neurointervention-
tionalist or neurosurgeon alone or by a conjoint interdisciplinary decision.

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by 88% of the university hospitals. In the remaining 12%, the 
choice options were either a decision by the neurointervention-
tionalist or neurosurgeon alone or by a conjoint interdisciplinary decision.

The number of neurointerventionists capable of treating 
AASAH is, on average, higher in university hospitals compared 
with nonuniversity hospitals (Table 5).

**Management Considerations**

Questions 7 and 8 asked whether aneurysms were treated at any 
time during the night by endovascular or neurosurgical services, 
respectively. Questions 9 and 10 asked for the last time of day 
when aneurysm treatment is started at the institution by neuro-
interventionists or neurosurgeons, respectively (Table 6). Ques-
tions 11 and 12 asked whether aneurysms are treated on weekends

| Table 4: Institutional characteristics by quartiles of all aneurysms and endovascularly treated aneurysms |
|---|---|---|---|---|---|
| Quartile | Q1 | Q2 | Q3 | Q4 |
| University | MaxCare | Special |
| 1 | <48.8 | <3 | 1 | 2 | 7 | 7 | 6 | 4 |
| 2 | 48.8 | 3 | 6 | 5 | 7 | 5 | 2 | 4 |
| 3 | 100 | 58 | 6 | 8 | 7 | 6 | 0 | 0 |
| 4 | 162.5 | 110 | 11 | 9 | 1 | 4 | 1 | 1 |

*Note:*—Q, quartiles; Ev, endovascular; University, university hospital; MaxCare, max-
imum care hospital; Special, specialist hospital.

| Table 5: Interventionalists per hospital |
|---|---|---|---|---|
| No. of Interventionalists | 1 | 2 | 3 | 4 | >4 |
| University hospital | 0 | 4 | 8 | 9 | 3 | 4 |
| Maximum care hospital | 4 | 9 | 4 | 4 | 1 | 2 |
| Specialist hospital | 0 | 7 | 1 | 1 | 0 | 1 |
| All | 4 | 20 | 13 | 13 | 5 | 3 |

*Note:*—M indicates median.

| Table 6: Last time of day when treatments are started |
|---|---|---|---|---|---|---|---|---|---|
| Starting Time | 6 PM | 7 PM | 8 PM | 9 PM | 9 PM |
| Aneurysm type | University | MaxCare | University | MaxCare | University | MaxCare |
| Endovascular | | | | | | |
| University hospital | 3 (13%) | 0 | 13 (54%) | 5 (21%) | 3 (13%) |
| Maximum care hospital | 3 (14%) | 2 (9%) | 10 (45%) | 4 (18%) | 3 (14%) |
| Specialist hospital | 3 (33%) | 1 (11%) | 4 (44%) | 0 | 1 (11%) |
| All | 8 (16%) | 3 (5%) | 27 (49%) | 9 (16%) | 7 (13%) |
| Neurosurgery | | | | | | |
| University hospital | 7 (29%) | 1 (4%) | 12 (50%) | 2 (8%) | 2 (8%) |
| Maximum care hospital | 8 (36%) | 2 (9%) | 7 (32%) | 2 (9%) | 3 (14%) |
| Specialist hospital | 2 (40%) | 0 | 2 (40%) | 0 | 1 (20%) |
| All | 17 (35%) | 3 (5%) | 21 (38%) | 4 (7%) | 6 (11%) |

| Table 7: Grouped starting times |
|---|---|---|---|---|
| % to Start Until | 7 PM | 8 PM | 9 PM | 9 PM |
| Endovascular | | | | |
| University hospital | 13 | .15 | 67 | .55 | 88 | .97 |
| Nonuniversity hospital | 29 | 74 | 87 | |
| All | 21 | 70 | 86 | |
| Neurosurgery | | | | |
| University hospital | 33 | .38 | 83 | .43 | 91 | .26 |
| Nonuniversity hospital | 51 | 84 | 91 | |
| All | 40 | 78 | 85 | |

*Note:*—χ2 test.

| Table 8: Grouped mean number of interventionalists for treatment starting times |
|---|---|---|---|
| Starting Time | No. |
| All until 7 PM | 2.4 |
| All until 8 PM | 2.8 |
| All until 9 PM | 2.8 |
| After 9 PM | 3.7 |
treatment is performed only on the following day. Four of these are university hospitals (13% of all university hospitals), and 1 is a maximum care hospital (3% of all nonuniversity hospitals).

Most responders in all 3 hospital groups stated that a DSA is performed only in the context of treatment (all, 53%; university, 58%; maximum care, 50%; specialist hospital, 44%). If the time of day led to a postponement of treatment to the following day, DSA would also only be performed the next day (Table 9).

DSA is the most commonly used technique (all, 82%; university, 88%; nonuniversity, 78%) to control treatment results after neurosurgical clipping (Table 10). Some institutions gave multiple answers to this question. CTA was used in 18% (all); and MRA, in 10% (all). Fourteen percent reported not performing any imaging control after neurosurgical treatment (university, 13%; nonuniversity, 15%). Responses to this question were corrected for the 4 institutions that did not provide neurosurgical clipping.

### DISCUSSION

Our survey was performed with the intention of documenting current clinical practice in diagnostic- and treatment-related aspects of acute aneurysmal SAH in Germany. With the high response rate of 74% including 77% of all German university hospitals, the survey is considered representative. Particularly, the comparison of all reported aneurysms in our survey with the total aneurysm treatment number in Germany shows that about 88% of all aneurysm treatments in Germany are represented by university hospitals (13% of all university hospitals), and 1 is a maximum care hospital (3% of all nonuniversity hospitals).

Comparing hospital categories, we observed that the share of clipped aneurysms is larger in university hospitals than in nonuniversity hospitals (Tables 2 and 3). An explanation could possibly be the role of university hospitals in the training of fellows. The share of clipped aneurysms could be larger to achieve sufficient training capacity for both specializations. Another possible explanation could be a higher grade of subspecialization of staff in university hospitals.

Complete obliteration of the aneurysm is strongly associated with the risk of rebleeding. While a final imaging control by DSA is imminent to the endovascular treatment method, imaging strategies to control the degree of occlusion after clipping are not consistent. While almost 82% (88% of universities) conduct control DSA after clipping, 14% still do not perform any imaging control at all after clipping. The number of centers that do not perform this imaging control has declined dramatically during the past 10 years. This surprising paradigm shift can possibly be explained by the growing importance of quality assurance and legal considerations, owing to increasing numbers of malpractice lawsuits. It could also be the result of evolved and improved endovascular techniques today that open a spectrum of retreatment options for insufficient obliteration after neurosurgical clipping that did not exist in the past. MRA is the least used technique for clipping controls. This might be due to the artifacts caused by clip material resulting in limited imaging quality.

All guidelines recommend an interdisciplinary decision-making process for aneurysm treatment, with critical involvement of both endovascular interventionalists and vascular neuro-
surgeons. On this point, almost (85%) all hospitals followed this recommendation.

One of the main intentions of this survey was to document the status quo in temporal aspects of AASAH treatment. Remarkably, all participating institutions, even those with only 1 or 2 interventionalists, also provide full endovascular treatment on weekends. Weekend coverage in neurosurgery is almost as high (96%), with 2 hospitals not providing clipping on weekends.

The overwhelming majority (98% each, \(P < .001\)) do not treat patients with AASAH during the night, either endovascularly or neurosurgically. Not treating “average patients with AASAH” at night is the standard in Germany.

We believe that the explanation for this finding is the fear of higher complication rates when neurosurgeons and interven- tionalists perform the delicate procedure of aneurysm repair under difficult circumstances. The literature strongly supports this belief. Different reports show that complication rates in medical procedures are higher at night.\(^{20-22}\) Furthermore, in many studies of aircraft pilots, it has been proved that fatigue has a negative effect on their error probability and error management.\(^{23-26}\) Both are crucial determinants in aneurysm treatment as well, and these data can probably also be applied to neurosurgeons and interventionalists, though so far the possibility has never been studied explicitly for aneurysm treatment, to our knowledge.

Most hospitals do not start AASAH treatment later than 8:00 PM. Universities tend to start later than nonuniversity hospitals. This finding seems to be because more interventionalists are available at the hospital when treatments are started later (Table 8). It seems comprehensible that more staff resources allow a higher flexibility in interventions late in the evening because it is easier to respect rest periods on the following day. Neurosurgical treatment tended to be postponed to somewhat earlier the following day. The postponement might be explained by longer procedure times and limited availability of intraoperative neuromonitoring in the evening hours.

Divergent from the policy of not treating ruptured aneurysms at night, a minority of 7% performed diagnostic DSAs at night even if the treatment was not until the following day. The largest group (53%, all; 58%, universities) stated, however, that they do not perform DFA if treatment is scheduled for the following day, regardless of time of day. To us, this approach makes the most sense because it supports minimal movement of untreated patients with AASAH and avoids an additional transport of patients between the intensive care unit and the angiography suite, particularly if the patient is finally treated endovascularly. Only 24% of all centers would start a diagnostic DSA after 8:00 PM.

Limitations
The questionnaire was sent to the leading neurointerventionalists at each hospital. Whether the answers were given separately or in consensus by the neurointerventionalist and the neurosurgeon was not surveyed. The lack of information about the manner of answering is considered a potential source of bias.

Twenty-six percent of all addressed hospitals did not respond. Comparison of the number of all reported aneurysms in our survey with the total number of all treated cerebral aneurysms in Germany shows that the 26% of nonresponding hospitals account for approximately 12% of all aneurysms in Germany. The management practice in AASAH in these hospitals remains unknown in this survey.

The questionnaire did not allow evaluation of average time intervals between aneurysm rupture and treatment. A substantially higher effort would have been necessary by the participating hospitals to survey this information, and the authors expected a relevant decline in the willingness to participate in the survey if this information were sought.

CONCLUSIONS
Our survey gives a detailed summary of the current practice in endovascular treatment of acute aneurysmal SAH and related topics in Germany. It reveals both similarities and differences in AASAH management among treatment-providing hospitals. Today most aneurysms in Germany are treated endovascularly, and university hospitals have a key role in AASAH treatment.

References
12. Connolly ES Jr, Rabinstein AA, Carhuapoma JR, et al; American Heart Association Stroke Council; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; Council on Cardiovascular Surgery and Anesthesia; Council on Clinical Car-


The Impact of Conscious Sedation versus General Anesthesia for Stroke Thrombectomy on the Predictive Value of Collateral Status: A Post Hoc Analysis of the SIESTA Trial

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ABSTRACT

BACKGROUND AND PURPOSE: Radiologic selection criteria to identify patients likely to benefit from endovascular stroke treatment are still controversial. In this post hoc analysis of the recent randomized Sedation versus Intubation for Endovascular Stroke TreAtment (SIESTA) trial, we aimed to investigate the impact of sedation mode (conscious sedation versus general anesthesia) on the predictive value of collateral status.

MATERIALS AND METHODS: Using imaging data from SIESTA, we assessed collateral status with the collateral score of Tan et al and graded it from absent to good collaterals (0–3). We examined the association of collateral status with 24-hour improvement of the NIHSS score, infarct volume, and mRS at 3 months according to the sedation regimen.

RESULTS: In a cohort of 104 patients, the NIHSS score improved significantly in patients with moderate or good collaterals (2–3) compared with patients with no or poor collaterals (0–1) (P = 0.01; mean, −5.8 ± 7.6 versus −1.1 ± 10.7). Tan 2–3 was also associated with significantly higher ASPECTS before endovascular stroke treatment (median, 9 versus 7; P < .001) and smaller mean infarct size after endovascular stroke treatment (median, 35.0 versus 107.4; P < .001). When we differentiated the population according to collateral status (0.1 versus 2.3), the sedation modes conscious sedation and general anesthesia were not associated with significant differences in the predictive value of collateral status regarding infarction size or functional outcome.

CONCLUSIONS: The sedation mode, conscious sedation or general anesthesia, did not influence the predictive value of collaterals in patients with large-vessel occlusion anterior circulation stroke undergoing thrombectomy in the SIESTA trial.

ABBREVIATIONS: EST = endovascular stroke treatment; CS = conscious sedation; GA = general anesthesia; RCT = randomized trial; SIESTA = Sedation versus Intubation for Endovascular Stroke TreAtment; Tan = collateral score of Tan et al.

Endovascular stroke treatment (EST) is now the first choice for acute ischemic stroke in the anterior circulation caused by large-vessel occlusion. However, selection criteria to identify patients likely to benefit from EST outside highly selective randomized trials (RCTs) are still controversial. It is also important to establish practicable selection criteria for thrombectomy failure to exclude patients prone to futility and save financial, facility, and personnel resources and, above all, avoid complications like cerebral reperfusion injuries.

Current data suggest that collateral blood flow status is a strong independent predictor of therapeutic success and functional outcome after EST. By a network of pre-existing anastomoses, compensatory cerebral collateral blood flow supplies oxygen-deprived brain areas to which the primary flow path is blocked due to large-vessel occlusion. The recently published post hoc analysis on the collateralization status from the seminal thrombectomy trial MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands) showed the highest interventional therapeutic effect in patients with moderate-to-good collateral blood flow.

Why should the chosen sedation/airway regimen influence the impact of collateralization during EST? Collateral effects depend on cerebral perfusion pressure and vasomotor regulation of the vessel diameter. On the one hand, intubation and general anesthesia (GA) are often associated with a substantial drop in blood pressure as was shown in previous EST studies. It is quite

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S. Schönenerberger and J. Pfaff contributed equally to this work.

The study was performed with departmental funding only.

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Indicates article with supplemental on-line tables.

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likely that hypotension may compromise even patients with a good collateral status, particularly if their cerebral autoregulation is impaired as is often the case in severe acute ischemic stroke. Moreover, inadvertent mechanical hyperventilation and subsequent hypocarbia can lead to cerebral vasoconstriction. Both hypotension and hypocarbia associated with GA may have disadvantageous effects on the insufficiently supplied penumbra. Indeed, many retrospective studies have suggested worse outcome and mortality associated with GA in EST. On the other hand, steering GA in ways that stabilize circulation and aim for normocarbia may theoretically serve to improve collateralization.

We recently conducted the Sedation versus Intubation for Endovascular Stroke TreAtment (SIESTA) study to compare GA with conscious sedation (CS) during EST. In that first RCT on peri-interventional management, strict target values for physiologic parameters, including blood pressure and CO₂, were predefined for both treatment groups, mainly to avoid hypocarbia and hypotension. SIESTA showed no difference between GA and CS with regard to early neurologic improvement measured by the NIHSS after 24 hours, and unadjusted long-term outcome was even better in patients in the GA group. Of note, SIESTA was not powered and designed to primarily investigate long-term functional outcome, and slight imbalances in reperfusion grades, for example, may still have influenced that result even though the results were not statistically significant. This result was in strong contrast to most previous, yet retrospective, studies on the subject.

Why was GA not inferior in SIESTA? We hypothesized that the protocolized way GA was conducted may not have compromised or even improved collateralization. In this post hoc analysis of imaging data from the SIESTA study, we mainly aimed to investigate whether the predictive value of collateral status for infarct volume and outcome is affected by the applied sedation mode (CS versus GA) and, more specifically, whether patients under a very standardized GA may have shown a favorable course despite a suboptimal collateral status at baseline.

MATERIALS AND METHODS

Design of the SIESTA Trial
Patient eligibility and the methods, including the study protocol, were previously published.

Briefly, SIESTA was a monocentric, prospective, randomized, parallel-group, open-label treatment trial with blinded end point evaluation. Patients with an NIHSS score of >10 and isolated or combined occlusion of the internal carotid artery or middle cerebral artery selected for EST were randomized 1:1 to either the nonintubated state in CS or to the intubated state in GA. The trial was approved by our institutional review board (Ethikkommission Medizinische Fakultät Heidelberg, ID S-650/2013).

Main Outcomes of the SIESTA Trial
The main finding of SIESTA was no superiority of CS versus GA with regard to early neurologic improvement (change in the NIHSS score from admission to 24 hours thereafter). There were no differences in most secondary outcomes between the groups either (including in-hospital and 3-month mortality, and variables of peri-interventional safety and feasibility).

Secondary radiologic outcomes relevant to the present analysis included the ASPECTS, the collateral status based on CTA on admission described by Tan et al., the modified TICCI score based on DSA at the end of EST, and the final infarct volume on follow-up CT at 18–24 hours after EST. Only patients with a full dataset (baseline CT including CTA, ASPECTS before EST, and follow-up CT within 18–24 hours after onset) were included in this post hoc analysis. More details and definitions can be found in the earlier publication of the SIESTA protocol.

Imaging Data Assessment and Analysis
All CT and CTA data were evaluated by 2 independent, experienced neuroradiologists who were blinded to clinical findings, type of anesthesia, and infarction side (J.P., M.A.M.). The ASPECTS score, which ranges from 0 to 10, was used as a quantitative measure of areas with early infarction signs, with higher scores indicating fewer ischemic changes.

Collaterals of the CTA source images were evaluated with the collateral score of Tan et al. and divided into the 4 categories: 0 (no collaterals; no filling of the occluded area), 1 (poor collaterals; >0% but <50% filling of the occluded area), 2 (moderate collaterals; >50% but <100% filling of the occluded area), and 3 (good collaterals; 100% filling of the occluded area), yielding the 2 groups with scores of 0–1 and 2–3. CTA was mostly performed in combination with noncontrast CT as part of our in-house protocol for stroke imaging but was sometimes repeated in patients transferred from other hospitals after external CTA. The latter was then used as a baseline for EST. Patients without a baseline CTA and ASPECTS were excluded from this analysis.

Statistical Analysis
For continuous data, mean (±SD) and median (interquartile range) values are presented. Absolute and relative frequencies are given for categoric and ordinal variables. In a first explorative analysis, patients were divided into 2 Tan groups: good-to-moderate versus poor collaterals (0–1 versus 2–3). To test for differences between the groups, we applied t tests, χ² tests, and Mann-Whitney U tests, as appropriate. In a second step, we divided the 2 groups into subgroups according to treatment arm in the SIESTA trial (CS or GA). Again, a descriptive analysis and tests were applied to look for any differences within the subgroups. In a third step, we applied linear and logistic regression analyses to examine the predictive value of Tan, ASPECTS, and the randomization arm on the NIHSS score after 24 hours; the mRS after 3 months; and final infarct volume. In addition, we added an interaction term between Tan and the randomization variable that was only included in the final model if it showed a significant influence on the outcome value. In a final step, Pearson or Spearman correlations of improvement of NIHSS, Tan, final infarct volume, and ASPECTS were estimated. We also conducted post hoc power analyses.

A P value < .05 was considered statistically significant. Because this was an explorative study, no adjustment for multiple testing was performed. For statistical analyses, we used SAS software (SAS Institute, Cary, North Carolina), Version 9.4, and R, Version 3.3.1.
RESULTS

Patient Characteristics

For the present analysis, 104 of 150 patients in SIESTA fulfilled the study-specific inclusion criteria. Of the 46 excluded patients, 43 had not received a baseline CTA before EST, and in 3, the final infarct volume after EST could not be determined due to symptomatic hemorrhage. The group with Tan 2–3 had a significantly better ASPECTS (P < .001); 83.9% had an ASPECTS of 8–10 compared with only 50% with Tan 0–1. The group with Tan 2–3 had a significantly poorer pre-mRS (P = .02) compared with Tan 0–1. Eight patients had to be converted from CS to GA (5 Tan 0–1 and 3 Tan 2–3). Further baseline, demographic, and clinical characteristics of the 2 collateral groups are shown in Table 1.

Outcomes According to Collateral Status

Tan 0–1 was associated with a significantly higher mean final infarct size (107.4 versus 35.0 cm³; P < .001) compared with Tan 2–3. A statistically significant improvement in the mean NIHSS score after 24 hours was found in patients with Tan 2–3 (mean, −5.8 ± 7.6 versus −1.1 ± 10.7; P = .01). Functional independence after 3 months measured by mRS 0–2 was not significantly different. Significantly lower in-house mortality (14.6% versus 1.8%, P = .02), but no higher 3-month mortality (26.8% versus 25%, P = .84) was found in Tan 2–3. Finally, the mean length of stay of patients with Tan 2–3 in the neuro-intensive care unit was significantly shorter (mean values, 2.7 versus 8.2 days; P < .001). The post hoc power analysis comparing Tan 0–1 versus 2–3 showed a power of 73.4% for the improvement of the NIHSS score after 24 hours, 99.6% for infarct size, and 68.5% for in-house mortality. There were no significant differences in the analysis of short-term peri-interventional safety and feasibility parameters between the collateral groups (Table 2).

Impact of Collateralization According to Sedation Mode

When the 2 collateralization groups were further subdivided according to the applied sedation mode used in SIESTA (CS versus GA), the only baseline difference was that patients with Tan 0–1 treated with GA were younger (mean, 75.5 versus 68.8 years; P < .005). Most outcomes were not different in comparison.

In the subgroup with Tan 0–1, the only significant differences were more long-term functional independence (mRS after 3 months dichotomized to 0–2 and 3–6, CS 8.7% versus GA 32%; P = .05) and more delayed extubations (17.4% versus 52%; P = .01) in GA.

In the group with Tan 2–3, the GA subgroup was associated with a significantly longer mean time to treatment (104.3 versus 152.0 minutes; P = .01), higher ASPECTS (P = .05), a higher rate of hypothermia (10.3% versus 33%, P = .04), and a higher rate of delayed extubation (3.4% versus 40.7%, P < .001). The post hoc power to detect differences between CS and GA was 51% for Tan 0–1 versus 28.5% for Tan 2–3 regarding mRS 0–2 after 3 months (On-line Table 1).

Association of Sedation Modes with Outcome Prediction by Radiologic Scores

Correlation analysis for the entire cohort showed only an association between infarct volume and NIHSS change after 24 hours (r = 0.58) and between infarct volume and ASPECTS (ρ = 0.6). An additional correlation analysis according to the applied sedation mode showed a moderate correlation between early NIHSS improvement and infarct volume (r = 0.71) and ASPECTS and infarct volume (ρ = −0.62) in the GA treatment group (On-line Table 2). Correlation analysis in the CS treatment group showed only a correlation between early NIHSS improvement and the mRS after 3 months (ρ = 0.61).

Regression analysis revealed that the presence of a moderate or good collateral status and favorable ASPECTS were strong predictors for smaller final mean infarct volume (coefficients: −51.75; 0.62) in the GA treatment group (On-line Table 2).

Table 1: Baseline demographic and clinical characteristics according to no or poor (Tan 0–1) and moderate or good collaterals (Tan 2–3)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Tan 0–1 (n = 48)</th>
<th>Tan 2–3 (n = 56)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (mean) (SD) (yr)</td>
<td>72.0 (8.7)</td>
<td>73.7 (4.3)</td>
<td>.52a</td>
</tr>
<tr>
<td>Female sex (No.) (%)</td>
<td>17 (35.4)</td>
<td>23 (41.1)</td>
<td>.56b</td>
</tr>
<tr>
<td>Premedication (No.) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelets</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>33 (71.7)</td>
<td>38 (69.3)</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>12 (26.1)</td>
<td>13 (23.6)</td>
<td></td>
</tr>
<tr>
<td>Dual</td>
<td>1 (2.2)</td>
<td>4 (7.3)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Oral anticoagulants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>42 (89.4)</td>
<td>36 (65.5)</td>
<td>.01b</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>37 (80.4)</td>
<td>30 (56.6)</td>
<td>.01b</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Vascular risk factors (No.) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>37 (77.1)</td>
<td>37 (66.3)</td>
<td>.22</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>13 (27.1)</td>
<td>10 (17.4)</td>
<td>.26</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>12 (25.0)</td>
<td>17 (30.4)</td>
<td>.54</td>
</tr>
<tr>
<td>Smokingc</td>
<td>11 (23.4)</td>
<td>4 (7.1)</td>
<td>.02b</td>
</tr>
<tr>
<td>Heart failure</td>
<td>10 (20.8)</td>
<td>19 (32.9)</td>
<td>.14b</td>
</tr>
<tr>
<td>Attrial fibrillation</td>
<td>24 (50.0)</td>
<td>30 (53.6)</td>
<td>.73b</td>
</tr>
<tr>
<td>Peripheral artery occlusive disease</td>
<td>1 (2.1)</td>
<td>4 (7.4)</td>
<td>.21b</td>
</tr>
<tr>
<td>Pretreatment imaging (No.) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASPECTS</td>
<td></td>
<td></td>
<td>&lt;.001b</td>
</tr>
<tr>
<td>10–8</td>
<td>24 (50)</td>
<td>47 (83.9)</td>
<td></td>
</tr>
<tr>
<td>7–6</td>
<td>22 (45.8)</td>
<td>7 (12.5)</td>
<td></td>
</tr>
<tr>
<td>&lt;6</td>
<td>2 (4.2)</td>
<td>2 (3.6)</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>2 (7–9)</td>
<td>2 (8–10)</td>
<td></td>
</tr>
<tr>
<td>Infarct volume (mean) (SD) (cm³)</td>
<td>107.4 (99.1)</td>
<td>35.0 (55.1)</td>
<td>&lt;.001a</td>
</tr>
<tr>
<td>Scores on admission (No.) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premorbid mRS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>30 (62.5)</td>
<td>24 (42.9)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>11 (22.9)</td>
<td>10 (17.9)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4 (8.3)</td>
<td>14 (25)</td>
<td></td>
</tr>
<tr>
<td>&gt;2</td>
<td>3 (6.3)</td>
<td>8 (14.3)</td>
<td></td>
</tr>
<tr>
<td>NIHSS on admission</td>
<td>17.9 (3.6)</td>
<td>16.9 (3.7)</td>
<td>.14a</td>
</tr>
<tr>
<td>GC/CS on admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>6 (12.5)</td>
<td>2 (3.6)</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>21 (43.8)</td>
<td>31 (55.4)</td>
<td></td>
</tr>
<tr>
<td>15–14</td>
<td>21 (43.8)</td>
<td>23 (41.2)</td>
<td></td>
</tr>
<tr>
<td>Occlusion (No.) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCA</td>
<td>26 (54.2)</td>
<td>39 (69.6)</td>
<td>.08b</td>
</tr>
<tr>
<td>ICA</td>
<td>3 (6.3)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>ICA + MCA</td>
<td>19 (39.6)</td>
<td>17 (30.4)</td>
<td></td>
</tr>
<tr>
<td>Occlusion side right</td>
<td>22 (45.8)</td>
<td>23 (44.1)</td>
<td>.63b</td>
</tr>
<tr>
<td>Treatment of stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV tPA + EST</td>
<td>32 (66.7)</td>
<td>31 (55.4)</td>
<td></td>
</tr>
<tr>
<td>EST</td>
<td>16 (33.3)</td>
<td>23 (44.4)</td>
<td></td>
</tr>
</tbody>
</table>

Note:—GCS indicates Glasgow Coma Scale; IQR, interquartile range.

*a* 1 t-test, 2-sided.

*b* χ² test, 3-sided.

*c* Lower sample size in Tan group 0–1 (n = 47).

d Lower sample size in Tan group 0–1 (n = 47) and Tan group 2–3 (n = 54).

e Mann–Whitney U test, 2-sided.

(r = 0.58) and between infarct volume and ASPECTS (ρ = −0.6). An additional correlation analysis according to the applied sedation mode showed a moderate correlation between early NIHSS improvement and infarct volume (r = 0.71) and ASPECTS and infarct volume (ρ = −0.62) in the GA treatment group (On-line Table 2). Correlation analysis in the CS treatment group showed only a correlation between early NIHSS improvement and the mRS after 3 months (ρ = 0.61).

Regression analysis revealed that the presence of a moderate or good collateral status and favorable ASPECTS were strong predictors for smaller final mean infarct volume (coefficients: −51.75; 0.62).
Table 2: SIESTA primary and secondary outcome results according to no or poor (Tan 0–1) and moderate or good collaterals (Tan 2–3)

<table>
<thead>
<tr>
<th></th>
<th>Tan 0–1 (n = 48)</th>
<th>Tan 2–3 (n = 56)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improvement in NIHSS (mean) (SD)</td>
<td>-1.1 (0.7)</td>
<td>-5.8 (7.6)</td>
<td>.01*</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical (No.) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS 0–2 after 3 mo</td>
<td>10 (20.8)</td>
<td>14 (25.0)</td>
<td>.82*</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>7 (14.6)</td>
<td>1 (1.8)</td>
<td>.02*</td>
</tr>
<tr>
<td>Mortality after 3 mo</td>
<td>12 (25.0)</td>
<td>15 (26.8)</td>
<td>.84*</td>
</tr>
<tr>
<td><strong>Logistics (mean) (SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of stay in hospital (days)</td>
<td>6.0 (3.7)</td>
<td>4.6 (2.6)</td>
<td>.06*</td>
</tr>
<tr>
<td>Length of stay in ICU (half-days)*</td>
<td>8.2 (9.2)</td>
<td>2.7 (2.2)</td>
<td>&lt;.0001*</td>
</tr>
<tr>
<td>Length of ventilation (hr)</td>
<td>30.1 (5.9)</td>
<td>3.8 (5.4)</td>
<td>.11*</td>
</tr>
<tr>
<td>Length of stay on stroke unit (half-days)†</td>
<td>7.6 (4.3)</td>
<td>7.0 (4.3)</td>
<td>.5*</td>
</tr>
<tr>
<td>Door-to-treatment (IV or IA) (min)*</td>
<td>122.8 (64.8)</td>
<td>129.6 (60.9)</td>
<td>.61†</td>
</tr>
<tr>
<td>Door-to-groin (min)</td>
<td>71.5 (32.1)</td>
<td>66.1 (21.4)</td>
<td>.52†</td>
</tr>
<tr>
<td>Feasibility of EST (No.) (%)</td>
<td>174.8 (57.1)</td>
<td>165.6 (60.5)</td>
<td>.32†</td>
</tr>
<tr>
<td>Degree of reperfusion (TICI)</td>
<td></td>
<td></td>
<td>.97†</td>
</tr>
<tr>
<td>0–1</td>
<td>3 (6.3)</td>
<td>5 (9)</td>
<td></td>
</tr>
<tr>
<td>2a</td>
<td>4 (8.3)</td>
<td>3 (5.4)</td>
<td></td>
</tr>
<tr>
<td>2b</td>
<td>24 (50.0)</td>
<td>25 (44.6)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>17 (35.4)</td>
<td>23 (41.1)</td>
<td></td>
</tr>
<tr>
<td>Substantial patient movement</td>
<td>1 (2.1)</td>
<td>2 (3.6)</td>
<td>.65b</td>
</tr>
<tr>
<td>Difficult vascular approach</td>
<td>3 (6.3)</td>
<td>7 (12.5)</td>
<td>.28b</td>
</tr>
<tr>
<td>Other</td>
<td>3 (6.3)</td>
<td>8 (14.3)</td>
<td>.18b</td>
</tr>
<tr>
<td><strong>Safety (No.) (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complications before EST</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impaired monitor installation</td>
<td>0 (0.0)</td>
<td>1 (1.8)</td>
<td>.35b</td>
</tr>
<tr>
<td>Other</td>
<td>1 (2.1)</td>
<td>0 (0.0)</td>
<td>.27b</td>
</tr>
<tr>
<td>Complications during EST</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Critical ventilation or oxygenation disturbance</td>
<td>2 (4.2)</td>
<td>1 (1.8)</td>
<td>.47b</td>
</tr>
<tr>
<td>Intervention-associated complications</td>
<td>0 (0.0)</td>
<td>2 (3.6)</td>
<td>.19b</td>
</tr>
<tr>
<td>Vessel perforation with ICH and/or SAH complications after EST</td>
<td>0 (0.0)</td>
<td>2 (3.6)</td>
<td>.19b</td>
</tr>
<tr>
<td>Hyper- or hypothermia</td>
<td>12 (25.0)</td>
<td>12 (21.4)</td>
<td>.67b</td>
</tr>
<tr>
<td>Delayed extubation</td>
<td>17 (35.4)</td>
<td>12 (21.4)</td>
<td>.11b</td>
</tr>
<tr>
<td>Ventilation-associated complications</td>
<td>6 (12.5)</td>
<td>3 (5.4)</td>
<td>.2b</td>
</tr>
<tr>
<td>Ventilation-associated pneumonia</td>
<td>6 (12.5)</td>
<td>3 (5.4)</td>
<td>.2b</td>
</tr>
</tbody>
</table>

Note: IA indicates intra-arterial; min, minimum; max, maximum; ICH, intracerebral hemorrhage; ICU, intensive care unit.

* ANCOVA, NIHSS as baseline covariate.
† t test, 2-sided.
* Mann-Whitney U test, 2-sided.
+ Lower sample size (41 and 46).
+ Lower sample size (41 and 50).
+ Lower sample size (41 and 47).
+ Lower sample size (45 and 49).
carboxy and cerebral vasodilatation or at least stabilization of nor-mocarboxy may have improved the function of the few collateral-
als that remained. Alternative mechanisms may have been the
potential neuroprotective effects of the applied sedatives21 or
the significantly higher rate of hypothermia under GA. These
speculations, however, demand further prospective mechanis-
tically designed studies to assess how GA is best conducted
during EST.

Our study has several limitations. First, SIESTA was a single-
center study, and its findings are difficult to generalize; the same
is true for post hoc analyses. Second, very small sample sizes of the
subgroups limit insights from this exploratory study. Third, in
SIESTA, exclusively single-phase CTAs were conducted, which
could have led to insufficient categorization of collateralization
concerning temporal collaterals. Finally, interpretation of the
CTAs may have been influenced by high-grade stenoses of the ICA
or a pre-existent congestive heart failure for which we had not
controlled.

CONCLUSIONS

Our results suggest that the benefit from thrombectomy can be
expected in patients with moderate and, especially, good collateral-
als largely irrespective of the chosen sedation mode, if both gen-
eral anesthesia and conscious sedation are performed according
to protocols involving physiology parameter targets. It is still pos-
sible that a suboptimally performed GA during EST may elimi-
inate the advantages of a good collateral status.

More prospective, multicenter studies with higher numbers of
patients are necessary to clarify whether patients, particularly
those with poor collateral statuses, may benefit from certain
neuroprotective effects of GA or other sedation modes during
thrombectomy.

Disclosures: Johannes Pfaff—UNRELATED: Payment for Lectures Including Service on
Speakers Bureau: Siemens; Travel/Accommodations/Meeting Expenses Unre-
lated to Activities Listed: Stryker. Simon Nagel—UNRELATED: Consultancy: Brain-
mix; Grants/Grants Pending: Brainmix*; Payment for Lectures Including Service on
Speakers Bureau: Medtronic, Pfizer, Bayer; Travel/Accommodations/Meeting Ex-
penses Unrelated to Activities Listed: Bayer, Boehringer Ingelheim, Medtronic, Pfizer.
Peter A. Ringleb—UNRELATED: Consultancy: Bayer, Boehringer Ingelheim, Covidiem,
Comments: Advisory Board member; Payment for Lectures Including Service on
Speakers Bureau: Medtronic; Travel/Accommodations/Meeting Expenses Unre-
lated to Activities Listed: Medtronic, Pfizer, Werner Hacke—UNRELATED: Consultancy: Boehringer Ingelheim, Medtronic, Neuravi, Grants/Grants Pending: Boehringer Ingelheim, Comments:
grant for ECASS 4 study*; Payment for Lectures Including Service on Speakers Bu-
reau: Boehringer Ingelheim, Medtronic, Daichi Sanyo, Neuravi. Martin Bendszus—
UNRELATED: Board Membership: Data and Safety Monitoring Board for Vascular
Dynamics, Guebert, Boehringer Ingelheim; Consultancy: Codman, Hoffmann-La
Roche, Guebert, Boehringer Ingelheim; Comments: speaker honoraria and travel
support; Travel/Accommoda-
tions/Meeting Expenses Unrelated to Activities Listed: C.R. BARD, ZOLL, Stryker,
Boehringer Ingelheim, Sedana Medical, Comments: speaker honoraria and travel
support; Travel/Accommoda-
tions/Meeting Expenses Unrelated to Activities Listed: C.R. BARD, ZOLL, Stryker,
Boehringer Ingelheim, Sedana Medical. *Money paid to the institution.

REFERENCES

meta-analysis of individual patient data from five randomised tri-
from ischemic stroke: a meta-analysis. JAMA 2016;316:1279–88
CrossRef Medline
endovascular therapy for acute ischemic stroke. Stroke 2011;42:
693–9 CrossRef Medline
Management of Stroke (IMS) III trial. Stroke 2014;45:759–64
CrossRef Medline
phy and intra-arterial treatment effect in patients with proximal ante-
induction of general anesthesia. Anesth Analg 2005;101:
622–28 Medline
tory parameter guided anesthesia in patients with ischemic stroke
undergoing endovascular recanalization. J Neurointerv Surg 2016;8:
335–41 CrossRef Medline
during endovascular treatment of ischemic stroke is a risk factor
Medline
Anesthetic management and outcome in patients during endovas-
cular therapy for acute stroke. Anesthesiology 2012;116:396–405
CrossRef Medline
11. Takahashi CE, Brambrink AM, Aziz MF, et al. Association of intrap-
rocedural blood pressure and end tidal carbon dioxide with out-
come after acute stroke intervention. Neurocrit Care 2014;20:
202–08 CrossRef Medline
versus general anesthesia during endovascular acute ischemic
stroke treatment: a systematic review and meta-analysis. AJNR Am
tion for Endovascular Stroke TreAtment (SIESTA); a randomized
sedation vs general anesthesia on early neurological improvement
among patients with ischemic stroke undergoing endovascular
thrombectomy: a randomized clinical trial. JAMA 2016;316:
1986–96 CrossRef Medline
15. Menon BK, Puetz V, Kochar P, et al. ASPECTS and other neuroim-
aging scores in the triage and prediction of outcome in acute stroke
16. Tan IY, Demchuk AM, Hopyan J, et al. CT angiography clot burden
score and collateral score: correlation with clinical and radiologic
outcomes in acute middle cerebral artery infarct. AJNR Am J Neu-
oradiol 2009;30:525–31 Medline
17. Tomrick T, Broderick J, Carrozella J, et al; Interventional Manage-
ment of Stroke II Investigators. Revascularization results in the
Interventional Management of Stroke II trial. AJNR Am J Neuroradiol
2008;29:852–87 Medline
18. Zaidat OO, Yoo AJ, Khatri P, et al; Cerebral Angiographic Revascu-
larization Grading (CARG) Collaborators, STIR Revascularization
working group, STIR Thrombolysis in Cerebral Infarction (TICI) Task
Force. Recommendations on angiographic revascularization grading
standards for acute ischemic stroke: a consensus state-
ment. Stroke 2013;44:2650–63 CrossRef Medline
19. The R Core Team. A Language and Environment for Statistical Com-


Effect of Retrievable Stent Size on Endovascular Treatment of Acute Ischemic Stroke: A Multicenter Study


ABSTRACT

BACKGROUND AND PURPOSE: In clinical practice, stent diameter is one of the variable properties important for endovascular treatment. A consensus guideline for stent retriever size selection has yet to be established. The aim of this study was to investigate the effects of different diameters of Solitaire retrievers on outcomes.

MATERIALS AND METHODS: Of 628 patients enrolled from the Endovascular Treatment for Acute Anterior Circulation Ischemic Stroke Registry, 256 were treated with the Solitaire 4-mm device and 372, with the 6-mm device. We matched patients treated with the 2 stent sizes using propensity score analysis. The successful outcome was reperfusion as measured by the modified Thrombolysis in Cerebral Infarction score immediately postprocedure and the dichotomized modified Rankin Scale score at 90 days. Symptomatic intracerebral hemorrhage and in-hospital mortality were also recorded.

RESULTS: After propensity score analysis, group outcomes did not differ. In addition, in patients with atherosclerosis-related occlusion, a higher reperfusion rate \( (P = .021) \) was observed in the Solitaire 4 group, as well as a shorter time interval \( (P = .025) \). Independent predictors of successful reperfusion in patients with atherosclerotic disease on logistic analysis were the small stent \( \text{OR, 3.217; 95\% CI, 1.129–9.162; } P = .025 \). In patients with atherosclerotic disease, favorable reperfusion was associated with deployment of a small stent.

CONCLUSIONS: We found no evidence of a differential effect of intra-arterial therapy based on the size of Solitaire retrievers. In patients with atherosclerotic disease, favorable reperfusion was associated with deployment of a small stent.

ORIGIN AL RESEARCH INTERVENTIONAL

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large-vessel occlusion accounts for 28%–46% of all ischemic strokes and leads to poor prognosis and high mortality. Since 2015, the results of several clinical randomized trials have suggested that intra-arterial treatment is safe and effective for anterior circulation large-vessel occlusion. The success also demonstrated the benefit of newer stent devices in endovascular recanlization therapies because most patients were treated with retrievable stents in these trials.

In these trials, most devices used for mechanical thrombectomy were retrievable stents such as the Solitaire FR (Covidien, Irvine, California) or the Trevo retriever (Stryker, Kalamazoo, Michigan). The Solitaire is a self-expanding and retrievable stentlike device that restores blood flow immediately by thrombus entrapment between the stent struts and the vessel wall, achieving substantially better safety and efficacy outcomes than former
devices. This device was first designed for aneurysms, with a variety of diameters made available to meet the needs of different sizes of intracranial vessels. For mechanical thrombectomy, stents with 4- and 6-mm diameters delivered through 0.021- and 0.027-inch microcatheters, respectively, optimize performance in intracranial large vessels in present day interventional therapy. The Trevo retriever is structurally similar to the Solitaire FR, with a stent cell geometry designed to integrate the clot into the stent for retrieval.

It has been reported that a difference in stent size potentially influences stent properties, including radial force, flexibility, and deliverability. The radial force represents the supporting action of the stent on the vessel wall to prevent elastic retraction, while flexibility and deliverability exemplify the ability to pass through the occluded site. Several studies have found that a stent with a large radial force is suitable for proximal vessels and atherosclerotic modified vessels with hardened or calcified plaque, while a more flexible stent should be used in a tortuous or distant vessel.

In addition, extensive evidence shows that the stent diameter is associated with in-stent restenosis and change in blood flow after intracranial stent implantation, as well as adverse events after percutaneous coronary intervention. These results demonstrated the impact of stent size on vascular interventional therapy and also showed the importance and necessity of research on device size in mechanical thrombectomy. However, as yet there is no established guideline for stent selection, with the choice being left entirely to the interventionist. Hence, uncertainties remain about the benefit and risk of endovascular intervention in relation to different sizes of stents. This study addresses the uncertainties regarding stent size for thrombectomy.

**MATERIALS AND METHODS**

**Study Design and Participants**

This is a retrospective observational study on the efficacy and safety of endovascular treatment of acute ischemic stroke in real-world practice. We aimed to evaluate the impact of the sizes of stentlike thrombectomy devices on the outcome of treated patients with ischemic stroke due to large-vessel occlusion of the anterior circulation. Patients were those registered in the Endovascular Treatment for Acute Anterior Circulation Ischemic Stroke Registry (ACTUAL) from January 2014, to June 2016. ACTUAL was a multicenter registry program involving 21 comprehensive stroke centers across 10 provinces in China. All patients with acute ischemic stroke who underwent intra-arterial treatment were registered in ACTUAL. The local ethics committees approved the use of retrospective patient data. The procedure protocol was standardized in each center.

Generally, patients would receive endovascular treatment under the following conditions: (1) They were diagnosed with acute ischemic stroke; (2) had large-artery occlusion in the anterior circulation, including the internal carotid artery, middle cerebral artery (MCA M1 or M2), or anterior cerebral artery A1 or A2; (3) had evidence obtained by CTA, MR angiography, or digital subtraction angiography; (4) were 18 years of age or older; (5) had a premorbid modified Rankin Scale score of <2; (6) had a pretreatment National Institutes of Health Stroke Scale score of ≥5; and (7) could be treated within 6 hours of stroke onset. For selected patients who did not meet these criteria, endovascular treatment was still performed on the basis of a favorable benefit-risk ratio estimate.

To retain the homogeneity of the enrolled patients, we excluded patients treated with intra-arterial thrombolysis alone, or diagnosed with concomitant aneurysm or arteriovenous malformations. For the present study, we selected patients treated with retrievable stents.

**Patients**

Of 698 patients from ACTUAL, 44 accepted angioplasty therapy and/or stent placement alone, 5 were treated with a thrombus aspiration device alone, 17 were treated with a microguidewire to disrupt clots alone, and 4 were fitted with the Trevo retriever rather than the Solitaire retriever. To maintain consistency of device type, we excluded patients treated with the Trevo retriever. Ultimately, a study cohort of 628 patients treated with the Solitaire stent retriever was enrolled.

**Procedures**

If they met the criteria for intravenous thrombolytic therapy, patients received intravenous therapy with alteplase within 4.5 hours after the onset of stroke before mechanical treatment. Patients beyond a time window of 4.5 hours or with a contraindication to intravenous thrombolysis were treated directly with mechanical treatment.

Regarding mechanical therapy, patients were treated via femoral access. Under roadmap guidance, a microcatheter was advanced over a guidewire placed through the thrombus, after which the guidewire was removed and DSA was performed to confirm the occlusion. Next, the Solitaire retriever was advanced through the microcatheter across the occluded segment. The stent was unsheathed simultaneous to the microcatheter being pulled back. After 3–5 minutes to allow full expansion, the stent was withdrawn along with the microcatheter. If occlusion persisted, the sequence was repeated (Fig 1).

Choices of anesthesia and rescue therapy were left to the discretion of the interventionist. Stent selection depended on vascular tortuous morphology and sites of occluded vessels in general. A large stent was preferred in a proximal or straight artery, while a small stent was usually chosen for tortuous or distant arteries. The preference of the operator was also important for stent selection.

**Outcomes**

Successful outcome was defined as achieving a modified TICI (mTICI) score of 2b–3 immediately postprocedure and a functional outcome at 90 days evaluated with the dichotomized modified Rankin Scale score (0–2 versus 3–6). Rates of in-hospital mortality and symptomatic intracerebral hemorrhage within 72 hours after endovascular treatment were recorded. Symptomatic intracerebral hemorrhage was diagnosed according to the Heidelberg Bleeding Classification. Technical complications with the device were also recorded, including vessel perforation, vessel dissection, subarachnoid hemorrhage, stent fracture, and failure to deploy. Outpatient or telephone follow-up was performed to assess the functional outcome by mRS score at each institution.
Statistical Analysis

Univariate analysis of baseline characteristics was compared between 2 groups according to stent diameter (4-mm Solitaire stent retriever [ST 4] versus 6 mm [ST 6]) with the Student t test (normal distribution) or the Mann-Whitney test (non–normal distribution) for continuous variables and a χ² test for categoric variables. In primary analysis, baseline variables differed statistically between the 2 groups. To control bias and minimize imbalance of baseline characteristics, we performed a 1:1 matched model based on the propensity score with the nearest neighbor matching algorithm without replacement. We compared patients treated with ST 4 and ST 6 using the Wilcoxon signed rank test and the McNemar test after matching. In addition, matched models of stroke subtype and vessel occlusion site were performed to conduct subgroup analysis. Furthermore, a logistic regression model with the propensity score as a covariate was computed to evaluate the effect of device choice.

The data were analyzed by SPSS Statistics, Version 22.0 (IBM, Armonk, New York), R statistical and computing software (Version 2.153; http://www.r-project.org/), SPSS Statistics–Essentials for R 22 (https://sourceforge.net/projects/ibmspssstat/), and PS-MATCHING 3.03 (SPSS Statistics extension bundle document; https://sourceforge.net/projects/psmspss/). Two-sided P values < .05 were statistically significant.

RESULTS

Study Population

Of the 628 enrolled patients, 59.2% (372/628) were treated with 4-mm, and 40.6% (256/628), with 6-mm Solitaire retrievers. There were 58.3% (366/628) men, and the average age was 66 years (range, 56–74 years). The median baseline NIHSS score was 17 (range, 12–21). Delay from symptom onset to door of the emergency department was 125 minutes (60–222 minutes). Delay from stroke onset to groin puncture was 270 minutes (205–350 minutes). When successful recanalization was defined as an mTICI score of 2b or 3, 84.4% (530/628) of the enrolled patients obtained successful recanalization of the targeting artery after endovascular treatment. In these patients who were recanalized (84.4%), the median time from puncture to reperfusion was 102 minutes (75–144 minutes). The proportion of patients with an mRS score of 0–2 at 90 days was 41.7% (262/628). Symptomatic intracerebral hemorrhage occurred in 16.1% (101/628) of patients within 24 hours after endovascular treatment, and death occurred in 24.2% (152/628) of patients. Device-related complications included vessel perforation, 1.3% (8/628); vessel dissection, 1.4% (9/628); subarachnoid hemorrhage, 2.1% (13/628); stent fracture, 0.2% (1/628); and failure to deploy, 0.2% (1/628).

Baseline Characteristics

Univariate analysis of baseline data suggested that no difference existed between the 2 groups except for the following: age (ST 6, 68 years; interquartile range [IQR], 58–75 years; ST 4, 64 years; IQR, 53–73 years; P = .003); atrial fibrillation (ST 6, 51.2%; ST 4, 37.2%; P < .001); ASPECTS (ST 6, 9; IQR, 7–10; ST 4, 9; IQR, 8–10; P < .001); NIHSS (ST 6, 17; IQR, 13–21; ST 4, 16; IQR, 12–20; P = .029); atherosclerotic occlusions (ST 6, 37.1%; ST 4, 46%; P = .027); cardiac embolism occlusions (ST 6, 57%; ST 4, 47.5%; P = .02); ICA occlusions (ST 6, 60.5%; ST 4, 23.1%; P < .001); MCA occlusions (ST 6, 39.1%; ST 4, 76.3%; P < .001); and favorable collateral flow (American Society of Interventional and Therapeutic Neuroradiology, Society of Interventional Radiology grade), 2–3 (ST 6, 38.8%; ST 4, 57.8%; P < .001). Baseline characteristics are summarized in Table 1.
Table 1: Baseline characteristics before and after matching

<table>
<thead>
<tr>
<th></th>
<th>Before Matching</th>
<th>After Matching</th>
<th>P</th>
<th>Before Matching</th>
<th>After Matching</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ST 6 (n = 256)</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>ST 4 (n = 372)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (median) (IQR) (yr)</td>
<td>68 (58–75)</td>
<td>64 (53–73)</td>
<td>.003</td>
<td>67 (56–75)</td>
<td>64 (53–73)</td>
<td>.103</td>
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<tr>
<td>Women (No.) (%)</td>
<td>112 (43.8%)</td>
<td>150 (40.3%)</td>
<td>.392</td>
<td>71 (42%)</td>
<td>64 (37.9%)</td>
<td>.505</td>
</tr>
<tr>
<td>AF (No.) (%)</td>
<td>131 (51.2%)</td>
<td>138 (37.2%)</td>
<td>.001</td>
<td>80 (47.3%)</td>
<td>67 (39.6%)</td>
<td>.160</td>
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<td>Hypertension (No.) (%)</td>
<td>158 (61.7%)</td>
<td>231 (62.1%)</td>
<td>.924</td>
<td>112 (66.3%)</td>
<td>105 (62.1%)</td>
<td>.500</td>
</tr>
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<td>Diabetes mellitus (No.) (%)</td>
<td>45 (17.6%)</td>
<td>66 (17.7%)</td>
<td>.958</td>
<td>35 (20.7%)</td>
<td>29 (17.2%)</td>
<td>.488</td>
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<td>Current smoker (No.) (%)</td>
<td>69 (27%)</td>
<td>92 (24.7%)</td>
<td>.531</td>
<td>49 (29%)</td>
<td>41 (24.3%)</td>
<td>.389</td>
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<td>SBP (median) (IQR) (mm Hg)</td>
<td>145 (130–160)</td>
<td>144 (130–160)</td>
<td>.537</td>
<td>148 (129–163)</td>
<td>148 (130–160)</td>
<td>.393</td>
</tr>
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<td>GLU (median) (IQR) (mmol/L)</td>
<td>6.9 (5.83–8.9)</td>
<td>6.7 (5.77–8.38)</td>
<td>.173</td>
<td>6.83 (5.6–9.25)</td>
<td>6.9 (5.81–8.69)</td>
<td>1.000</td>
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<tr>
<td>ASPECTS (median) (IQR)</td>
<td>9 (7–10)</td>
<td>9 (8–10)</td>
<td>.001</td>
<td>7 (7–10)</td>
<td>8 (8–10)</td>
<td>.784</td>
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<td>NIHSS (median) (IQR)</td>
<td>13 (7–21)</td>
<td>16 (12–20)</td>
<td>.029</td>
<td>17 (13–21)</td>
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<tr>
<td>IV (No.) (%)</td>
<td>81 (31.6%)</td>
<td>119 (32%)</td>
<td>.927</td>
<td>56 (33.1%)</td>
<td>61 (36.1%)</td>
<td>.657</td>
</tr>
<tr>
<td>Time from onset to visit (median) (IQR) (min)</td>
<td>130 (75–230)</td>
<td>120 (60–214)</td>
<td>.058</td>
<td>138 (64–224)</td>
<td>120 (58–214)</td>
<td>.316</td>
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<tr>
<td>Stroke subtype</td>
<td></td>
<td></td>
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<td>Atherosclerotic (No.) (%)</td>
<td>95 (37.1%)</td>
<td>171 (46%)</td>
<td>.027</td>
<td>68 (40.2%)</td>
<td>73 (43.2%)</td>
<td>.444</td>
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<td>Cardiac embolism (No.) (%)</td>
<td>146 (57%)</td>
<td>177 (47.5%)</td>
<td>.02</td>
<td>90 (53.3%)</td>
<td>85 (50.3%)</td>
<td>.657</td>
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<td>Undetermined etiology (No.) (%)</td>
<td>15 (5.9%)</td>
<td>24 (6.5%)</td>
<td>.763</td>
<td>11 (6.5%)</td>
<td>11 (6.5%)</td>
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<tr>
<td>Artery occlusion site</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td>ICA (No.) (%)</td>
<td>155 (60.5%)</td>
<td>86 (23.1%)</td>
<td>&lt;.001</td>
<td>78 (46.2%)</td>
<td>76 (45%)</td>
<td>.791</td>
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<td>MCA (No.) (%)</td>
<td>100 (39.1%)</td>
<td>284 (76.3%)</td>
<td>&lt;.001</td>
<td>90 (53.3%)</td>
<td>93 (55%)</td>
<td>.607</td>
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<tr>
<td>ACA (No.) (%)</td>
<td>1 (0.4%)</td>
<td>2 (0.5%)</td>
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<td>1 (0.6%)</td>
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<td>1.000</td>
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<td>Collateral flow grade (ASITN/SIR)</td>
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<tr>
<td>0–1 (No.) (%)</td>
<td>156 (61.2%)</td>
<td>156 (42.2%)</td>
<td>.099</td>
<td>93 (55%)</td>
<td>83 (49.1%)</td>
<td>.589</td>
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<tr>
<td>2–3 (No.) (%)</td>
<td>99 (38.8%)</td>
<td>214 (57.8%)</td>
<td>.001</td>
<td>76 (45%)</td>
<td>86 (50.9%)</td>
<td>.261</td>
</tr>
</tbody>
</table>

Note: ASITN/SIR indicates American Society of Interventional and Therapeutic Neuroradiology, Society of Interventional Radiology; AF, atrial fibrillation; GLU, glucose; ACA, anterior cerebral artery; SBP, systolic blood pressure.

Table 2: Clinical outcomes before and after matching

<table>
<thead>
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<th></th>
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<th>After Matching</th>
<th>P</th>
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<td><strong>ST 4 (n = 372)</strong></td>
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<tr>
<td>mTICI</td>
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<tr>
<td>0–2a (No.) (%)</td>
<td>51 (19.9%)</td>
<td>47 (12.6%)</td>
<td>.013</td>
<td>31 (18.3%)</td>
<td>26 (15.4%)</td>
<td>.532</td>
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<tr>
<td>2b–3 (No.) (%)</td>
<td>205 (80.1%)</td>
<td>325 (87.4%)</td>
<td>.003</td>
<td>138 (81.7%)</td>
<td>143 (84.6%)</td>
<td></td>
</tr>
<tr>
<td>Workflow time</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Time from puncture to reperfusion (median) (IQR) (min)</td>
<td>111.5 (80–153)</td>
<td>97 (72–140)</td>
<td>.007</td>
<td>108 (75–147)</td>
<td>100 (75–156)</td>
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<tr>
<td>Time from stent deployment to reperfusion (median) (IQR) (min)</td>
<td>61 (30–94)</td>
<td>44 (20–75)</td>
<td>.001</td>
<td>58 (30–87)</td>
<td>45 (21–82)</td>
<td>.021</td>
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<td>Passes (median) (IQR)</td>
<td>2 (1–3)</td>
<td>2 (1–3)</td>
<td>.001</td>
<td>2 (1–3)</td>
<td>2 (1–3)</td>
<td>.375</td>
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<tr>
<td>≤3 (No.) (%)</td>
<td>210 (82%)</td>
<td>323 (86.8%)</td>
<td>.099</td>
<td>106 (62.7%)</td>
<td>119 (70.4%)</td>
<td>.154</td>
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<td>Rescue therapy (No.) (%)</td>
<td>134 (52.3%)</td>
<td>184 (49.5%)</td>
<td>.478</td>
<td>85 (50.3%)</td>
<td>84 (49.7%)</td>
<td>1.000</td>
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<tr>
<td>Complications</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
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<td>Vessel dissection (No.) (%)</td>
<td>3 (1.2%)</td>
<td>6 (1.6%)</td>
<td>.744</td>
<td>2 (1.2%)</td>
<td>5 (3.0%)</td>
<td>.453</td>
</tr>
<tr>
<td>Arterial perforation (No.) (%)</td>
<td>2 (0.8%)</td>
<td>6 (1.6%)</td>
<td>.482</td>
<td>2 (1.2%)</td>
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<tr>
<td>Stent failure to deploy (No.) (%)</td>
<td>1 (0.4%)</td>
<td>0</td>
<td>.408</td>
<td>1 (0.6%)</td>
<td>0</td>
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<tr>
<td>Isolated SAH (No.) (%)</td>
<td>4 (1.6%)</td>
<td>9 (2.4%)</td>
<td>.459</td>
<td>3 (1.8%)</td>
<td>1 (0.6%)</td>
<td>.625</td>
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<tr>
<td>Symptomatic ICH (No.) (%)</td>
<td>41 (16%)</td>
<td>60 (16.1%)</td>
<td>.970</td>
<td>22 (13%)</td>
<td>17 (16%)</td>
<td>.511</td>
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<tr>
<td>Asymptomatic ICH (No.) (%)</td>
<td>92 (35.9%)</td>
<td>118 (31.7%)</td>
<td>.271</td>
<td>56 (33.1%)</td>
<td>67 (39.6%)</td>
<td>.248</td>
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<td>mRS 90 days</td>
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<tr>
<td>0–2 (No.) (%)</td>
<td>89 (34.8%)</td>
<td>173 (46.5%)</td>
<td>.003</td>
<td>64 (37.9%)</td>
<td>79 (46.7%)</td>
<td>.087</td>
</tr>
<tr>
<td>3–6 (No.) (%)</td>
<td>167 (65.2%)</td>
<td>199 (53.5%)</td>
<td>.022</td>
<td>105 (62.1%)</td>
<td>90 (53.3%)</td>
<td></td>
</tr>
<tr>
<td>In-hospital mortality (No.) (%)</td>
<td>74 (28.9%)</td>
<td>78 (21%)</td>
<td>.002</td>
<td>38 (22.5%)</td>
<td>39 (23.1%)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Note: ICH indicates intracerebral hemorrhage.

Outcomes before and after matching

Table 2 shows the outcomes before and after matching. Primary results of outcomes before matching suggested that the ST 4 group had a higher rate of reperfusion postprocedure (P = .013) and a favorable independent outcome at 90 days (P = .003), as well as lower in-hospital mortality (P = .022). Efficacy with regard to time was also observed in the ST 4 group, including reduced time of the procedure (P = .007) and time from stent deployment to reperfusion (P < .001), as well as fewer passes of thrombectomy (P = .001).

However, primary univariate analysis of baseline characteristics showed an imbalance between the 2 groups (Table 1). To minimize the impact of unbalanced factors, we matched a 1:1 model based on the propensity score in which unbalanced base-
line characteristics and other variables influencing outcomes were taken into account (Table 1).

After propensity score matching, baseline variables were equally distributed in the 2 groups (Table 1). Outcomes of efficacy and safety did not differ between the groups, except for a shorter time from stent deployment to reperfusion in the ST 4 group (P = .021).

**Subgroup Analysis**

Primary analysis of baseline data also revealed that selection bias was present in the stroke type and occluded vessels. ST 4 was used more than ST 6 for patients with atherosclerotic disease (46% versus 37.1%, P = .027) and MCA occlusion (76.3% versus 39.1%, P < .001), while ST 6 was more frequently used than ST 4 in patients with cardiogenic stroke (57% versus 47.5%, P = .02) and ICA occlusion (60.5% versus 23.1%, P < .001). To explore the effect of device choice on stroke type and vessel occlusion site, we performed subgroup analyses of models of atherosclerotic disease, cardiac embolism, ICA, and MCA (Tables 3 and 4 and Online Tables 1–3).

Results suggested better outcomes for the ST 4 group in stroke classification models. In the atherosclerotic disease model, the ST 4 group demonstrated favorable reperfusion (P = .012, Table 4).
and better independent outcomes at 90 days ($P = .032$). In addition, increased time efficacy ($P = .001$), fewer attempts ($P = .042$), and lower frequency of rescue therapy ($P = .027$) were also observed in the ST 4 group. In the cardiac embolism model, lower mortality was reported in the ST 4 group ($P = .035$, On-line Table 1). When patients were stratified into those with ICA and MCA occlusions, the effects of the stent diameter size on functional outcomes did not show differences in the 2 patient groups (On-line Tables 2 and 3).

Propensity score analysis was also performed in these 4 models, the results of which showed a difference after matching in only the atherosclerotic disease model. Matched analysis of the atherosclerotic disease model showed favorable recanalization ($P = .021$) and time efficacy ($P = .013$) and fewer attempts ($P = .025$) in the ST 4 group (Table 4).

Finally, a logistic regression model was conducted to assess potential predictors of mTICI postprocedure, in which the propensity score acted as a covariate. As a result, ST 4 (OR, 3.217; 95% CI, 1.129–9.162; $P = .029$) and the propensity score (OR, 52.84; 95% CI, 3.468–805.018; $P = .004$) were identified as independent predictors of favorable reperfusion for patients with atherosclerotic disease (On-line Tables 4 and 5).

**Discussion**

To the best of our knowledge, this is the first study to investigate the effect of different diameter sizes of stent retrievers on endovascular treatment. Whereas in the primary analysis, we found that patients in the small-stent group obtained better outcomes of efficacy and safety, after we adjusted the imbalance of baseline data, no difference was apparent. In patients with atherosclerotic disease, propensity score matching analysis suggested that a small stent was an independent predictor of successful reperfusion.

Our study aimed to describe the relationship between stent size and outcomes. Although the outcomes did not differ, the time interval between stent deployment and reperfusion was shorter when a small stent was used. Because this interval represents the validity time of stent action, the result suggests greater deliverability with a smaller stent. Consequently, a small stent may be a better choice, especially for tortuous vessels. Also, as is well-known, any delay in the time before reperfusion can lead to worse outcomes, and the prognosis improves the sooner endovascular reperfusion is achieved. Hence, choosing a small stent with excellent deliverability could achieve quicker lesion location and thus avoid wasting time.

Selection bias of stent choice exists in the real world. In this study, a small stent was mainly used for patients with MCA occlusion, while the large stent was used mainly for large-vessel occlusion attributable to ICA occlusion and cardiac embolism. This approach appears reasonable, and results of our primary analysis suggested a difference in outcomes for the cardiac embolism model. However, after adjusting for imbalance and bias, propensity score analysis revealed no difference in the outcomes of both the ST 4 and ST 6 groups in the cardiac embolism and MCA and ICA models. It seems that in these cases, outcomes do not rely on stent size, and both choices may thus be equally feasible.

The most interesting finding was that the small stent was associated with better reperfusion in patients with atherosclerotic disease (On-line Table 4). Large vessels occluded with atherosclerotic lesions, accompanied by in situ stenosis to some extent, result in tortuous and complicated vascular morphology. When one uses thrombectomy via a stent retriever, the vessels tend to be reoccluded after initial reperfusion because of subsequent platelet aggregation. A small stent advanced through a thinner microcatheter is more flexible and can pass through lesions in complex pathways comfortably and rapidly, with better deliverability. The small size is also associated with a low stent-release force, making the release of the stent smoother and safer with greater accuracy. On the other hand, the radial force decreases incrementally with increasing stent diameter, so a small stent with a large radial force could maintain vessel wall stability during the procedure. These stent characteristics help to increase time efficiency and recanalization. Another interesting finding was that attempted passes observed with the small stent were fewer. The endovascular procedure unavoidably injures the arterial wall and induces local inflammation and proliferation of smooth-muscle cells, resulting in intimal hyperplasia and restenosis. Loh et al and Angermaier et al reported that >3 attempts would not only be futile with a low additional successful revascularization but also increase the risk of vascular injury and other complications. Hence, a smaller stent with fewer passes could reduce the risk of restenosis and mechanical injury, providing practical clinical value.

It was reported that long stents were an independent predictor of major adverse cardiac events after acute myocardial infarction. Postprocedural new DWI lesions occurred after carotid artery stent placement more often in patients with longer stents.

In this study, stent retrievers of 4 mm in diameter included lengths of 15 and 20 mm; stent retrievers of 6 mm in diameter included lengths of 20 and 30 mm. The retrievers with larger diameters are longer. Therefore, it is highly possible that the stent length influences the effects of interventional therapy.

Our study illustrates that both sizes of the Solitaire stent retriever for thrombectomy appear clinically applicable, providing efficacy and safety. The small stent is associated with better recanalization in large-vessel occlusion caused by intracranial atherosclerotic disease. In Asia, atherosclerotic disease is the main cause of acute ischemic stroke, unlike in Western countries. In China, the incidence of atherosclerotic disease accounts for 33%–50% of strokes, higher than in the West (8%–10%). Therefore, a small stent may be a better choice for this type of patient. However, these results cannot be generalized until a multicenter randomized controlled trial is designed to test and verify the assumption.

This is the first study to explore the influence of choosing different-sized stents on the effect of endovascular therapy for large-vessel occlusion in China. Our data came from a multicenter study, the samples of which were representative, reflecting real-world clinical practice. We also used a statistical method, namely propensity score matching analysis, which could control bias effectively and minimize the imbalance among groups in observational studies.

Our research also has several limitations. The study was a retrospective, multicenter program, and the data were self-reported by the site investigator, which included selection bias. The registry
did not include CTA or MRA scans at 24 hours after the operation, so the value of mTICI only represented the immediate reperfusion postprocedure. Thrombus burden was not evaluated before treatment based on CTA because not all patients underwent preprocedural CTA examination. Vessel stenoses at 3 months were not assessed in this study due to lack of vascular image results. Some values were also missing from the original reporting data.

CONCLUSIONS
In this analysis of patients with acute large-vessel ischemic stroke, no differences in efficacy and safety were observed in patients treated with Solitaire retrievable stents of differing diameters. Using smaller retrievers was associated with improved recanalization for occlusion of atherosclerotic etiology. With a 4-mm stent, procedure times were shortened and pass attempts were reduced.

APPENDIX
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REFERENCES
the outcome in carotid artery stenting? Eur J Vasc Endovasc Surg 2007;33:135–41; discussion 142–43 CrossRef Medline


ABSTRACT

BACKGROUND AND PURPOSE: The e-ASPECTS software is a tool for the automated use of ASPECTS. Our aim was to analyze whether baseline e-ASPECT scores correlate with outcome after mechanical thrombectomy.

MATERIALS AND METHODS: Patients with ischemic strokes in the anterior circulation who were admitted between 2010 and 2015, diagnosed by CT, and received mechanical thrombectomy were included. The ASPECTS on baseline CT was scored by e-ASPECTS and 3 expert raters, and interclass correlation coefficients were calculated. The e-ASPECTS was correlated with functional outcome (modified Rankin Scale) at 3 months by using the Spearman rank correlation coefficient. Unfavorable outcome was defined as mRS 4–6 at 3 months, and a poor scan was defined as e-ASPECTS 0–5.

RESULTS: Two hundred twenty patients were included, and 147 (67%) were treated with bridging protocols. The median e-ASPECTS was 9 (interquartile range, 8–10). Intraclass correlation coefficients between e-ASPECTS and raters were 0.72, 0.74, and 0.76 (all, P < .001). e-ASPECTS (Spearman rank correlation coefficient = −0.15, P = .027) correlated with mRS at 3 months. Patients with unfavorable outcome had lower e-ASPECTS (median, 8; interquartile range, 7–10 versus median, 9; interquartile range, 8–10; P = .014). Sixteen patients (7.4%) had a poor scan, which was associated with unfavorable outcome (OR, 13.6; 95% CI, 1.8–104). Independent predictors of unfavorable outcome were e-ASPECTS (OR, 0.79; 95% CI, 0.63–0.99), blood sugar (OR, 1.01; 95% CI, 1.004–1.02), atrial fibrillation (OR, 2.64; 95% CI, 1.22–5.69), premorbid mRS (OR, 1.77; 95% CI, 1.21–2.58), NIHSS (OR, 1.11; 95% CI, 1.04–1.19), general anesthesia (OR, 0.24; 95% CI, 0.07–0.84), failed recanalization (OR, 8.47; 95% CI, 3.5–20.2), and symptomatic intracerebral hemorrhage (OR, 25.8; 95% CI, 2.5–268).

CONCLUSIONS: The e-ASPECTS correlated with mRS at 3 months and was predictive of unfavorable outcome after mechanical thrombectomy, but further studies in patients with poor scan are needed.

ABBREVIATIONS: AIS = acute ischemic stroke; MT = mechanical thrombectomy; sICH = symptomatic intracranial hemorrhage

Mechanical thrombectomy (MT) in acute ischemic stroke (AIS) due to a large intracranial vessel occlusion in the anterior circulation has been proven to be an effective therapy. With the success of the recent trials, an increasing number of patients with AIS will be evaluated for eligibility for this therapy. However, because there are no strict ex-/inclusion guidelines, patient selection for MT remains a challenging process. In the end, this evaluation process should not withhold therapy from patients who might benefit from MT but should preclude patients who will not benefit. During the evaluation process, multiple factors need to be cautiously reviewed. Noncontrast CT is still the most available imaging tool worldwide. Early signs of infarction on NCCT scans are a potent predictor of clinical outcome in patients with AIS. In 2000, Barber et al introduced the Alberta Stroke Program Early CT Score. ASPECTS divides the middle cerebral artery territory into 10 predefined anatomic areas and grades the presence of early infarct signs by parenchymal hypodensity on NCCT. This increasingly used score has already proved a reliable predictor of clinical outcome in patients with AIS treated with intravenous rtPA and/or MT.

Unfortunately, the determination of early signs of ischemia and their translation into the ASPECTS have a considerable interrater variability, which is, among other factors, influenced by rater experience. However, during the evaluation process for per-
forming MT or before transfer of a patient to a comprehensive stroke center performing MT, scoring variability could negatively influence the decision-making process and lead to false patient in-/exclusion. The e-ASPECTS software (Brainomix, Oxford, UK; www.brainomix.com) is a standardized, fully automated, CE mark–approved ASPECTS scoring tool for NCCT, which has previously demonstrated scoring on an expert level.\textsuperscript{14,15} We analyzed whether e-ASPECT scores correlate with outcome after mechanical thrombectomy and whether low scores are predictors of unfavorable outcome. In particular, we were interested in whether patients with low e-ASPECTS (0–5, poor scans) were very likely to have a bad outcome.

**MATERIALS AND METHODS**

From a prospectively collected stroke data base, we identified 430 patients with AIS in the anterior circulation who underwent MT between May 2010 and May 2015. All patients were treated with endovascular revascularization therapy and, in case of eligibility, with intravenous thrombolysis after an interdisciplinary decision by the neurologist and neurointerventionalist on call. Historically, during MT, patients were treated under general anesthesia; and since 2009, we have been following a strict standardized operating procedure. In September 2013, an additional standardized operating procedure for conscious sedation was introduced, and selected patients were treated following this procedure with MT. Since April 2014, eligible patients were included in our single-center randomized sedation trial, Sedation vs. Intubation for Endovascular Stroke TreAtment (SIESTA).\textsuperscript{16} After the procedure, all patients were treated according to in-house standardized operating procedures in our neurointensive care unit and/or our stroke unit. In our data base, clinical data at baseline and during the hospital stay as well as radiologic and laboratory information are prospectively entered and used for analysis when appropriate.

Recanalization was assessed with the Thrombolysis in Cerebral Infarction Score by a blinded investigator (J.P.). TICI 0–2a was scored as failed, and TICI 2b–3 was scored as successful recanalization. The outcome was measured with the modified Rankin Scale after 3 months and was obtained through rehabilitation reports, outpatient assessments, or a standardized interview by an unblinded investigator. Unfavorable outcome was defined as a modified Rankin Scale score between 4 and 6; favorable outcome, as mRS 0–3; and good outcome, as mRS 0–2. Symptomatic intracranial hemorrhage (sICH) was defined according to the European Cooperative Acute Stroke Study II (blood at any site in the brain and clinical deterioration with an increase in the NIHSS score of at least 4 points compared with the lowest value within the first 7 days or any intracranial hemorrhage leading to death).

NCCT scans of the included patients were obtained from the same multisection CT scanners. Between May 2010 and January 2014, images were acquired from a Somatom Volume Zoom (Siemens, Erlangen, Germany, \( n = 150 \)). Incremental sections had a thickness of 6 mm with an in-plane resolution of 512 \( \times \) 512 mm. Between February 2014 and May 2015, NCCTs were acquired from a Somatom Definition AS (Siemens, \( n = 70 \)) with a section thickness of 4 mm and an in-plane resolution of 512 \( \times \) 512 mm. NCCT scans were retrospectively scored by e-ASPECTS (Version 5.0), as well as by 3 stroke experts, and software and experts were blinded to any patient data and clinical information except for the side of the unilateral ischemic stroke. The experts had 6–12 years of extensive experience in neurovascular imaging interpretation (J.P. and C.H., board-certified neuroradiologists; S.N., board-certified neurologist). e-ASPECTS is based on a combination of advanced image-processing and machine-learning algorithms. Several image-enhancement filters are applied to the input DICOM CT image to deal with noise, differences between scanners, and image artifacts. A 3D registration module corrects for any tilt, rotation, and other transformations. The ASPECTS regions are then segmented; this segmentation provides a standardized reference for the cortical regions. The scoring module operates on the standardized 3D images, classifying signs of ischemic damage and assigning them to ASPECTS regions. It applies statistical learning methods to image features to determine whether a region is likely to be damaged.\textsuperscript{14,15} An e-ASPECTS score between 0 and 5 was considered a poor scan.

**Statistical Analysis**

Our primary end point was defined as unfavorable outcome as opposed to good outcome because we wanted to test the hypothesis that patients with low e-ASPECTS are indeed under a higher risk of futile treatment. Nominal data are presented as frequencies; ordinal data, as median with interquartile range; and metric data, as mean \( \pm \) SD. To show univariate differences in outcome groups, we used the Fisher exact test, the \( \chi^2 \) test, the Mann-Whitney \( U \), or unpaired \( t \) tests when appropriate according to data category. For multivariate analysis to show predictors of unfavorable and good outcome, we used a stepwise forward binary logistic regression model with correction for all significant variables (\( P \leq .05 \)) in univariate analyses. Odds ratios are presented as values with 95% confidence intervals. For the agreement between e-ASPECTS with each expert we used the intraclass correlation coefficient. For correlation of the e-ASPECTS and the mRS at 3 months, we used the Spearman rank correlation coefficient.

**Ethics Approval**

Our local ethics committee approved the prospective data base and retrospective analysis herein. Due to its monocentric and retrospective character, the requirement for subsequent written patient informed consent was waived.

**RESULTS**

Two hundred twenty patients of 430 met the inclusion criteria for this analysis (ie, in-house NCCT with no or minor motion artifacts before MT; Fig 1). Patients’ baseline characteristics are shown in the On-line Table. This shows that our cohort is very typical for patients with acute large intracranial vessel occlusion. The median NIHSS at baseline was 18 (interquartile range, 15–21), but in contrast to previous randomized controlled trials, we also included around 9% of patients with a premorbid mRS of >2 (ie, 14 patients with an mRS of 3 and 6 with an mRS of 4). Most patients had either an M1 occlusion or a carotid-T occlusion. One hundred forty-seven (67%) patients were treated with rtPA-based bridging protocols. After prior exclusion of 43 (10%) patients due to severe motion artifacts rendering ASPECTS scoring for the
FIG 1. Exclusion criteria for patients with AIS who received MT entering this analysis. Severe motion artifacts were defined as artifacts that impair differentiation of anatomic structures (eg, basal ganglia, subarachnoid space) and/or clear identification of intracranial hemorrhage by the human rater. The asterisk indicates percentage regarding included patients.

human rater impossible, an additional 3 (1.4%) scans could not be processed by e-ASPECTS due to technical reasons (upload or processing of the DICOM data). The median e-ASPECTS was 9 (interquartile range, 8–10) The distribution of e-ASPECTS and human raters’ scores are shown in Fig 2. Only 16 patients (7.4%) had a poor scan, which was strongly associated with unfavorable outcome (OR, 13.6; 95% CI, 1.8–104; P = .012). Overall, after 3 months, the primary end point of unfavorable outcome was met by 123 (55.9%) patients, and 61 (27.7%) patients reached the secondary end point of good outcome.

The intraclass correlation coefficients between e-ASPECTS and each rater were 0.72, 0.74, and 0.76, respectively (all, P < .001). The agreement within the human raters was very robust as well (intraclass correlation coefficients, 0.7, 0.77, and 0.75; all, P < .001). Although the overall agreement of raters and e-ASPECTS was good, in some cases, considerably different scoring results occurred and an example with a low e-ASPECTS (4) is presented in Fig 3. Only e-ASPECTS (Spearman rank correlation coefficient = −0.19, P = .004) correlated inversely but significantly with mRS at 3 months, indicating that a lower ASPECTS is associated with a higher mRS after 3 months. ASPECTS scoring of the other 2 readers differed from the e-ASPECTS scores to the extent that a significant statistical correlation between their ASPECTS scores and clinical outcome could not be detected. Spearman rank correlation coefficient for e-ASPECTS and mRS in our analysis differed from the Spearman rank correlation coefficient in the study of Barber et al (−0.6998) because Barber et al used only 3 categories of the mRS for correlation and their cohort consisted of consecutive patients with suspected stroke in the anterior circulation, whereas our patients all had proved large-vessel occlusion.

One hundred ninety-eight (90%) patients were treated with modern stent retrievers (mostly Solitaire; Covidien, Irvine, California), and 195 (88.6%) patients underwent thrombectomy under general anesthesia. In the univariate analysis for the primary end point, among other significant differences, patients with unfavorable outcome had lower e-ASPECTS (median, 8; interquartile range, 7–10 versus median, 9; interquartile range, 8–10; P = .014; On-line Table). Bridging therapy or treatment and procedural times, however, were not significantly different in patients with unfavorable outcome versus patients with favorable outcome (mRS, 0–3). For multivariate analysis, we included the variables age, premorbid mRS, atrial fibrillation, previous stroke, baseline blood sugar, and hemoglobin A1c, as well as NIHSS, hyperdense vessel sign, e-ASPECTS, general anesthesia, recanalization, and sICH (all P < .05 in univariate analysis). Independent predictors of unfavorable outcome were e-ASPECTS (OR, 0.79; 95% CI, 0.63–0.99; P = .049) but also blood sugar (OR, 1.01; 95% CI, 1.004–1.02; P = .005), atrial fibrillation (OR, 2.64; 95% CI, 1.22–5.69; P = .013), premorbid mRS (OR, 1.77; 95% CI, 1.21–2.58; P = .003), NIHSS (OR, 1.11; 95% CI, 1.04–1.19; P = .003), general anesthesia (OR, 0.24; 95% CI, 0.07–0.84; P = .007), failed recanalization (OR, 8.47; 95% CI, 3.5–20.2; P < .001), and sICH (OR, 25.8; 95% CI, 2.5–268; P = .007).

In the analysis of the secondary end point, factors associated with good outcome were mean age (66 ± 12 versus 74 ± 11 years; P < .001), premorbid mRS (median, 0; interquartile range, 0–1 versus median, 1; interquartile range, 0–2; P = .002), atrial fibrillation (34.4% versus 52.2%; P = .023), blood sugar (118 ± 33 versus 139 ± 57 mg/dL; P = .015), creatinine (0.89 ± 0.25 versus 1.1 ± 0.78 mg/dL; P = .03), general anesthesia (80.3% versus 91.8%; P = .03), NIHSS (median, 16; interquartile range, 11–19 versus median, 19; interquartile range, 15–22; P < .001), successful recanalization (88.5% versus 58.9%; P < .001) and sICH (0% versus 8.8%, P = .012). The e-ASPECTS, however, was not associated with good outcome (median, 9; interquartile range, 8–10 versus median, 9; interquartile range, 7–10; P = .249). After multivariate analysis (sICH was not included in the model because no patient with good outcome had sICH), only age (OR, 0.96; 95% CI, 0.93–0.98), blood sugar levels (OR, 0.99; 95% CI, 0.99–1.0), NIHSS (OR, 0.91; 95% CI, 0.86–0.97), and successful recanalization (OR, 5.45; 95% CI, 2.18–13.61) remained independent predictors of good outcome.

**DISCUSSION**

Our study confirmed that the e-ASPECTS software performs in a manner similar to that of stroke experts in detecting early ischemic damage in the MCA territory. Furthermore, we could demonstrate for the first time that fully automatically derived e-ASPECTS scores correlated inversely with patient outcome 3 months after MT (Spearman rank correlation coefficient = −0.15, P = .027). Patients with poor scans (ASPECTS 0–5) at baseline had a significantly high probability of unfavorable outcome (OR, 13.6; 95% CI, 1.8–104). On the basis of the multivariate regression analysis, a 1-point decrease in the e-ASPECTS increases the risk for an unfavorable clinical outcome by 20%. Most important, indicating the robustness of our results, we could also confirm
other known predictors of outcome after acute ischemic stroke, such as recanalization, sICH, atrial fibrillation, NIHSS, pre-morbid functionality, and blood sugar levels.

The ASPECTS is a validated, reliable, and reproducible grading system to assess early ischemic changes on noncontrast CT studies in patients with acute ischemic stroke of the anterior circulation. The Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke trials (HERMES) collaboration has recently shown a clear association between favorable clinical outcome after MT and ASPECTS of ≥6. Additionally, a subgroup analysis of the Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands (MR CLEAN) also demonstrated that patients with moderate early ischemic changes (ASPECTS 5–7) benefit from mechanical thrombectomy. On the other hand, there are other studies that could not show a correlation between ASPECTS 5–7 and clinical outcome after 3 months, and the HERMES data revealed that there is no clear benefit for patients with an ASPECTS of 0–5. Another study found that patients with ASPECTS 0–4 before mechanical thrombectomy had higher rates of serious adverse events and hemiconiectomy. Furthermore, death within 1 week and 30 days after treatment was more frequent. Therefore, the effect of endovascular treatment for patients with a poor scan (ASPECTS 0–5) is unclear, with perhaps only a slim margin for benefit. Additionally, multivariate regression analysis to show the independent prognostic effects of the ASPECTS has not been performed in these previous trials.

Because the probability of achieving functional independence declines and the risk of severe disability and death rises with lower ASPECTS, this scoring system appears important for patient evaluation for endovascular stroke treatment. Our data indicate that ASPECTS can provide important technical support in estimating a patient’s prognosis. Furthermore, in the present analysis, 2 of 3 expert raters’ scores did not correlate with the clinical outcome, whereas e-ASPECT scores did. This nicely illustrates 2 features: First, as already shown by others, the ASPECTS has considerable variability even among experts. This may be even more pronounced in the acute treatment decision for understandable reasons, such as emotional issues and stress. Second, an automated scoring tool can be advantageous here due to its “objectivity.” Hence, e-ASPECTS could contribute to decision-making for patient selection in the community hospital or telemedicine services and/or patient transfer into a comprehensive stroke center for MT. Other important imaging variables derived from CT angiography and CT perfusion have also been shown to carry prognostic information that can inform treatment decision-making, but NCCT is still the most commonly used imaging tool in acute stroke.

FIG 2. Distribution of ASPECTSs according to the 3 human raters and e-ASPECTS.
Our analysis focused on the prognostic value of ASPECTS, specifically e-ASPECTS for unfavorable outcome, as opposed to good outcome. According to current guidelines considering endovascular stroke therapy, a favorable ASPECTS is not an unconditional prerequisite, especially within 6 hours from onset (American Heart Association guidelines/European Stroke Organisation–European Foundation of Minimally Invasive Neurological Therapy guidelines). The question does not seem to be whom to treat but for whom treatment could be disadvantageous due to missing success or the increased likelihood of complications because patients with ASPECTS \(\leq 5\) have a lower chance of independent living or even survival. The e-ASPECTS was not a predictor of good outcome in this analysis, which indicates that patients with low scores still have a considerable probability of achieving clinical improvement through therapy; therefore, this analysis reinforces the need for a prospective controlled trial to investigate the potential benefit of thrombectomy in patients with a low initial ASPECTS.

Our study has several limitations: 1) Because we treated patients with broad inclusion criteria (ie, higher premorbid mRS and so forth), one cannot expect outcome results similar to those in the recent seminal MT trials, but rather similar to real-life data. 2) This analysis was based on a prospective single-center cohort data base, and data were analyzed retrospectively; therefore, caution should be exercised when generalizing the results. Our data regarding the mode of sedation need to be interpreted with caution. Most (88.6%) patients were treated under general anesthesia; and only a minority, with conscious sedation. We only introduced this mode of sedation in September 2013, and until April 2014, a selection bias in our cohort was present. The results of the SIESTA trial, however, indicated that in our center, general anesthesia is not associated with impaired outcome. 3) The performance of e-ASPECTS might have been compromised due to the available section thicknesses of 4 and 6 mm; the optimal thickness for analysis is 1 mm. Moreover, there was no ground truth (ie, diffusion-weighted imaging or CT perfusion) defined for ASPECTS scoring for this analysis. However, the e-ASPECTS software has previously shown similar and noninferior performance to that of stroke experts, and most centers do not have sophisticated imaging tools and rely on NCCT, which makes this an important analysis. 4) Additionally, the number of patients with a poor scan of \(\leq 5\) ASPECTS points was low, and our results need to be confirmed by analysis of large registries of patients undergoing MT, at best by randomized controlled trials including those patients in whom considerable uncertainty still exists with respect to the efficacy and safety of MT (ie, patients with extensive ischemic brain damage at baseline). The e-ASPECTS software could be a suitable tool for patient stratification in such trials.

The strengths of this study were that our cohort was very typical for patients undergoing MT and that we included numerous clinical, laboratory, and radiologic data in our analysis. The multivariate model confirmed many previously described prognostic factors, while the predictive value of e-ASPECTS prevailed, thereby indicating the robustness of our results.

CONCLUSIONS

The e-ASPECTS correlated with outcome overall and was predictive of unfavorable outcome after mechanical thrombectomy. e-ASPECTS might facilitate treatment decision-making, especially in centers without modern imaging tools for tissue perfusion and collateral status. It is easy to use, has a robust and reliable performance, and removes intra- and interrater variability. Because there are few patients with poor initial CT scans who improve after treatment, further prospective studies in those patients are needed and individual decision-making remains necessary.

FIG 3. Example of a patient with extensive early signs of ischemic damage on the baseline NCCT (A). The processed e-ASPECTS results is a score of 4. The human raters scored an ASPECTS of 6, 8, and 9, respectively, highlighting considerable disagreement in this particular case (B). An M1 occlusion was present, onset to treatment time was 143 minutes, TICI 2a was achieved, and no sICH occurred. Unfortunately, this patient had died within 3 months.
lateral to Activities Listed: Stryker. Christian Herweg—UNRELATED: Consultancy: Brainomix; Comments: temporary consultancy related to a project different from the one from which the current article originated; Payment for Lectures Including Service on Speakers Bureaus: Bristol-Myers Squibb, Brainomix; once in 2016, Travel/Accommodations/Meeting Expenses Unrelated to Activities Listed: Stryker. Brainomix: travel expenses for attending a national meeting in 2016. Julian Bösel—UNRELATED: Grants/Grants Pending: Patient-Centered Outcomes Research Institute, Brainomix Ltd: award pending for SETPOINT2 Trial; Travel/Accommodations/Meeting Expenses Unrelated to Activities Listed: Zoll, Bard Medical, Sedana Medical, Searatherm, Boehringer Ingelheim, Brainomix Ltd: speaker’s honoraria and travel support. Peter A. Ringleb—UNRELATED: Consultancy: advisory board member for Boehringer Ingelheim; Coviden; Payment for Lectures Including Service on Speakers Bureaus: lecture fee from Boehringer Ingelheim, Bayer, Pfizer, Daichi Sanyo, Markus Möhlenbruch—UNRELATED: Payment for Lectures Including Service on Speakers Bureaus: Codman, MicroVention, phenoX, Stryker. Martin Bendzus—UNRELATED: Board Membership: Data and Safety Monitoring Board for Vascular Dynamics; Consultancy: Codman, Roche, Guerbet, Boehringer Ingelheim; Grants/Grants Pending: Deutsche Forschungsgemeinschaft, Hopf Foundation, Novartis, Siemens, Guerbet, Stryker, Coviden; Payment for Lectures Including Service on Speakers Bureaus: Novartis, Roche, Guerbet, Teva Pharmaceutical Industries, Bayer, Codman, Simon Nagel—UNRELATED: Consultancy: Brainomix; S.N has had an ongoing consultancy appointment with Brainomix since 2015 independent from the current study; Grants/Grants Pending: Brainomix: The University Hospital Heidelberg received grants from Brainomix for prior studies; Payment for Lectures Including Service on Speakers Bureaus: Bayer, Medtronic, Pfizer, Travel/Accommodations/Meeting Expenses Unrelated to Activities Listed: Boehringer Ingelheim, Brainomix. *Money paid to the institution.

REFERENCES


Acute Basilar Artery Occlusion: Differences in Characteristics and Outcomes after Endovascular Therapy between Patients with and without Underlying Severe Atherosclerotic Stenosis


ABSTRACT

BACKGROUND AND PURPOSE: Prediction of underlying intracranial atherosclerotic stenosis before endovascular therapy might be helpful for appropriate therapeutic planning in patients with acute ischemic stroke. This study aimed to compare the characteristics and treatment outcomes in patients with acute basilar artery occlusion relative to the existence or nonexistence of underlying intracranial atherosclerotic stenosis.

MATERIALS AND METHODS: Sixty-two patients with acute basilar artery occlusion underwent multimodal endovascular therapy. All patients underwent stent-retriever thrombectomy as a first-line endovascular therapy. Patients with underlying intracranial atherosclerotic stenosis underwent additional intracranial angioplasty and stent placement. The clinical and imaging characteristics and treatment outcomes were retrospectively analyzed and compared between patients with and without intracranial atherosclerotic stenosis.

RESULTS: Underlying intracranial atherosclerotic stenosis was identified at the occlusion site in 15 patients (24.1%). Occlusion in the proximal segment of the basilar artery was more common in patients with intracranial atherosclerotic stenosis (60% versus 6.4%, \( P < .001 \)), whereas occlusion in the distal segment was more common in those without it (91.5% versus 26.7%, \( P < .001 \)). Bilateral thalamic infarction on a pretreatment DWI was less common in patients with intracranial atherosclerotic stenosis (0% versus 27.7%, \( P = .027 \)) compared with those without it. There were no significant differences in the rates of successful revascularization, favorable outcome, symptomatic hemorrhage, and mortality between the 2 groups.

CONCLUSIONS: Underlying intracranial atherosclerotic stenosis was not uncommon in patients with acute basilar artery occlusion. The occlusion segment of the basilar artery and the presence or absence of bilateral thalamic infarction on a pretreatment DWI might be helpful for predicting underlying intracranial atherosclerotic stenosis in patients with acute basilar artery occlusion. Patients with and without underlying intracranial atherosclerotic stenosis who underwent endovascular therapy had similar outcomes.

ABBREVIATIONS: BAO = basilar artery occlusion; ICAS = intracranial atherosclerotic stenosis

Acute ischemic stroke due to basilar artery occlusion (BAO) is associated with the highest mortality and morbidity among strokes attributable to intracranial large-vessel occlusions.\(^1,2\) Morbidity and mortality rates have been reported to be up to 95%, and the chances for good outcome are extremely low without active treatment.\(^2,3\) The rates of death or dependency have been 76%–78%, even when patients with acute BAO were treated with intravenous or intra-arterial thrombolysis.\(^3\) Stent-retriever thrombectomy is increasingly being used in patients with acute BAO and shows a high recanalization rate.\(^4\) Many case series have shown that stent-retriever thrombectomy is a safe and feasible treatment technique in patients with acute BAO.\(^4-7\)

Embolism from cardiac or proximal large-artery sources and in situ thrombosis superimposed on underlying intracranial atherosclerotic stenosis (ICAS) have been identified as major causes of acute BAO.\(^6\) ICAS is one of the most common causes of ischemic stroke worldwide and is particularly prevalent in Asian, black, Hispanic, and Indian populations.\(^3\) Strategies for endovascular therapy in patients with acute stroke with underlying ICAS should be different from those without it. In this regard, prediction of underlying ICAS before endovascular therapy might be important and helpful to neurointerventionalists in the planning of endovascular therapy in patients with acute BAO; however, this has not yet been systematically studied, to our knowledge. In ad-
diation, very few studies have investigated outcomes after endovascular therapy in patients with acute BAO due to underlying ICAS. Accordingly, this study aimed to investigate the imaging and clinical characteristics for predicting underlying ICAS in patients with acute BAO and to compare the clinical outcomes of endovascular therapy in those patients relative to the existence or nonexistence of underlying ICAS.

**MATERIALS AND METHODS**

**Patients**

From December 2010 to February 2016, 62 patients with acute stroke due to BAO received stent-retriever thrombectomy at a regional comprehensive stroke center. We retrospectively analyzed clinical and radiologic data of these 62 patients, including age, sex, stroke risk factors, intravenous thrombolysis, time to procedure, procedural time, time to revascularization, and etiology of stroke according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification. On admission, all patients were assessed with the NIHSS by a stroke neurologist. Patients underwent nonenhanced CT and MR imaging before endovascular therapy. The inclusion criteria for stent-retriever thrombectomy were as follows: 1) presentation within 12 hours of stroke onset, 2) baseline NIHSS score of ≥4, 3) no intracranial hemorrhage detected on cranial CT or MR imaging, 4) BAO detected with MR angiography and conventional angiography, 5) no bilateral diffuse pontine ischemia on DWI, and 6) a premorbid mRS score of ≤2. The institutional ethics committee approved this retrospective analysis and waived the requirements for informed consent on the basis of study design.

**Endovascular Therapy**

All endovascular therapy was performed by one interventional neuroradiologist with 14 years of experience in neurovascular intervention. Written informed consent for endovascular therapy was obtained from a family member for all patients. Cerebral angiography and endovascular therapy were performed with the patient under conscious sedation. In cases of agitation, an IV bolus of midazolam was given and repeated if necessary. After detecting arterial occlusion on diagnostic angiography, we used stent-retriever thrombectomy with a Solitaire stent (Covidien, Irvine, California) or Trevo stent (Stryker, Kalamazoo, Michigan) as the first-line endovascular therapy method. When stent-retriever thrombectomy was unsuccessful, manual aspiration thrombectomy with intermediate catheters was performed as a rescue treatment. The details of the techniques used for stent-retriever thrombectomy and manual aspiration thrombectomy were described previously. Underlying ICAS was determined when severe (≥70%) stenosis of the basilar artery was seen on the initial diagnostic angiography or on the follow-up angiography after a mechanical thrombectomy procedure. The degree of arterial stenosis was determined with the Warfarin Aspirin Symptomatic Intracranial Disease criteria. If underlying ICAS was revealed, intracranial angioplasty was performed with a Gateway PTA balloon catheter (Stryker). The diameter of the balloon was undersized to 80% of the normal vessel diameter just distal to the stenosis. The balloon was inflated slowly 1 or 2 times with a screw-type pressure inflation device at 4–6 atm for 60 seconds. After balloon angioplasty, intracranial stent placement with the Wingspan stent system (Stryker) was performed whenever possible. The stent diameter was sized to exceed the diameter of the normal vessel by 0.5 mm. The stent length was selected to cover the entire stenotic segment. All patients who underwent intracranial angioplasty or stent placement received aspirin and clopidogrel (Plavix) orally or via a nasogastric tube for at least 3 months after the procedure.

**Outcome Measures**

For all patients, we assessed posterior circulation ASPECTS on pretreatment DWI, according to Tei et al. The presence or absence of thalamic infarction and its involved territory was also evaluated. The territory of thalamic infarctions was classified into anterior, posteromedial, ventrolateral, and posterolateral according to their arterial supply. Classification of BAO, revascularization status, posttreatment CT findings, posterior circulation ASPECTS, and thalamic infarction on pretreatment DWI were assessed by 2 neuroradiologists (with 3 and 5 years of experience, respectively) who were blinded to any clinical information. Conclusions were reached by consensus.

Neurologic evaluation was performed by a stroke neurologist immediately and 24 hours and 3 months after treatment; when any change occurred in clinical symptoms; and before the patient was discharged. Clinical outcome was assessed with the mRS by a stroke neurologist 3 months after treatment. When patients could not visit for neurologic evaluation, they were assessed via phone call. Good clinical outcome was defined as an mRS score of ≤2. Symptomatic hemorrhage was defined as a documented hemorrhage associated with a decline of ≥4 points in the NIHSS score or 1-point deterioration in the level of consciousness.

**Statistical Analysis**

Sixty-two patients were divided into 2 groups for comparison, namely the ICAS group and the non-ICAS group. The baseline characteristics and clinical outcomes of the 2 groups were compared. Statistical analyses were performed with the use of SPSS software (Version 21.0; IBM, Armonk, New York). The χ² test or Fisher exact test was used for categoric and binary variables, and the Mann-Whitney U test, for continuous variables. P < .05 was considered significant.

**RESULTS**

Baseline patient characteristics are shown in Table 1. The mean age was 69 years, and 36 (58.1%) were men. The etiology of ischemic stroke was cardioembolism in 32 patients (51.6%), large-
Of the 62 patients, 15 (24.2%) had underlying ICAS at the occlusion site. Of these 15 patients, 1 had preocclusive severe stenosis on diagnostic angiography and 14 had occlusion on initial diagnostic angiography. These 14 patients had stenosis of ≥70% on follow-up angiography after first-line stent-retriever thrombectomy. Of 15 patients with underlying ICAS, 5 underwent intracranial angioplasty alone and 8 received angioplasty with stent placement (Fig 1). Two patients did not undergo angioplasty or stent placement due to device inaccessibility. Overall, 17.7% (11/62) of patients were treated by additional manual aspiration thrombectomy after failure of first-line stent-retriever thrombectomy.

The mean procedural time was longer in the ICAS group than in the non-ICAS group (39 minutes versus 28 minutes, \( P = .006 \)). Occlusion in the proximal segment of the basilar artery was more frequent in the ICAS group (9/15, 60%) than in the non-ICAS group (3/47, 6.4%) \( (P < .001) \). In contrast, occlusion in the distal segment of the basilar artery was more frequent in the non-ICAS group (43/47, 91.5%) than in the ICAS group (4/15, 26.7%) \( (P < .001) \). Otherwise, there were no significant differences between the 2 groups in age, sex, stroke risk factors, intravenous thrombolysis, time to procedure, time to recanalization, baseline NIHSS score, and DWI posterior circulation ASPECTS.

On a pretreatment DWI, thalamic infarction was seen in 24 patients (38.7%). Of the 24 patients with thalamic infarctions, 13 had bilateral thalamic infarctions and 11 had unilateral thalamic infarctions. All bilateral thalamic infarctions occurred in paramedian regions. Five patients in the ICAS group had thalamic infarctions, and all of these 5 patients showed unilateral thalamic infarction. Nineteen patients in the non-ICAS group had thalamic infarction. Of these 19 patients, 13 had bilateral thalamic infarctions and 6 had unilateral thalamic infarction. There was no significant difference in the rate of thalamic infarction between the 2 groups, but the rate of bilateral thalamic infarction was significantly lower in the ICAS group (0/15, 0%) compared with the non-ICAS group (13/47, 27.7%) \( (P = .027) \).

Of the 62 patients, 15 (24.2%) had underlying ICAS at the occlusion site. Of these 15 patients, 1 had preocclusive severe stenosis on diagnostic angiography and 14 had occlusion on initial diagnostic angiography. These 14 patients had stenosis of ≥70% on follow-up angiography after first-line stent-retriever thrombectomy. Of 15 patients with underlying ICAS, 5 underwent intracranial angioplasty alone and 8 received angioplasty with stent placement (Fig 1). Two patients did not undergo angioplasty or stent placement due to device inaccessibility. Overall, 17.7% (11/62) of patients were treated by additional manual aspiration thrombectomy after failure of first-line stent-retriever thrombectomy.

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### Table 1: Baseline characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n = 62)</th>
<th>Patients with ICAS (n = 15)</th>
<th>Patients without ICAS (n = 47)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean) (yr)</td>
<td>69.6 ± 11.95</td>
<td>67.1 ± 10.03</td>
<td>70.3 ± 12.50</td>
<td>.205</td>
</tr>
<tr>
<td>Male sex (No. [%])</td>
<td>36 [58.1]</td>
<td>12 [80.0]</td>
<td>24 [51.1]</td>
<td>.048</td>
</tr>
<tr>
<td>Risk factor (No. [%])</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>37 [59.7]</td>
<td>11 [73.3]</td>
<td>26 [55.3]</td>
<td>.216</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14 [22.6]</td>
<td>6 [40.0]</td>
<td>10 [21.3]</td>
<td>.727</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>16 [25.8]</td>
<td>6 [40.0]</td>
<td>10 [21.3]</td>
<td>.382</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>5 [8.1]</td>
<td>0 [0.0]</td>
<td>5 [10.6]</td>
<td>.323</td>
</tr>
<tr>
<td>IV thrombolysis (No. [%])</td>
<td>17 [27.4]</td>
<td>7 [46.7]</td>
<td>10 [21.3]</td>
<td>.094</td>
</tr>
<tr>
<td>Occlusion sites (No. [%])</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td>12 [19.4]</td>
<td>9 [60.0]</td>
<td>3 [6.4]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Middle</td>
<td>3 [4.8]</td>
<td>2 [13.3]</td>
<td>1 [2.1]</td>
<td>.343</td>
</tr>
<tr>
<td>Distal</td>
<td>47 [75.8]</td>
<td>4 [26.7]</td>
<td>43 [91.5]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Baseline NIHSS score (mean) (IQR)</td>
<td>12.4 ± 6.23</td>
<td>12.7 ± 5.95</td>
<td>12.3 ± 6.37</td>
<td>.773</td>
</tr>
<tr>
<td>Time to procedure (mean) (min)</td>
<td>289.6 ± 129.6</td>
<td>309.3 ± 139.6</td>
<td>283.3 ± 127.6</td>
<td>.532</td>
</tr>
<tr>
<td>Procedure time (mean) (min)</td>
<td>30.9 ± 17.76</td>
<td>39.0 ± 19.4</td>
<td>28.3 ± 16.56</td>
<td>.006</td>
</tr>
<tr>
<td>Time to recanalization (mean) (min)</td>
<td>131.0 ± 136.22</td>
<td>348.3 ± 343.84</td>
<td>312.2 ± 134.12</td>
<td>.459</td>
</tr>
</tbody>
</table>

Note: IQR indicates interquartile range; pc-ASPECTS, posterior circulation ASPECTS.

FIG 1. A 74-year-old male patient with acute stroke due to acute basilar artery occlusion. A, Left vertebral artery angiogram shows an occlusion (arrow) at the proximal segment of the basilar artery. B, Angiogram obtained after 1 passage of the stent retriever reveals a severe underlying atherosclerotic stenosis (arrow) at the proximal segment of the basilar artery. C, Left vertebral angiogram obtained after intracranial angioplasty and stent placement shows complete recanalization of the basilar artery with good distal perfusion. Arrows indicate the proximal and distal ends of the Wingspan stent. D, Photograph shows small fragmented thrombi retrieved with a Solitaire stent.

artery atherosclerosis in 21 patients (33.9%), and undetermined etiology in 9 patients (14.5%). IV rtPA was administered in 17 patients (27.4%). The mean NIHSS score on admission was 12, with scores ranging from 4 to 25.
The clinical outcomes of 62 patients are summarized in Table 2. Overall, successful revascularization (modified TICI grades 2b or 3) was achieved in 96.8% (60/62) of the patients, and favorable outcomes (mRS 0–2), in 53.2% (33/62) of the patients. There was 1 patient (1.6%) with symptomatic hemorrhage, and the mortality rate was 16.1% (10/62). There was no significant difference between the 2 groups in the rates of successful revascularization, favorable outcome, symptomatic hemorrhage, and mortality.

### DISCUSSION

The main findings of our study are as follows: 1) Underlying ICAS of ≥70% was identified in 24.2% of the patients with acute ischemic stroke due to BAO; 2) occlusion in the proximal segment was more frequently seen in patients with BAO with underlying ICAS, whereas occlusion in the distal segment was more frequently observed in those without underlying ICAS; and 3) bilateral thalamic infarction on pretreatment DWI was seen only in patients without underlying ICAS.

The incidence of underlying ICAS in acute ischemic stroke caused by intracranial large-artery occlusion has been reported to be 17%–60%. It is well-known that ICAS is more prevalent in Asian countries, and accordingly, the highest incidence was reported by a Chinese center. The results of our study are in line with those reports; 24% of patients with acute BAO had underlying ICAS of ≥70%. The possibility of underlying ICAS should be considered when performing endovascular therapy in patients with acute BAO, especially when encountering a difficulty during mechanical thrombectomy in regions where ICAS is more prevalent. The primary revascularization rate of stent-retriever thrombectomy in patients with acute stroke due to large-vessel occlusions was reported to be up to 70%–80%. Underlying ICAS in the occluded artery can be an important cause of failed stent-retriever thrombectomy, especially in Asian patients.

Predicting the presence of underlying ICAS before and during stent-retriever thrombectomy will be helpful for neurointerventionists for appropriate therapeutic planning. Our study suggested that the occlusion site can be a useful marker in predicting underlying ICAS of patients with acute BAO. In our study, 73% of patients with underlying ICAS had occlusions in the proximal and middle segments of the basilar artery, while 92% of those without underlying ICAS had occlusions in distal segment of the basilar artery. The results from our study are in accordance with those in a recently published study by Kim et al., which included 51 patients with acute vertebrobasilar artery occlusion. They found that 69.3% of patients with ICAS had occlusions in the proximal and middle segments of the basilar artery, while 87.5% of those with embolism had occlusions in the distal segment.

Thalamic infarctions are often detected on a pretreatment DWI in patients with acute BAO. However, to our knowledge, there have been no reports regarding the association between thalamic infarction on a pretreatment DWI and underlying ICAS. In our study, there was no significant difference between the ICAS group and the non-ICAS group in the incidence of thalamic infarction; however, the incidence of bilateral thalamic infarction differed significantly between patients with underlying ICAS and those without it. No patients with underlying ICAS showed bilateral thalamic infarctions on pretreatment DWI. This difference might be related to the occlusion segment of the basilar artery. In this study, all bilateral thalamic infarction occurred in the bilateral paramedian region, which is supplied by a single thalamoperforating artery (the artery of Percheron).

The main reasons for the poor outcomes after endovascular therapy in the study of Kim et al may be heterogeneity of the rescue treatment and intracranial angioplasty with or without stent placement as a rescue treatment DWI in patients with underlying ICAS would be low.

The optimal treatment for patients with acute BAO with underlying ICAS remains unclear. In the present study, 86.7% of patients (13/15) with underlying ICAS were treated with intracranial angioplasty with or without stent placement after first-line mechanical thrombectomy. We achieved high rates of successful revascularization (100%) and favorable outcome (60%), no symptomatic hemorrhage, and a low mortality rate (13.3%) in these 15 patients. Recently, Yoon et al reported the results of emergent angioplasty and stent placement in 40 patients with acute ischemic stroke due to underlying ICAS. They reported high rates of successful revascularization (95%) and favorable outcome (62.5%) and low rates of symptomatic hemorrhage (7.5%) and mortality (15%). They suggested that intracranial angioplasty with or without stent placement is safe and feasible in hyperacute stroke secondary to underlying ICAS. Gao et al reported a 100% successful revascularization rate and a favorable 3-month outcome rate of 46% in a series of 13 patients with acute BAO and underlying ICAS who were treated with stent-retriever thrombectomy and intracranial stent placement.

In contrast to our study, Kim et al recently reported a low rate of good outcome (10.5% with mRS 0–2 at 3 months) and a high mortality rate (21.1%) after endovascular therapy in 19 patients with acute vertebrobasilar occlusion due to ICAS. The main reasons for the poor outcomes after endovascular therapy in the study of Kim et al may be heterogeneity of the rescue treatment after primary mechanical thrombectomy, the low rate of angioplasty/stent placement as a rescue treatment, and long procedural time. In their study, one-third of patients received intra-arterial infusion of tirofiban, one-third of patients underwent angioplasty alone, and another one-third of patients underwent stent place-

<table>
<thead>
<tr>
<th>Table 2: Outcomes after endovascular therapy in 62 patients with acute stroke due to BAO</th>
<th>All Patients (n = 62)</th>
<th>Patients with ICAS (n = 15)</th>
<th>Patients without ICAS (n = 47)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mTICI 2b or 3 (No.) (%)</td>
<td>60 (96.8)</td>
<td>15 (100.0)</td>
<td>45 (95.7)</td>
<td>NS</td>
</tr>
<tr>
<td>mRS 0–2 (No.) (%)</td>
<td>33 (53.2)</td>
<td>9 (60.0)</td>
<td>24 (51.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Symptomatic hemorrhage (No.) (%)</td>
<td>1 (1.6)</td>
<td>0 (0.0)</td>
<td>1 (2.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Mortality (No.) (%)</td>
<td>10 (16.1)</td>
<td>2 (13.3)</td>
<td>8 (17.0)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Note: mTICI indicates modified TICI; NS, nonsignificant.
ment. The results of our study together with previous reports suggest that intracranial angioplasty with or without stent placement is promising in patients with acute BAO due to underlying ICAS. In addition, the procedural time was much longer in the study of Kim et al (96 versus 39 minutes in patients with ICAS and 61 versus 28 minutes in those without ICAS) than in our study.

Our study had several limitations, including a retrospective, noncontrolled study design and a limited number of patients. Prospective, multicenter studies are needed to further determine the clinical and radiologic characteristics of patients with BAO with underlying ICAS. In addition, prospective clinical trials are also needed to confirm the efficacy and safety of intracranial angioplasty and stent placement in patients with BAO with underlying ICAS compared with other treatment options such as intraarterial infusion of antiplatelet drugs.

**CONCLUSIONS**

Underlying ICAS is common in patients with acute stroke due to BAO. The occlusion site can be used as a useful marker for predicting underlying ICAS in patients with acute BAO. There was no difference in treatment outcomes after endovascular therapy between patients with underlying ICAS and those without it.

**REFERENCES**


ABSTRACT

BACKGROUND AND PURPOSE: Tandem aneurysms are defined as multiple aneurysms located in close proximity on the same parent vessel. Endovascular treatment of these aneurysms has rarely been reported. Our aim was to evaluate the safety and efficacy of a single Pipeline Embolization Device for the treatment of tandem aneurysms of the internal carotid artery.

MATERIALS AND METHODS: A retrospective analysis of consecutive aneurysms treated with the Pipeline Embolization Device between 2009 and 2016 at 3 institutions in the United States was performed. Cases included aneurysms of the ICA treated with a single Pipeline Embolization Device, and they were divided into tandem versus solitary. Angiographic and clinical outcomes were compared.

RESULTS: The solitary group (median age, 58 years) underwent 184 Pipeline Embolization Device procedures for 184 aneurysms. The tandem group (median age, 50.5 years) underwent 34 procedures for 78 aneurysms. Aneurysms were primarily located along the paraophthalmic segment of the ICA in both the single and tandem groups (72.3% versus 78.2%, respectively, \(P = .53\)). The median maximal diameters in the solitary and tandem groups were 6.2 and 6.7 mm, respectively. Complete occlusion on the last angiographic follow-up was achieved in 75.1% of aneurysms in the single compared with 88.6% in the tandem group (\(P = .06\)). Symptomatic thromboembolic complications were encountered in 2.7% and 8.8% of procedures in the single and tandem groups, respectively (\(P = .08\)).

CONCLUSIONS: Tandem aneurysms of the ICA can be treated with a single Pipeline Embolization Device with high rates of complete occlusion. While there appeared to be a trend toward higher thromboembolic complication rates, this did not reach statistical significance.

ABBREVIATION: PED = Pipeline Embolization Device

Multiple intracranial aneurysms account for 14%–34% of the distribution of all intracranial aneurysms.1–3 When these aneurysms are located in close proximity to each another on the same parent vessel, they are referred to as “tandem aneurysms.” The treatment of tandem aneurysms has rarely been reported in the literature. These aneurysms are most commonly found along the internal carotid artery and may arise within the same anatomic segment or involve adjacent segments. Rarely, they are identified in the posterior circulation.1,4–9 Flow diversion with the Pipeline Embolization Device (PED; Covidien, Irvine, California) was initially approved by the US Food and Drug Administration for treatment of large or giant, wide-neck cerebral aneurysms of the ICA from the petrous to superior hypophyseal segments.10 Numerous studies have since demonstrated the safety and efficacy of the PED in the treatment of aneurysms with varying morphologies and anatomic locations.11–16 Currently, only a few studies with small numbers of patients have evaluated endovascular treatment of tandem aneurysms with coil embolization,8 stent-assisted coiling,9 or flow diversion.9 In this study, we compare the outcomes following deployment of a single PED in 2 groups of patients, those with solitary ICA aneurysms and those with tandem ICA aneurysms.

MATERIALS AND METHODS

A retrospective analysis of consecutive aneurysms treated with PED deployment between 2009 and 2016 at 3 academic institutions in United States was performed. Inclusion criteria consisted of all adult patients with saccular intracranial ICA aneurysms treated with a single PED. Both ruptured and unruptured aneurysms were included. Patients were then divided into 2 groups: solitary aneurysms and tandem aneurysms. Tandem aneurysms
consisted of >1 intracranial ICA aneurysm within the same anatomic segment or involving adjacent anatomic segments. We collected the following information: patient demographics, aneurysm and PED characteristics, procedural complications, and angiographic and functional outcomes. Institutional review board approval was obtained at all 3 centers before commencement of the study.

Procedural Details
Patients undergoing elective aneurysm treatment received aspirin, 325 mg, and clopidogrel, 75 mg, daily for 3–14 days before the intervention. Platelet function testing was routinely performed with whole-blood lumi-aggregometry, light transmission aggregometry, or the VerifyNow P2Y12 assay (Accumetrics, San Diego, California). Clopidogrel nonresponders were identified on the basis of established cutoff values at the individual institutions and were guided by manufacturer’s recommendations. If a patient was identified as a clopidogrel responder, clopidogrel was continued. If a patient was identified as a clopidogrel nonresponder, the choice to continue the same dose of clopidogrel, administer a 1-time 600-mg clopidogrel boost within 24 hours of the procedure, or switch to ticagrelor was at the discretion of the interventionalist performing the procedure. Patients undergoing treatment of a ruptured aneurysm received a loading dose of aspirin, 650 mg, and clopidogrel, 600 mg, immediately before the intervention. Patients underwent local anesthesia with sedation or general anesthesia at the discretion of the individual institutions, and all patients were anticoagulated with heparin throughout the procedure, with an activated clotting time target of 250–300 seconds. The type of the guide catheter and microcatheter used for PED deployment was at the discretion of the individual institutions. The deployment and apposition of the PED to the ICA wall was documented by fluoroscopy. Dual antiplatelet therapy was continued for at least 3 months after the procedure, and aspirin, indefinitely thereafter.

Angiographic and Clinical Outcome
Angiographic outcome was assessed with digital subtraction angiography or MR angiography based on follow-up protocols used at each individual institution. Aneurysm occlusion on follow-up DSA imaging was assessed by the treating interventionalist. Follow-up MRAs were assessed by a diagnostic radiologist and the treating interventionalist. Occlusion was categorized as complete occlusion (100%), near-complete occlusion (90%–100%), and partial occlusion (< 90%). Functional outcomes were assessed by using the modified Rankin Scale at last follow-up.

Statistical Analysis
Statistical analysis was performed by using SPSS, Version V 21.0 (IBM, Armonk, New York). In univariate analysis, variables were compared between groups with the Mann-Whitney U test for nonparametric numeric variables and the χ² test for categoric variables. Statistical significance was defined as P < .05. Multivariate logistic regression was performed on candidate predictor variables to identify independent differences in outcome between both groups.

RESULTS
Baseline Characteristics
The solitary aneurysm group (median age, 58 years) underwent 184 PED placement procedures for the treatment of 184 aneurysms, and the tandem aneurysm group (median age, 50.5 years) underwent 34 PED placement procedures for the treatment of 78 aneurysms. Current smoking was identified in 22.8% and 52.9% of patients undergoing procedures in the solitary and tandem groups, respectively (P < .001). The pretreatment mRS was 0–2 in 97.8% and 94.1% of procedures in the solitary and tandem aneurysm groups, respectively (P = .23). Treatment of acute aneurysmal subarachnoid hemorrhage occurred in 2.2% and 8.8% of procedures in the solitary and tandem aneurysm groups, respectively (P = .11).

Aneurysm Characteristics
Aneurysms were primarily located along the paraophthalmic segment of the ICA in both the solitary and tandem aneurysm groups (72.3% versus 78.2%, respectively, P = .53). The median maximal diameter of the aneurysm was 6.2 mm in the solitary aneurysm group and 6.7 mm in the tandem aneurysm group. The median neck diameter of the aneurysm was 4 mm in the solitary group and 3.9 mm in the tandem group (Table 1). Aneurysms other than the largest aneurysm in the tandem aneurysm group had a median maximal diameter of 3 mm (range, 1–12 mm) and a median neck width of 2.4 mm (range, 1–6 mm). This finding was significantly different from the respective measurements of the largest treated aneurysm in the tandem aneurysm group and the solitary aneurysm group (P < .001 and P < .001, respectively) (Table 2). A daughter sac was present in 25.1% and 15.4% of aneurysms in the single and tandem aneurysm groups, respectively (P = .08).

Treatment Outcome
There was no significant difference in the length of the procedure in the treatment of solitary aneurysms compared with tandem aneurysms (69.5 versus 76 minutes, respectively, P = .52). Similarly, there was no significant difference in the length (P = .42) or diameter (P = .26) of PEDs used in either group. The median length of angiographic follow-up was significantly longer in the tandem aneurysm group compared with the solitary aneurysm group, 18 months (mean, 19.2 months) versus 12 months (mean, 15.4 months), respectively (P = .008). On the last angiographic follow-up, complete occlusion was achieved in 75.1% of aneurysms in the solitary aneurysm group compared with 88.6% in the tandem aneurysm group (P = .06). After stratifying the tandem aneurysm group into the largest aneurysm and other aneurysms within the tandem group, the rate of complete occlusion was not significantly higher compared with solitary aneurysms (P = .21) (Table 3). Retreatment was performed in 4.9% and 5.7% of the solitary and tandem aneurysm groups, respectively (P = .81). At last follow-up, the mRS improved in 27.5% and 27.3% of patients and worsened in 7% and 0% of the solitary and tandem aneurysm groups, respectively (P = .33). Symptomatic thromboembolic complications were encountered in 2.7% and 8.8% of procedures in the solitary and tandem aneurysm groups, respectively (P = .08). Symptoms were permanent (lasting >30
One procedure for the treatment of a solitary aneurysm was complicated by both an ischemic stroke and an intraparenchymal hemorrhage. There were no mortalities in either group (Table 4).

**DISCUSSION**

In this study, we report a multicenter experience with single PED placement for the treatment of tandem intracranial aneurysms of the internal carotid artery. Factors that influenced the decision to attempt treatment of tandem aneurysms with a single flow diverter included close proximity of the aneurysms, a favorable local angioarchitecture of the parent vessel, and small aneurysm size. Tandem aneurysms were compared with solitary aneurysms with respect to rates of aneurysm occlusion and complications. Complete occlusion rates were higher in the tandem aneurysms group compared with solitary aneurysms, with a trend toward statistical significance. A potential confounder was the small size of the adjacent aneurysms in the tandem group when the largest aneurysm was excluded. Therefore, after stratifying tandem aneurysms based on size, the difference was not statistically significant (Table 3). Despite a trend toward higher symptomatic thromboembolic complication rates in the tandem group, no statistically significant difference was identified. These findings mirror a prior study that associated a higher aneurysm occlusion rate but also procedural complications with simultaneous treatment of multiple aneurysms with the PED.13

**Endovascular Treatment of Tandem Aneurysms**

The surgical management of tandem aneurysms can be challenging, especially when paraophthalmic or posterior circulation sites are involved.6 Endovascular treatment is therefore a favorable alternative for these subgroups. Fang et al6 reported on the use of stent-assisted coiling in the treatment of 21 patients with 42 tandem aneurysms, most of which were located within the ICA or middle cerebral artery; 1 patient had tandem aneurysms located within the posterior circulation.6 Of these, 57.1% of patients presented with a ruptured aneurysm. At last angiographic follow-up (mean, 25.4 months), complete occlusion was achieved in 76.5%. There were no symptomatic thromboembolic complications. The authors concluded that stent-assisted coiling may have an advantage over the PED in the treatment of ruptured and posterior circulation aneurysms. However, there was no direct comparison within the study.

Lin et al6 reported on endovascular treatment of 13 patients with 28 tandem aneurysms. In 1 case, the aneurysms were located within the posterior circulation. Seven patients were treated with stent-assisted coiling, while the remaining 6 patients were

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**Table 1: Baseline characteristics**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Solitary Aneurysm</th>
<th>Tandem Aneurysms</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of PEDs placed</td>
<td>184</td>
<td>34</td>
<td>–</td>
</tr>
<tr>
<td>Aneurysms treated with single PED</td>
<td>184</td>
<td>78</td>
<td>–</td>
</tr>
<tr>
<td>1</td>
<td>184</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>–</td>
<td>28</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>–</td>
<td>3</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>–</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>–</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>166 (90.2%)</td>
<td>31 (91.2%)</td>
<td>.86</td>
</tr>
<tr>
<td>Male</td>
<td>18 (9.8%)</td>
<td>3 (8.8%)</td>
<td></td>
</tr>
<tr>
<td>Median age (median) (range) (yr)</td>
<td>58 (24–82)</td>
<td>50.5 (19–75)</td>
<td>.006</td>
</tr>
<tr>
<td>Smoking (No.)</td>
<td>42 (22.8%)</td>
<td>18 (52.9%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pretreatment mRS (No.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2</td>
<td>180 (97.8%)</td>
<td>32 (94.1%)</td>
<td>.23</td>
</tr>
<tr>
<td>3–5</td>
<td>4 (2.2%)</td>
<td>2 (5.9%)</td>
<td></td>
</tr>
<tr>
<td>Aneurysm location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cavernous</td>
<td>25 (13.6%)</td>
<td>7 (9%)</td>
<td>.53</td>
</tr>
<tr>
<td>Paraphalamic</td>
<td>133 (72.3%)</td>
<td>61 (78.2%)</td>
<td></td>
</tr>
<tr>
<td>Posterior communicating</td>
<td>26 (14.1%)</td>
<td>10 (12.8%)</td>
<td></td>
</tr>
<tr>
<td>Aneurysm measurements (median) (range) (mm)</td>
<td>6.2 (1.6–28.3)a</td>
<td>6.7 (2–40)b</td>
<td>.48</td>
</tr>
<tr>
<td>Maximal diameter</td>
<td>4 (1–14.3)b,c</td>
<td>3.9 (1.8–8.5)c</td>
<td>.14</td>
</tr>
<tr>
<td>Neck size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subarachnoid hemorrhage (No.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute (&lt;2 weeks)</td>
<td>4 (2.2%)</td>
<td>3 (8.8%)</td>
<td>.11</td>
</tr>
<tr>
<td>Remote (&gt;2 weeks)</td>
<td>19 (10.3%)</td>
<td>2 (5.9%)</td>
<td></td>
</tr>
<tr>
<td>Prior treatment (No.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endovascular</td>
<td>23 (12.5%)</td>
<td>2 (2.6%)</td>
<td>.031</td>
</tr>
<tr>
<td>Surgery</td>
<td>6 (3.3%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>2 (1.1%)</td>
<td>1 (1.3%)</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel responders (No.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>123 (68.7%)d,e</td>
<td>24 (75%)</td>
<td>.48</td>
</tr>
<tr>
<td>No</td>
<td>56 (31.3%)</td>
<td>8 (25%)</td>
<td></td>
</tr>
</tbody>
</table>

---

**Table 2: Aneurysm size**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Solitary Aneurysm</th>
<th>Tandem Aneurysms</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median maximal diameter (range) (mm)</td>
<td>6.2 (1.6–28.3)a,b</td>
<td>6.7 (2–40)b</td>
<td>.001</td>
</tr>
</tbody>
</table>

---

**Table 3: Occlusion rate**

<table>
<thead>
<tr>
<th>Occlusion Rate</th>
<th>Solitary Aneurysm</th>
<th>Tandem Aneurysms</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete (100%)</td>
<td>109 (75.1%)</td>
<td>36 (90%)</td>
<td>.21</td>
</tr>
<tr>
<td>Near-complete (95%–99%)</td>
<td>12 (8.3%)</td>
<td>2 (5%)</td>
<td></td>
</tr>
<tr>
<td>Partial (&lt;90%)</td>
<td>24 (16.6%)</td>
<td>2 (5%)</td>
<td></td>
</tr>
</tbody>
</table>

---

a Data are missing for 25 aneurysms.
b Data are missing for 50 aneurysms.
c Data are missing for 2 aneurysms.
d Data are missing for 5 procedures.
e Data are missing for 2 procedures.

---

days) in 1.6% and 2.9% of procedures, respectively (P = .60). One procedure for the treatment of a solitary aneurysm was complicated by both an ischemic stroke and an intraparenchymal hemorrhage. There were no mortalities in either group (Table 4).
Hemodynamics of Tandem Aneurysm Occlusion

Mut et al.9 examined the hemodynamics of tandem aneurysm occlusion following PED placement. They proposed that aneurysms located on the convex side of the parent artery wall have an inflow stream entering the aneurysm through the proximal aspect of the neck, while the aneurysms located in the concave part of the wall have an inflow through the distal aspect. Following PED placement, the aneurysms on the concave side of the parent artery have a larger reduction in aneurysm inflow, mean velocity, shear rate, and wall shear stress and smoother flow patterns, leading to faster occlusion compared with their convexity counterparts. They also reported that the energy content in the aneurysm (total kinetic energy calculated over the aneurysm sac) at the convex side changed from 30% of the energy of the parent artery to 13%, while in the aneurysm at the concave side, it changed from 18% to approximately 3%. When the energy content (or energy loss) approaches zero, the blood flow is expected to cease with subsequent blood coagulation and obliteration of the aneurysm.

In the present study, the side of the aneurysm orifice in respect to the parent artery geometry had no correlation with complete occlusion because 4 of 8 (50%) aneurysms with incomplete occlusion were located on the concave portion of the parent artery. However, in 5 of 8 (62.5%) cases of incomplete occlusion, the aneurysm was part of a tandem sequence of 2 aneurysms that were separated by at least 1 ICA segment. For example, 1 aneurysm was located in the cavernous segment of the ICA, while the second was located along the ophthalmic segment. Moreover, complete occlusion occurred in the proximal aneurysm in all cases, while the distal aneurysm failed to occlude. In the remaining cases, all aneurysms within the tandem sequence along the ophthalmic segment remained patent. Another factor that may explain the failure to occlude in tandem aneurysms is the size of aneurysm because in 5 of 8 (62.5%) cases of incomplete occlusion, the aneurysm was the larger aneurysm that failed to occlude. However, due to the limited number of cases, further studies with greater numbers of patients are required to investigate this hypothesis.

### Complications

The natural history of tandem aneurysms is not well-understood. Kaminogo et al.2 reported no significant difference in the rate of acute SAH between single and multiple aneurysms at the time of presentation, which is supported by the present study. Inagawa,1 on the other hand, reported a positive correlation between the multiplicity of the aneurysms and a risk of aneurysm rupture.

Following endovascular procedures, Lin et al.8 reported no significant difference in the rate of complications between stent-assisted coiling and the PED for the treatment of tandem aneurysms. However, in their study, the number of PEDs placed for aneurysm treatment was variable. Moreover, no previous study has compared the outcomes following PED placement in the treatment of tandem-versus-solitary aneurysms.

In the present study, symptomatic thromboembolic complications were encountered following 3 procedures (8.8%) for PED placement in the treatment of tandem aneurysms compared with 2.7% in the treatment of solitary aneurysms (P = .08). Permanent

### Table 4: Outcome measures

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Solitary Aneurysm</th>
<th>Tandem Aneurysms</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of procedure (mean)</td>
<td>69.5 (16–192)</td>
<td>76 (19–194)</td>
<td>.52</td>
</tr>
<tr>
<td>PED dimensions (median)</td>
<td>19 (12–35)</td>
<td>20 (6–30)</td>
<td>.42</td>
</tr>
<tr>
<td>PED diameter</td>
<td>4 (2.5–5.5)</td>
<td>4 (3.5–5)</td>
<td>.26</td>
</tr>
<tr>
<td>Last angiographic follow-up</td>
<td>12 (1–79)</td>
<td>18 (4.8–59)</td>
<td>.008</td>
</tr>
<tr>
<td>Complete (100%)</td>
<td>109 (75.1%)</td>
<td>62 (88.6%)</td>
<td>.06</td>
</tr>
<tr>
<td>Near-complete (90%–99%)</td>
<td>12 (8.3%)</td>
<td>4 (5.7%)</td>
<td></td>
</tr>
<tr>
<td>Partial (&lt;90%)</td>
<td>24 (16.6%)</td>
<td>4 (5.7%)</td>
<td></td>
</tr>
<tr>
<td>Retreatment (No.)</td>
<td>7 (4.9%)</td>
<td>4 (5.7%)</td>
<td>.81</td>
</tr>
<tr>
<td>Posttreatment mRS (No.)</td>
<td>169 (98.8%)</td>
<td>32 (97%)</td>
<td>.42</td>
</tr>
<tr>
<td>Improved</td>
<td>2 (1.2%)</td>
<td>1 (3%)</td>
<td></td>
</tr>
<tr>
<td>No change</td>
<td>112 (65.5%)</td>
<td>24 (72.7%)</td>
<td>.33</td>
</tr>
<tr>
<td>Worsened</td>
<td>12 (7%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Neurologic complications (No.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic thromboembolic</td>
<td>5 (2.7%)</td>
<td>3 (8.8%)</td>
<td>.08</td>
</tr>
<tr>
<td>Permanent</td>
<td>3 (1.6%)</td>
<td>1 (2.9%)</td>
<td>.60</td>
</tr>
<tr>
<td>Symptomatic hemorrhagic</td>
<td>2 (1.3%)</td>
<td>1 (2.9%)</td>
<td>.39</td>
</tr>
</tbody>
</table>

* Data are missing for 32 procedures.  
* Data are missing for 15 procedures.  
* Data are missing for 39 aneurysms.  
* Data are missing for 8 aneurysms.  
* Data are missing for 13 procedures.  
* Data are missing for 1 procedure.
symptoms (lasting >30 days) as a result of ischemic stroke were encountered in 1.6% and 2.9% of procedures for the treatment of solitary and tandem aneurysms, respectively (P = .6). Although there was a tendency for tandem aneurysms to occur in smokers, smoking per se had no significant correlation with thromboembolic complications.

Limitations
We acknowledge that our study is limited by its retrospective nature. Although the inclusion of multiple institutions improves the generalizability of the findings, it introduces variability in patient management, follow-up protocols, imaging studies, and evaluation of aneurysm occlusion. There was also variation in patient characteristics and aneurysm size between both comparison groups, and only a relatively small number of complications were observed in each group, limiting the power of the study to detect small differences between groups. However, this is the largest comparison of tandem and single aneurysms treated by the PED in the literature, to our knowledge, and there were attempts to control for significant differences between comparison groups during analysis of outcomes.

CONCLUSIONS
Tandem aneurysms of the internal carotid artery can be treated with a single PED with high rates of complete aneurysm occlusion. The higher rates of aneurysm occlusion in the tandem group compared with the solitary group could be confounded by differences in aneurysm size. While there did appear to be a trend toward higher thromboembolic complication rates in the tandem group, this did not reach statistical significance.


REFERENCES
Non-Contrast-Enhanced Silent Scan MR Angiography of Intracranial Anterior Circulation Aneurysms Treated with a Low-Profile Visualized Intraluminal Support Device


ABSTRACT

BACKGROUND AND PURPOSE: The Low-Profile Visualized Intraluminal Support Device comprises a small-cell nitinol structure and a single-wire braided stent that provides greater metal coverage than previously reported intracranial stents, as well as assumed strong susceptibility artifacts. This study aimed to assess the benefits of non-contrast-enhanced MRA by using a Silent Scan (Silent MRA) for intracranial anterior circulation aneurysms treated with Low-Profile Visualized Intraluminal Support Device stents.

MATERIALS AND METHODS: Thirty-one aneurysms treated with Low-Profile Visualized Intraluminal Support Device stents were assessed by using Silent MRA, 3D TOF-MRA, and x-ray DSA. The quality of MRA visualization of the reconstructed artery was graded on a 4-point scale from 1 (not visible) to 4 (excellent). Aneurysm occlusion status was evaluated by using a 2-grade scale (total occlusion/remnant [neck or aneurysm]). Weighted k statistics were used to evaluate interobserver and intermodality agreement.

RESULTS: The mean scores ± SDs for Silent MRA and 3D TOF-MRA were 3.16 ± 0.79 and 1.48 ± 0.67 (P < 0.5), respectively, with substantial interobserver agreement (k = 0.66). The aneurysm occlusion rates of the 2-grade scale (total occlusion/remnant [neck or aneurysm]) were 69%/31% for DSA, 65%/35% for Silent MRA, and 92%/8% for 3D TOF-MRA, respectively. The intermodality agreements were 0.88 and 0.30 for DSA/Silent MRA and DSA/3D TOF-MRA, respectively.

CONCLUSIONS: Silent MRA seems to be useful for visualizing intracranial anterior circulation aneurysms treated with Low-Profile Visualized Intraluminal Support Device stents.

ABBREVIATIONS: CE = contrast-enhanced; LVIS Jr. = Low-Profile Visualized Intraluminal Support Device; UTE = ultrashort TE

Endovascular treatment involving coil embolization is commonly used to manage both ruptured and unruptured intracranial aneurysms.1-2 In recent years, intracranial stents, including the Neuroform3,4 (Stryker, Kalamazoo, Michigan) and Enterprise stents5,6 (Codman & Shurtleff, Raynham, Massachusetts), have been implemented for the stent-assisted coil embolization of wide-neck aneurysms. Both types of stents comprise nitinol and are self-expandable. The Neuroform stent features an open-cell design with stainless steel and platinum markers7,8 whereas the Enterprise stent is a closed-cell design with tantalum markers.9,10

This study implemented the Low-Profile Visualized Intraluminal Support Device11-14 (LVIS Jr. stent; MicroVention, Tustin, California), a self-expandable nitinol single-wire braided stent comprising 1.5-mm cells. The LVIS Jr. stent contains 3 radiopaque tantalum markers on the proximal and distal tines and 3 tantalum helical strands in the stent body13,14; thus, it provides higher metal coverage (12%-21%)11-13 relative to previously reported stents. Accordingly, stent-related magnetic susceptibility during MR imaging is a topic of research interest.

Despite reports of the use of 3D TOF-MRA after stent-assisted coil embolization,9 the radiofrequency shielding and susceptibility artifacts make it difficult to visualize flow in an intracranial stent with this technique. Because the LVIS Jr. stent is composed of nitinol and features a braided component and higher metal coverage relative to earlier stents, this device may not facilitate depiction of an intracranial stent with 3D TOF-MRA for radiofrequency shielding and susceptibility artifacts.
MRA (Silent MRA) is a non-contrast-enhanced MRA technique that uses an ultrashort TE (UTE) combined with arterial spin-labeling, which is used as a preparation pulse to visualize blood flow. Subsequent data acquisition is based on 3D radial sampling. Because UTE decreases the susceptibility artifacts associated with metallic devices, Silent MRA could potentially reduce the artifacts associated with braided, high-metal-coverage stents. Accordingly, we evaluated the efficacy of Silent MRA versus 3D TOF-MRA for intracranial anterior circulation aneurysms treated with LVIS Jr. stent-assisted coil embolization.

**MATERIALS AND METHODS**

**Patient and Aneurysm Characteristics**

Between July 2015 and September 2016, 32 aneurysms in 29 patients treated with LVIS Jr. stent-assisted coil embolization for anterior circulation aneurysms were retrospectively examined. We obtained approval for this study from the ethics review board. Written informed consent was not required because of the retrospective nature of this study. One patient was excluded from the study due to postoperative deep brain stimulation with an MR imaging–unsafe device. The remaining 28 patients with 31 aneurysms comprised 13 men and 15 women with a mean age of 60.8 ± 11.3 years (range, 41–77 years). Twenty-one aneurysms were treated with a single stent, and 10 were treated with 2 stents (ie, 41 LVIS Jr. stents were used in 31 aneurysms). We deployed the following stent sizes (diameter × length): 2.5 × 13 mm (n = 21); 2.5 × 17 mm (n = 14); 2.5 × 23 mm (n = 3); and 3.5 × 18 mm, 3.5 × 23 mm, and 3.5 × 28 mm (n = 1 each). The distribution of aneurysm locations was as follows: anterior communicating artery (n = 15), internal carotid artery (n = 3), and middle cerebral artery (n = 13).

For all patients, Silent MRA and 3D TOF-MRA were performed in a single scanning session. The average interval between aneurysm treatment and both MRA evaluations was 5.6 days (range, 1–83 days; median, 1 day). The average interval between the most recent DSA evaluation and both MRA evaluations was 1.6 days (range, 1–9 days; median, 1 day).

**Silent MRA**

Silent MRA was performed with a Silent Scan. However, the details of the Silent Scan algorithm were undisclosed. Silent Scan is a combination of a 3D acquisition and reconstruction technology. This technique requires highly stable system power electronics (gradients and radiofrequency) and fast radiofrequency switching capability within the radiofrequency coil structure. This process slowly steps the gradients while collecting data during a 3D acquisition. The data acquisition is based on a 3D radial sampling, and an arterial spin-labeling technique is used as a preparation pulse to visualize blood flow. In Silent MRA, control images (nonlabelled images) are scanned before the labeling pulse. Labeled images are scanned after the labeling pulse, and the labeled blood exhibits low signal intensity. The angiographic images of blood flow are the result of subtraction of labeled images from control images.

**Intra-Arterial DSA Technique**

X-ray catheter-based intra-arterial cerebral DSA was performed with the following biplane angiographic system: Artis Q BA Twin (Siemens, Erlangen, Germany). The image matrix and FOV were 1024 × 1024 and 170 × 170 mm, respectively. The temporal resolution was 3 frames per second. Selective manual internal carotid artery injections were administered according to the aneurysm location. Rotational 3D angiography was performed for additional confirmation of the findings. Additional selected working angles were obtained to clarify the aneurysmal anatomy at the discretion of the neurosurgical interventionist.

**MRA Scan Parameters**

Silent MRA and 3D TOF-MRA were performed on a 3T MR imaging unit (Discovery MR750w; GE Healthcare) with a 12-channel array.
head-neck coil system. The following scan parameters were used for Silent MRA: TR/TE, 642.8/0.016 ms; flip angle, 5°; FOV, 180 × 180 mm; matrix, 180 × 180; section thickness, 1.0 mm (with section interpolation); NEX, 1.4; bandwidth, ±31.2 kHz; acquisition time, 12 minutes 13 seconds; and reconstructed voxel size, 1.0 × 1.0 × 0.5 mm.

The 3D TOF-MRA scan parameters were as follows: TR/TE, 20/2.9 ms; flip angle, 18°; FOV, 200 × 200 mm; acquisition matrix, 416 × 224; section thickness, 1.0 mm (with section interpolation); NEX, 1; bandwidth, ±41.7 kHz; acquisition time, 4 minutes 45 seconds (3 slabs, overlap between a slab: 14 sections, 1 slab: 38 sections); reconstruction matrix, 512; and reconstructed voxel size, 0.39 × 0.39 × 0.5 mm.

**Image Analysis**

Each DSA, Silent MRA, and 3D TOF-MRA series was anonymized by random number assignment. We evaluated DSA images and the 2 types of MRA images. The 2 types of MRA images were assessed separately to minimize bias due to knowledge of the results of the other MRA image. We used MIP and source images. All images were independently evaluated in random order by 2 neuroradiologists (M.S. and R.I., who have 15 and 6 years of experience in neuroradiology, respectively) on the PACS. In all images, the window-width and window-level could be modified for evaluation. The locations of the treated aneurysms to be evaluated were provided to the 2 observers because the pretreatment x-ray DSA images were unavailable.

The quality of Silent MRA- and 3D TOF-MRA-based visualization of the reconstructed arteries was evaluated. Two neuroradiologists independently reviewed both types of MRAs and rated visualization of the flow in each stent subjectively on a 4-point scale as follows: 1, not visible (near-complete signal loss or no signal); 2, poor (structures are slightly visible but with substantial artifacts or blurring); 3, acceptable (acceptable diagnostic quality with medium artifacts or blurring); 4, excellent (good diagnostic quality with minimal artifacts or blurring). Figure 1 shows a sample of the 4-point scale. Aneurysm occlusion was evaluated by using a 2-grade scale (total occlusion/remnant [neck or aneurysm]). The most recent DSA images were used as a reference standard.

**Statistical Analysis**

The scores of MIP images from the 2 observers were averaged, and the scores were compared between techniques by using the Wilcoxon signed rank test. A P value < .05 was statistically significant. Weighted κ statistics were used to evaluate interobserver and intermodality agreement. According to Landis and Koch, κ was interpreted as follows: <0, no agreement; 0–0.19, poor agreement; 0.20–0.39, fair agreement; 0.40–0.59, moderate agreement; 0.60–0.79, substantial agreement; and 0.80–1.00, almost perfect agreement. All statistical analyses were performed by using SPSS software, Version 22 (IBM, Armonk, New York).

**RESULTS**

The mean scores (±SDs) for Silent MRA and 3D TOF-MRA differed significantly, with respective values of 3.16 ± 0.79 and 1.48 ± 0.67 (P < .05), and substantial interobserver agreement was observed (κ = 0.66). The aneurysm occlusion rates of the 2-grade scale (total occlusion/remnant [neck or aneurysm]) were 69%/31% for DSA, 65%/35% for Silent MRA, and 92%/8% for 3D TOF-MRA. Intermodality agreement values of 0.88 and 0.30 were obtained for DSA/Silent MRA and DSA/3D TOF-MRA, respectively. Figures 2-4 are representative images.
DISCUSSION

This study demonstrated superior visualization of the reconstructed artery with Silent MRA compared with 3D TOF-MRA in patients treated with LVIS Jr. stents. With consensual x-ray DSA as a reference standard, the intermodality agreement was better with Silent MRA than with 3D TOF-MRA. Moreover, Silent MRA showed strong concordance with DSA for the detection of occluded aneurysms, despite the small diameter of the LVIS Jr. stent. Several studies have evaluated LVIS Jr. stent-assisted coil embolization; however, none have used MRA for follow-up evaluations after treatment with LVIS Jr. stents, though 3D TOF-MRA, Silent MRA, and contrast-enhanced (CE)-MRA have been used to follow up patients who underwent other stent-assisted coil embolizations. Cho et al reported a good correlation between 3D rotational angiography and 3D TOF-MRA, which was attributed to the very small voxel size, whereas Irie et al reported the efficacy of Silent MRA in stent-assisted coil embolization. Although the authors reported superior visualization of neck remnants with Silent MRA versus 3D TOF-MRA, they assessed only closed-cell Enterprise stents. Takano et al reported on a Silent MRA study in Y-configuration stent-assisted coil embolization. The visualization ability of Silent MRA was superior to that of 3D TOF-MRA in a study that included Neuroform, Enterprise, and LVIS Jr. stents. In this study, Silent MRA showed neck remnants more precisely than did 3D TOF-MRA. In contrast, Agid et al reported that CE-MRA better depicted flow in a stent, compared with 3D TOF-MRA, in a study that included Neuroform, Enterprise, and LEO (Balt Extrusion, Montmorency, France) stents. CE-MRA and DSA had similar visualization abilities; however, CE-MRA was associated with several complications such as nephrogenic systemic fibrosis, gadolinium accumulation, and anaphylactic shock.

In this study, although Silent MRA had a larger matrix size than 3D TOF-MRA, it yielded superior visualization of the reconstructed artery. This outcome was attributed to the use of a UTE, which minimizes phase dispersion of the labeled blood flow signal and reduces magnetic susceptibility artifacts. Specifically, the TE was 2.9 ms during 3D TOF-MRA, but only 0.016 ms during Silent MRA. In our study, Silent MRA with a UTE allowed the precise visualization of in-stent flow. A LVIS Jr. stent diameter of 2.5 mm was used for 38 stent placements in 28 patients (93%). During 3D TOF-MRA, the in-stent signal in this type of stent is affected by susceptibility artifacts caused by stents and coils. Therefore, the use of a small-diameter stent is more likely to reduce the in-stent signal. In contrast, Silent MRA allows precise visualization of the in-stent signal. The UTE used with this technique can minimize phase dispersion of the labeled blood flow signal in the voxel and reduce the magnetic susceptibility artifacts. Accordingly, artifacts caused by stents or coils are reduced.

Notably, Silent MRA yields better detection of aneurysm occlusions compared with 3D TOF-MRA. Because 3D TOF-MRA uses the inflow effect to visualize blood flow signal, a higher flip

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FIG 3. A 71-year-old man. A, Stent-assisted coil embolization of the anterior communicating artery is performed with a LVIS Jr. stent (2.5 x 17 mm). The neck remnant is indicated by the long white arrow. Short black arrows indicate stent edges. B, X-ray digital angiography shows the stent edges (short black arrows). C, Silent MRA shows minimal signal loss at the stented segment (outlined arrow). The neck remnant is depicted almost equally well as with digital subtraction angiography (long white arrow). D, 3D time-of-flight MRA shows almost complete signal loss in the stented segment (outlined arrow). The neck remnant is not depicted. The scores of Silent MRA by 2 observers are 4 and 4. The scores of 3D TOF-MRA are 1 and 1.
Agid et al.,26 CE-MRA is superior to x-ray DSA for the detection of remnant by a lack of x-ray penetration of the coil mass itself. According to a finding that was attributed to the reduction in susceptibility artifacts as a result of using a UTE during Silent MRA. In addition, the blood flow saturation effect was reduced when using arterial spin-labeling for blood flow depiction. Thus, Silent MRA might be useful for follow-ups of patients treated with LVIS Jr. stents.

Silent MRA can be used to visualize the in-stent flow. Moreover, it can depict a neck remnant also shown with x-ray DSA. Therefore, Silent MRA can be used as a substitute for the x-ray DSA.

One of the disadvantages of Silent MRA is motion artifacts due to the long scanning duration. However, only a few cases showed severe motion artifacts. In many cases, the artifacts were caused by an oral motion, so there was not much influence on the depiction of intracranial blood vessels. The acquisition time required for Silent MRA is very long for clinical use, but it offers advantages in the visualization of in-stent flow.

Our study had some limitations. First, the sample size was small; preferably, we would add additional cases. Second, we did not evaluate CE-MRA, which is known to be useful for follow-ups after stent-assisted coil embolization and depiction of helmet-type remnants. Therefore, comparative evaluations with CE-MRA are also required. Third, in this study, we evaluated only anterior circulation aneurysms. Additional study is needed because posterior circulation aneurysm cases may yield different results. Fourth, a Pointwise Encoding Time Reduction with Radial Acquisition (PETRA) MRA sequence (Siemens) with similarities to Silent MRA has been reported, and this sequence may yield results similar to those of the present study. A comparison of these sequences should be performed in the future.

We did not set the time interval between the MRA readings. This study may be biased by a neuroradiologist’s recognition of previous MRA images. Experienced neuroradiologists might recognize 2 types of MRA images of the same subject. Therefore, this evaluation may, in effect, be nonblinded. Moreover, in this study, there are some of cases of differences in the duration of the period between the evaluation of DSA and MRA images (average, 1.6 days; range, 1–9 days; median, 1 day). These differences may lead to changes in remnant size.

Most interesting, in our series, a helmet-type remnant was detected in 3 patients by Silent MRA. This remnant type is caused by a lack of x-ray penetration of the coil mass itself. According to Agid et al., CE-MRA is superior to x-ray DSA for the detection of helmet-type remnants. Notably, Silent MRA may similarly detect helmet-type remnants and has the advantage of being a non-contrast-enhanced technique. Figure 4 demonstrates a helmet-type remnant.

The self-expandable, single-wire braided nature of the LVIS Jr. stent allows greater metal coverage of the blood vessel, compared with conventional open-cell and closed-cell stents. The open-cell Neuroform stent and closed-cell Enterprise stent yield 11% and 10% coverage, respectively, and flow-diverter stents yield approximately 30%–35% coverage. In contrast, the LVIS Jr. stent yields approximately 12%–21% coverage. Furthermore, the adaptation blood vessel diameter is smaller with the LVIS Jr. stent compared with the Neuroform and Enterprise stents. Because the metal quantity per unit blood vessel area increases with the LVIS Jr. stent, 3D TOF-MRA depictions of the neck remnants of aneurysms are thought to be more difficult following LVIS Jr. stent placement, compared with Neuroform and Enterprise stent placement.

Nevertheless, our study observed a good intermodality agreement between DSA and Silent MRA during an evaluation of aneurysm occlusion. In particular, Silent MRA and x-ray DSA yielded results of similar quality, but the visualization of in-stent flow. Moreover, it can depict a neck remnant also shown with x-ray DSA. Therefore, Silent MRA can be used as a substitute for the x-ray DSA.

One of the disadvantages of Silent MRA is motion artifacts due to the long scanning duration. However, only a few cases showed severe motion artifacts. In many cases, the artifacts were caused by an oral motion, so there was not much influence on the depiction of intracranial blood vessels. The acquisition time required for Silent MRA is very long for clinical use, but it offers advantages in the visualization of in-stent flow.

Our study had some limitations. First, the sample size was small; preferably, we would add additional cases. Second, we did not evaluate CE-MRA, which is known to be useful for follow-ups after stent-assisted coil embolization and depiction of helmet-type remnants. Therefore, comparative evaluations with CE-MRA are also required. Third, in this study, we evaluated only anterior circulation aneurysms. Additional study is needed because posterior circulation aneurysm cases may yield different results. Fourth, a Pointwise Encoding Time Reduction with Radial Acquisition (PETRA) MRA sequence (Siemens) with similarities to Silent MRA has been reported, and this sequence may yield results similar to those of the present study. A comparison of these sequences should be performed in the future.

We did not set the time interval between the MRA readings. This study may be biased by a neuroradiologist’s recognition of previous MRA images. Experienced neuroradiologists might recognize 2 types of MRA images of the same subject. Therefore, this evaluation may, in effect, be nonblinded. Moreover, in this study, there are some of cases of differences in the duration of the period between the evaluation of DSA and MRA images (average, 1.6 days; range, 1–9 days; median, 1 day). These differences may lead to changes in remnant size.

FIG 4. A 45-year-old woman. A, Stent-assisted coil embolization is performed with LVIS Jr. stents (2.5 × 13 mm and 2.5 × 17 mm) for a left middle cerebral artery bifurcation. The neck or aneurysm remnant is not depicted. Short black arrows indicate stent edges. B, X-ray digital angiography indicates stent edges (short black arrows). C, Silent MRA depicts the aneurysm remnant (long white arrow). Stented segments are slightly visible, and moderate signal loss is apparent on Silent MRA (outlined arrows). D, 3D time-of-flight MRA does not depict the neck or aneurysm remnant and yields a complete signal loss at the stented segment (outlined arrows). The scores of Silent MRA by 2 observers are 3 and 2. The scores of 3D TOF-MRA are 1 and 1.
CONCLUSIONS
Silent MRA is superior to 3D TOF-MRA in the quality of visualization of a reconstructed artery and has strong concordance with DSA for the detection of aneurysm occlusions. Moreover, Silent MRA may detect helmet-type remnants, thus eliminating the need for gadolinium contrast agents. Silent MRA might therefore be useful for intracranial anterior circulation aneurysms treated with LVIS Jr. stent-assisted coil embolization.

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REFERENCES
17. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159–74 CrossRef Medline


Jugular Anomalies in Multiple Sclerosis Are Associated with Increased Collateral Venous Flow


ABSTRACT

BACKGROUND AND PURPOSE: To date, research on extracranial venous collaterals has been focused on structure, with relatively little attention paid to hemodynamics. We addressed this limitation by quantitatively comparing collateral flow in patients with multiple sclerosis and healthy controls by using phase-contrast MR imaging. We hypothesize that patients with MS with structurally anomalous internal jugular veins will have elevated collateral venous flow compared with healthy controls.

MATERIALS AND METHODS: The sample consisted of 276 patients with MS and 106 healthy controls. We used MRV to classify internal jugular veins as stenotic and nonstenotic based on an absolute cross-sectional area threshold in 276 patients with MS and 60 healthy controls; 46 healthy controls lacked this imaging. Individual and total vessel flows were quantified by using phase-contrast MR imaging on all patients. Veins were classified by extracranial drainage type: internal jugular veins (I), paraspinal (II), and superficial (III). Differences among healthy controls, patients with MS, nonstenotic patients, and stenotic subgroups in total venous flow by vessel type were evaluated in a general linear model for statistical analysis.

RESULTS: In the MS group, 153 patients (55%) evidenced stenosis, whereas 12 (20%) healthy controls were classified as stenotic (P < .001). Compared with healthy controls, the MS group showed lower type I flow and increased type II flow. Stenosis was associated with reduced flow in the type I vessels [F(1,272) = 68; P < .001]. The stenotic MS group had increased flow in the type II vessels compared with the nonstenotic MS group [F(1,272) = 67; P < .001].

CONCLUSIONS: Compared with healthy controls, patients with MS exhibit reduced venous flow in the main extracerebral drainage vein (internal jugular vein). In contrast, flow in the paraspinal venous collaterals is elevated in patients with MS and exacerbated by venous stenosis. Collateral drainage may be a compensatory response to internal jugular vein flow reduction.

ABBREVIATIONS: CSA = cross-sectional area; HC = healthy control; IJV = internal jugular vein; PC = phase-contrast

Multiple sclerosis is an inflammatory, demyelinating disease of the CNS. The exact origin remains elusive, though epidemiologic studies have shown that it is multifactorial and likely caused by an interaction between environmental and genetic factors. Although autoimmune etiology is the current consensus, a recent vascular hypothesis of MS suggested chronic cerebrospinal venous insufficiency as a major culprit. The chronic cerebrospinal venous insufficiency hypothesis postulates that abnormalities in the structure and hemodynamics of intracranial and extracranial veins may induce MS symptoms. Initial research on chronic cerebrospinal venous insufficiency used Doppler sonography and catheter venography to quantify flow and visualize vascular anatomy, respectively. Since then, however, several attempts to validate the initial findings yielded mixed results. The lack of standardized image modalities and analytic methods, as well as low statistical power, may explain the discrepant conclusions.

MR imaging, unlike ultrasonography, is an operator-independent method that can detect demyelinating and iron-laden lesions in the brain parenchyma and confirm the MS diagnosis. The advantages of MR imaging, in addition to lesion detection, are the abilities to rapidly generate a 3D map of the vasculature by using venography and to quantify blood flow in large and small extracranial blood vessels by using phase-contrast (PC) flow quantification. These methods have been already successfully applied
to detecting vascular and flow abnormalities in the internal jugular vein (IJV) in healthy older adults and within a subset of patients with MS. Research on venous abnormalities in MS thus far has been limited to the IJV, and little is known about extracranial venous collateralization. The extrajugular drainage system consists of the vertebral venous system, the deep cervical veins, which anatomically are paraspinal toward the heart; and the anterior and external jugular veins, which receive blood from facial and superficial areas. Although the presence and structure of collateral veins have been assessed by using time-resolved imaging of contrast kinetics venography, flow values were not quantitatively evaluated. The purpose of this work was to examine the relation of extracranial venous anatomy and flow in a large cohort of patients with MS and healthy controls (HCs) taken from our neuroimaging data base.12 Because of the complexity of the extracranial venous system, we have classified these vessels into 3 groups based on anatomic MR information and their drainage path: primary (ie, IJV), paraspinal, and superficial. We hypothesized that increased venous paraspinal and superficial flow will also be observed for cases that evidence abnormal IJV structure and flow. In contrast, a subset of patients with MS may have a distinct collateral venous flow pattern compared with patients with MS and HCs without structural venous anomalies.

MATERIALS AND METHODS

Participants

The sample consisted of 276 patients with MS (194 women; mean, 48.8 years; SD, 10.9 years) and 106 HCs (58 women; M, 42.4 years; SD, 15.4 years). The patients with MS were classified into 3 types: relapsing-remitting (n = 157), primary-progressive (n = 30), and secondary-progressive (n = 39), whereas 30 patients did not have a known subtype. Patients with MS were excluded if they had a history of hypertension, previous vascular intervention, or presence of hypercoagulable state. Pregnant women and patients with cognitive impairment who were incapable of signing an informed consent form were also excluded. HCs were excluded if they had a history of diabetes, chronic renal disease, psychiatric or neurologic disorder, or substance abuse. All patients with MS and HCs with any contraindicated implant(s) were not included in this study.

Data Acquisition

All data were collected under Health Insurance Portability and Accountability Act guidelines and institutional review board approval. 3D contrast-enhanced MRV and 2D TOF MRV were used to assess the anatomy of the extracranial vessels on all patients with MS and 60 HCs because 46 of the 106 HCs lacked this imaging. Blood flow was quantified with PC-MR imaging at the C2–C3 cervical level for all patients with MS and HCs. Data from patients with MS were collected from 2 sites by using a 3T Trio Scanner (Siemens, Erlangen, Germany),3,7 and HC images were acquired on a 3T Verio scanner (Siemens)7 at the MR Research Facility at Wayne State University. On both scanners, a 16-channel head/neck coil arrangement was used. Imaging parameters and inclusion/exclusion criteria have been described in a previous publication.7

Image Processing and Analysis

All data were processed and reviewed retrospectively with Signal Processing In Nuclear MR software (SPIN; MR Imaging Institute for Biomedical Research, Detroit, Michigan). Two raters evaluated MRV (3D time-resolved imaging of contrast kinetics or 2D TOF MRV if available) to assess stenosis of the IJVs in all samples by using established methods.7 Patients were classified as stenotic if the IJV met the following stenosis criteria: if the cross-sectional area (CSA) was less than 25 mm² at the segment caudal to the C3 vertebral level and less than 12.5 mm² at the segment cranial to the C3 vertebral level.3,4 Atretic or aplastic IJVs that showed no signal on venography were also categorized as stenotic. The cutoff of 25 mm² was chosen assuming 70% stenosis in an IJV diameter of 1 cm.3,14 Discernable arterial and venous structures that flow to and from the cerebrum were identified and subtyped by using venography and PC flow sequences.

PC flow sequences were processed by 3 raters who were blinded to participants’ characteristics. Vessels were demarcated by using an intensity threshold–based method, with manual tracing if necessary (Fig 1). Boundaries for each vessel were checked on the PC magnitude and phase maps. A list of vessels that were traced for each cervical level is given in the Table. Flow rates (mL/s) were calculated based on integrated flow velocities within the vessel lumen. Velocities that exceeded 50 cm/s were unwrapped by SPIN software by using a robust automatic unwrapping algorithm that compares pixel-wise phase values in the x, y, and z directions and ensures that only pixels that are aliased are unwrapped.15

Venous structures were classified by drainage mode into 3 types (Table): type I, IJV; type II, paraspinal veins; and type III, superficial veins. For all statistical analyses, total venous flows,
which is the bilateral sum of all included vessels within a vessel type, were used for each type.

**Statistical Methods**

Individual and group differences in flow measured in the 3 vessel types were assessed within a general linear model framework. Flow at the C2–C3 cervical level served as the dependent variable; age and sex were entered as covariates. First, we gauged the differences in flow between 2 diagnostic groups (group, patients with MS versus HCs) across 3 vessel types, with vessel type being a within-patient variable and group being a between-patient variable. A full model that included all interactions was tested first, and nonsignificant interactions were removed before evaluating a reduced model. All significant interactions were decomposed by using post hoc analyses of simple effects. For all statistical analyses, we used SYSTAT 13.0 (Systat Software, San Jose, California).

Before data processing, interrater reliability in assessing flow volume per cardiac cycle (mL/CDC) was tested by using an intraclass correlation coefficient—2 statistic that assumes random raters. Total vessel flow for the ICA, vertebral artery, and IJV, as well as their sum (right + left) vessel flow, were tested in prior studies of patients with MS and healthy adults. For this study, we evaluated the reliability of total cerebral blood flow values (ICA + vertebral artery for the C2–C3 neck level), as well as total type II and III venous flow indicators. All rater pairs met a reliability of intraclass correlation coefficient—2 > 0.9 for vessel totals. Agreement between raters for anatomic assessment was calculated by using a Cohen κ statistic from a sample of 15 patients with MS and 15 HCs. The raters had an agreement of 0.87. For Cohen κ, we considered values above 0.75 as excellent, values of 0.40–0.75 as modest, and values below 0.40 as low.

**RESULTS**

**Anatomic Assessment**

Among patients with MS, 153 (60%) had venous stenosis. No age differences between the groups were found (P=.84). Stenosis was more prevalent among men (39/82; 72%) than women (94/194; 48%; P < .001). Among HCs, only 60 (M, 37.9 years; SD, 10.9 years) were evaluated for stenosis because of a lack of anatomic venography imaging data (2D TOF MRV and 3D contrast enhanced MRA) on the remaining 46 HCs. Stenosis was identified in 12 HCs (20%, 5 men and 7 women; P = .24).

**Differences in Flow between Diagnostic Groups and among Vessel Types**

Small age differences were noted in venous flow [F(1378) = 15.92; P < .001]; significance was reached only for type I vessels (r = −0.13; P = .015). Neither sex- nor group-related differences were found (both main effects, F < 1). However, a significant vessel × group interaction was observed [F(2756) = 23; P < .001]. Decomposition of that interaction into simple effects revealed greater flow in type I vessels among HCs compared with patients with MS [8.43 ± 0.27 mL/s versus 7.32 ± 0.18 mL/s; F (1378) = 12; P = .001] and lesser flow in type II vessels for HCs compared with patients with MS [0.70 ± 0.17 mL/s versus 2.11 ± 0.11 mL/s; F (1378) = 49; P < .001]. No flow differences in type III vessels were observed between the HCs and the patients with MS [1.22 ± 0.70 mL/s versus 1.40 ± 0.11 mL/s; F (1378) = 2.0; no significance]. Fig 2 shows the mean total flows by venous drainage type plotted for the MS and HC groups.

**Venous Stenosis and Venous Flow in Patients with MS**

Among patients with MS, mild age differences in flow were observed [F(1272) = 11; P = .001; r = −.18, P = .03 for type II vessels, with the effect for type I and type III being nonsignificant]. The presence of stenosis was associated with a significant overall reduction in venous flow [F(1272) = 4; P = .038]. However, the main effect was qualified by a significant vessel type × stenosis interaction [F(2544) = 71.23; P < .001].

Decomposition of the interaction revealed that stenosis was associated with reduced flow in the type I vessels compared with the nonstenotic cohort [6.20 ± 0.21 mL/s versus 8.86 ± 0.26 mL/s; F(1272) = 68; P < .001]. In contrast, patients with MS with stenosis had increased flow in the type II vessels [2.79 ± 0.14 mL/s versus 1.08 ± 0.17 mL/s; F(1378) = 67; P < .001]. A smaller but significant increase in flow was observed in type III vessels of patients with stenosis [1.37 ± 0.089 versus 0.99 ± 0.11; F(1272) = 8; P = .005]. No effects of MS subtype were observed [main effect F(2221) = 1, nonsignificant; all interactions F < 1]. Fig 3 details the mean total flows for nonstenotic-MS, stenotic-MS, and HC groups.

**DISCUSSION**

The main finding in this study is that in patients with MS compared with HCs, venous flow is reduced in the IVJ but increased in the paraspinal and other collateral veins. Moreover, in patients with MS, the presence of visible structural abnormalities, such as venous stenosis, is associated with a further decrease in jugular flow and an increase in drainage through the collateral veins.

Under normal physiologic conditions, encephalic drainage depends on body position. In the supine position, the IJVs drain venous stenosis, is associated with a further decrease in jugular flow and an increase in drainage through the collateral veins. In the upright position, the IJVs merge with the subclavian vein to form the brachiocephalic vein, which drains the venous blood back to the heart. Along the way, several tributaries may enter the IJVs at the cervical level. The collateral veins’ primary function is to augment venous drainage. The findings in this study suggest that blood may be draining via anastomosis through such structures as the anterior.
condylar confluence and into the vertebral venous system. Increased intra-abdominal and intrathoracic pressures have also been known to shunt blood through the vertebral and epidural networks. Although HCs are not exempt from having stenosis, and variations have been reported in non-disease states, the percentage of stenotic HCs is far less (20%) than the percentage of stenotic patients with MS (55%; \( P < .001 \)). Of note, flow in nonstenotic patients with MS is similar to HCs for all venous types, whereas stenotic patients with MS show markedly reduced IJV flow and elevated type II and III venous flow compared with nonstenotic counterparts and control patients. Although our method has been consistent in predicting jugular stenosis and resultant outflows, it is uncertain whether altered venous outflow stems from the disease or some other cause.

Our results are in accord with the findings of McTaggart et al, who showed greater IJV flattening and a trend toward venous collaterals specifically in MS compared with HCs. They have, however, used TOF and time-resolved imaging of contrast kinetics MRV without quantifying the flow. Using a fixed CSA as well as quantitative flow measurement, as reported here, removes the subjectivity of a nominal assessment. A pilot study by Zamboni et al also showed that HCs tend to drain blood via the IJVs as opposed to collaterals. Torres et al, however, found that the recruitment of extracranial veins as collaterals was a common finding in patients without MS by using contrast-enhanced MR angiography and venography imaging. Zivadinov et al reported no evidence of increased collaterals in MS by using TOF and time-resolved imaging of contrast kinetics. Their method for evaluating collaterals was ordinal: any collaterals that were \( >5 \) mm in diameter (or \( 7 \) mm for the segment of the inferior segment of the external jugular vein) were noted as prominent. This shows that anatomic assessment alone is not enough to show differences between patients with MS and HCs and may provide an incomplete picture of the cerebral hemodynamics.

**FIG 2.** Comparison of total mean flows (mL/s) for vessel types between diagnostic groups. The error bars represent standard errors of the mean.

**FIG 3.** Comparison of total mean venous flow (mL/s) by vessel type among nonstenotic-MS (NST-MS), stenotic-MS (ST-MS), and HC groups. The error bars represent standard errors of the mean.
In contrast with recent studies that used a percentage method for assessing jugular stenosis, we used an absolute threshold for the CSA measurement. We posit that the percentage method is limited because of the variation in IJV size and shape and its venous tributaries, as well as its compliance, sometimes manifesting as pinpoints, elliptic, or crescentic shapes. In our previous work, we have shown differences between the 2 methods and how using a percentage stenosis method leads to higher rates of stenosis in both HC and MS groups compared with an absolute method. A CT-based analysis of CSA that used a percentage method revealed high variability of the IJV and increasing mean CSA values along the caudal direction of the IJV. This vessel property served as the rationale for using absolute CSA thresholds for both the upper and lower neck levels.

An investigation of structural and functional alterations in the veins of patients with MS based on postcontrast 3D volumetric interpolated brain examination data revealed a high prevalence of stenosis when using a nominal assessment method. PC-MR imaging analysis of blood flow velocity demonstrated reflux. Although the authors claimed that 6 of the 28 patients had nearly completely occluded IJVs, they reported that the flow was not abnormal in these cases. This is an unusual finding given that a completely occluded vessel should have no flow. Their findings differ from ours, which suggest that the IJV morphology analysis method may affect the conclusion pertaining to the effects of morphology on venous flow.

Our findings should be interpreted in the context of several limitations. The imperfect resolution of MR imaging methods may affect the prediction of stenosis and flow. TOF- and time-resolved imaging of contrast kinetics venography have been shown to have lower specificity and positive predictive value relative to catheter venography. The latter, while remaining the “gold standard” for assessing stenosis, is invasive, and it does not provide global and quantifiable functional information about the venous system. Moreover, MR venography methods are in good agreement with contrast venography, though MRV may have the tendency to overestimate vessel stenosis.

The 2D PC-MR imaging flow sequence in this study is limited to capturing velocities only in the cranial and caudal directions because the data are collected in the plane perpendicular to the major arteries and veins of the neck. Advanced MR techniques such as 4D flow can successfully capture the spiral/vortexed flow property at the jugular bulb in persons with and without luminal irregularities. In a recent study, the application of a 4D flow technique combined with 3D contrast-enhanced MRA and Doppler sonography was used to evaluate venous structure and function in MS and other neurologic diseases. In that study, only a small group of participants met the criterion of chronic cerebrospinal venous insufficiency, with patients and HCs equally represented. The authors also concluded that a small amount of reflux in the cerebrospinal venous system may be a normal variant. Although these findings are discordant with ours, the study suffers from 2 notable drawbacks: the low intraobserver agreement when using 3D MRA to assess venous stenosis and the large age ranges used in their group comparisons yielding high variability in the flow estimates. Although 4D flow MR imaging enables diverse velocity field–based analyses, it is limited by low spatial and temporal resolution, systematic errors and noise, and the inability to resolve instantaneous and small-scale velocities. Further improvements in the reliability and validity of this promising approach are needed before these discrepancies can be resolved.

Morphologic IJV changes may also be due to several other factors: head and neck position, intrathoracic pressure, extrinsic compression from the coil, and swallowing movement artifacts. Small arteries and venules are difficult to measure when using PC-MR imaging, so it is not certain how the microvasculature is affected by a primary venous stenosis. Moreover, age, sex, hand side, and body mass index have been shown to affect IJV CSA; our stenosis criteria measurement did not account for those factors. Recent semiautomatic estimation of IJV calibers at all neck levels reported 37.47 ± 19.00 mm² for the left IJV and 45.03 ± 21.86 mm² for the right IJV at the C2 level. At 70% stenosis, this would be a CSA of 11.24 mm² and 13.5 mm², respectively, which lends further credence to our initial upper neck level threshold of 12.5 mm². Buch et al, while reporting normal variations in the caliber of IJVs in patients with MS and HCs, noted a C1 neck level average CSA of 47.7 ± 24.8 mm² and 66.0 ± 29.7 mm² for the left and right IJVs, respectively; 70% of these values would be 14.3 mm² and 19.8 mm², which lends further credence to our initial upper neck level threshold of 12.5 mm². Future studies should use the aforementioned indices when diagnosing for venous stenosis. Because the HC data were pooled from multiple studies at the same imaging center, 46 of the HCs lacked anatomic venographic imaging because it was not included for that particular study. On the other hand, the flow measurements from that study helped increase the statistical power of the analysis. Future studies should include additional HCs to allow for the comparison of a higher percentage of stenotic cases with the other subgroups. Last, the comparison of MRV findings should be interpreted with caution because the groups that did have venography were not age-matched, which may skew the results because of the younger age of the HC group because age has been correlated with CSA for all cervical levels.

CONCLUSIONS
PC-MR imaging is a viable method for quantifying the extent of compensation in the extracranial venous system in MS and has demonstrated an increase in collateral flow caused by the presence of jugular stenosis. It is possible that this increase in collateral drainage is a compensatory response in the MS-affected brain to reduction of the IJV flow.

ACKNOWLEDGMENTS
The authors would like to thank Magnetic Resonance Innovations, Inc. - India for their assistance in data processing and Dr. Phillip Levy for usage of healthy control data.
REFERENCES

18. Nylin G, Hedlund S, Regnstrom O. Studies of the cerebral circula-
Functional Connectivity in Virally Suppressed Patients with HIV-Associated Neurocognitive Disorder: A Resting-State Analysis

J.R. Chaganti, A. Heinecke, T.M. Gates, K.J. Moffat, and B.J. Brew

ABSTRACT

BACKGROUND AND PURPOSE: HIV-associated neurocognitive disorder still occurs despite virally suppressive combination antiretroviral therapy. In the pre-combination antiretroviral era and in patients without HIV suppression, HIV-associated neurocognitive disorder was caused by synaptic and dendritic injury resulting in impairment of neural networks, characterized by decreased attention, psychomotor slowing, and working memory deficits. Whether similar pathogenesis is true for HIV-associated neurocognitive disorder in the context of viral suppression is not clear. Resting-state fMRI has been shown to be efficient in detecting impaired neural networks in various neurologic illnesses. This pilot study aimed to assess resting-state functional connectivity of the brain in patients with active HIV-associated neurocognitive disorder in the context of HIV viral suppression in both blood and CSF.

MATERIALS AND METHODS: Eighteen patients with active HIV-associated neurocognitive disorder (recent diagnosis with progressing symptoms) on combination antiretroviral therapy with viral suppression in both blood and CSF and 9 demographically matched control subjects underwent resting-state functional MR imaging. The connectivity in the 6 known neural networks was assessed. To localize significant ROIs within the HIV and control group, we performed a seed-based correlation for each known resting-state network.

RESULTS: There were significant group differences between the control and HIV-associated neurocognitive disorder groups in the salience (0.26 versus 0.14, \(t = 2.6978, df = 25, P = .0123\)) and executive networks (0.52 versus 0.32, \(t = 2.2372, df = 25, P = .034\)). The covariate analysis with neuropsychological scores yielded statistically significant correlations in all 6 studied functional networks, with the most conspicuous correlation in salience networks.

CONCLUSIONS: Active HIV-associated neurocognitive disorder in virally suppressed patients is associated with significantly decreased connectivity in the salience and executive networks, thereby making it potentially useful as a biomarker.

ABBREVIATIONS: cART = combination antiretroviral therapy; HAND = HIV-associated neurocognitive disorder; NC = neurocognitive; rs-fMRI = resting-state fMRI

HIV-associated neurocognitive disorder (HAND) persists in the era of potent combination antiretroviral therapy (cART), even when confounding conditions are excluded and patients are virally suppressed.\(^1,2\) HAND is a broad term to encompass neurocognitive disorders including asymptomatic neurocognitive impairment, mild neurocognitive impairment, and HIV-associated dementia with prevalence ranging from 18% to 52%. The diagnosis of different stages of HAND is based on the recommendations from updated research nosology for HIV-associated neurocognitive disorders\(^3\) and includes neuropsychological testing and neurologic evaluation. The variation in the prevalence depends on whether patients with confounding conditions and unsuppressed HIV viral load are included. Nonetheless, even in the absence of confounds and the presence of viral suppression in both blood and CSF, HAND still occurs and may develop for reasons that are unclear.\(^3,4\)

HAND is characterized by decreased attention, psychomotor slowing, and working memory deficits.\(^5,6\) While HAND in the pre-cART era was characterized as subcortical, the advent of cART has shifted the impairment to include higher order cognitive abilities such as executive functioning.\(^3,5\) The higher order cognitive dysfunction was substantiated by a number of task-based functional MR imaging studies that demonstrated increased use of reserve brain regions during working memory tasks in patients with HIV and mild dementia and in those...
who were neuroasymptomatic.7,8 These studies showed that there are abnormal levels (initial increase and later reduced activity) of activation in the dorsolateral prefrontal cortex and parietal cortices. However, these studies did not include patients who were virally suppressed in both blood and CSF.

Resting-state fMRI (rs-fMRI) has been established as a powerful tool to measure the brain networks, which are implicated in cognitive disorders. Currently, there are only 5 studies that have examined resting-state networks in HAND.9-13 These studies have noted abnormalities, especially early in the course of HIV infection.9 Some studies have shown conflicting results (Ipser et al11 and Guha et al12). However, no studies have been specifically designed to address the pathogenesis of HAND in the cART era. Thus, additional criteria are required. Patients with HAND must be virally suppressed in both blood and CSF and should demonstrate symptoms of HAND that are recent and progressive and are not related to the legacy effect from the past (cognitive abnormalities that reflect “burn-out” disease).

Consequently, the aim of this study was to analyze the effect of HIV infection on various resting networks in virally controlled patients with active HAND as a means of understanding the pathogenesis in the cART era.

MATERIALS AND METHODS

Eighteen patients with HIV with HAND were enrolled. All had been on a stable cART regimen for at least the previous 12 months, and all had HIV RNA levels of <20 copies per mL in both blood and CSF. All had recent onset of symptoms within the past 6 months. All were assessed by a neurologist, and all had blood and CSF analyses to exclude other causes of cognitive impairment. All had β2-microglobulin and neopterin measured in both blood and CSF. (Both β2-microglobulin and neopterin are markers of immune activation and inflammation and are known to be elevated in many neuroinflammatory conditions and are shown to be mildly elevated in patients who have suppressed plasma and CSF HIV RNA to below the detection limits of clinical assays). All were diagnosed with HAND by the American Academy of Neurology criteria,14 with a full neuropsychological assessment. Of these 18 patients with HAND, 12 were identified with mild neurocognitive impairment (12/18); 4 patients, with asymptomatic neurocognitive impairment; and 2, with HIV-associated dementia (2/18). Individuals with a prior history of drug abuse, significant head injury, psychiatric illness, and Hepatitis C coinfection were excluded. Nine HIV seronegative matched controls were included in the study. None of the patients had any white matter abnormalities or microhemorrhages on anatomic MR imaging protocols. Local ethics approval was obtained from the St Vincent’s Hospital Human Research Ethics Committee, and all the participants provided written informed consent before enrollment (Table 1).

Neurocognitive Evaluation

Neurocognitive testing was performed with a brief research test battery described previously, which has been validated for use in the HIV-positive population.14,15 Briefly, the test battery consisted of a brief computerized battery (CogState) supplemented with a small selection of standardized pencil-and-paper tests to cover 5 cognitive domains: 1) speed of information processing, 2) attention/working memory, 3) motor coordination, 4) verbal learning, and 5) verbal memory (Table 2). CogState is sensitive to HAND17 and uses playing cards as stimuli to minimize the influences of culture and education on testing. Other tests were selected to provide greater coverage of other cognitive domains affected by HAND (psychomotor speed and motor coordination). Additionally, premorbid intellectual functioning was estimated with the National Adult Reading Test or a demographic-based regression equation when the National Adult Reading Test could not be validly administered. Psychological measures included the Depression, Anxiety, and Stress Scales and the Mini-International Psychiatric Interview (Version 5.0.). Functional decline for HAND status classification was measured via a standard Independence of Activities of Daily Living questionnaire.18

Table 1: Demographic, HIV, and neurocognitive characteristics of the study sample

<table>
<thead>
<tr>
<th></th>
<th>HIV+ (n = 18)</th>
<th>Control (n = 9)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean) (SD) (yr)</td>
<td>53.7 (7.5)</td>
<td>55 (4.0)</td>
<td>.6897</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>100</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Ethnicity (% white)</td>
<td>100</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Education (mean) (SD) (yr)</td>
<td>13.0 (3.0)</td>
<td>15 (2.0)</td>
<td>.0043</td>
</tr>
<tr>
<td>Duration stable on cART</td>
<td>2 (2)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>(median) (IQR) (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 cell count (median)</td>
<td>657 (550)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(IQR) (cells/mm³)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nadir CD4 (median) (IQR)</td>
<td>194.5 (263.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite neurocognitive</td>
<td>-0.69 (0.75)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>z score (median) (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note:—NA indicates not applicable; IQR, interquartile range; +, positive.

Table 2: Tests included in the brief neurocognitive research battery

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speed of information processing</td>
<td>CogState Detection Task</td>
</tr>
<tr>
<td></td>
<td>CogState Identification Task</td>
</tr>
<tr>
<td></td>
<td>Trail-Making Test: Parts A and B</td>
</tr>
<tr>
<td></td>
<td>WAIS-III Digit Symbol Coding</td>
</tr>
<tr>
<td>Attention/working memory</td>
<td>CogState One Back Task</td>
</tr>
<tr>
<td>Motor functioning</td>
<td>CogState Two Back Task</td>
</tr>
<tr>
<td></td>
<td>Grooved Pegboard: Dominant and Non-Dominant Hand</td>
</tr>
<tr>
<td>Verbal learning</td>
<td>CogState International Shopping</td>
</tr>
<tr>
<td></td>
<td>List Task: Learning</td>
</tr>
<tr>
<td>Verbal memory</td>
<td>CogState International Shopping</td>
</tr>
<tr>
<td></td>
<td>List Task: Delayed Recall</td>
</tr>
</tbody>
</table>

Note:—WAIS-III indicates Wechsler Adult Intelligence Scale-III.

Image Acquisition

All imaging was performed with a 3T MR imaging scanner (Ingenia; Philips Healthcare, Best, the Netherlands) with a 24-channel head coil. High-resolution 3D T1-weighted volume and rs-fMRI scans were obtained. Volumetric scanning was performed with T1 fast-field echo (TR, 7600 ms [shortest]; TE, 3.5 ms; bandwidth, 191.5 Hz/pixel; flip angle, 7°; acquisition matrix, 256/256; section thickness, 1-mm isometric voxel [3D encoding] with an acceleration of 2× sensitivity encoding).

We used a resting-state scan sequence in which participants were instructed to focus on a white cross presented on a screen...
during the scan. They were also asked not to think of anything in particular. The parameters were the following: total duration, 7.39 minutes; TR/TE, 3000/35 ms; flip angle, 90°; 150 dynamics with the shortest dynamic scan time; acquisition matrix, 250/230/94; section thickness, 4 mm acquired parallel to the anterior/posterior commissure plane.

**Preprocessing.** The data processing was performed on Brain-Voyager QX, Version 2.8.4 (Brain Innovation, Maastricht, the Netherlands). Anatomic images were corrected for inhomogeneity with an automatic intensity-based approach (which included a brain extraction). The functional data were corrected for the differences in section scan-time acquisition, motion in 3 planes (with the first volume as reference), and linear and nonlinear temporal drifts with a high-pass filter based on a general linear model with a Fourier basis set (1 linear, 2 sine, and 2 cosine functions). Native functional and anatomic data were coregistered in 2 steps with first, the header-based positioning information and, second, an intensity-based alignment algorithm.

**Image Analysis.** Subsequently both the anatomic and functional data were normalized with affine transformation into the anterior/posterior commissural planes and finally to Talairach space with an inbuilt function of BrainVoyager, which uses a piecewise linear approach.19,20

On the basis of the standardized (Talairach) 3D anatomic dataset, white matter and ventricle voxels were defined for each subject. From both anatomic areas, the average time courses were extracted and used in combination with motion confounds (6 parameters) to regress out specific sources of noise within the functional data.21 ROI time-series were computed by selecting a seed location based on predefined coordinates in the Talairach Atlas (based on the Brodmann file available in the BrainVoyager standard installation) and taking the average of all voxels from the following ROIs: Brodmann areas 2 (somatosensory cortex-network), 8 (intraparietal sulcus-dorsal attentional networks), 9 (dorsolateral prefrontal cortex-executive network), 13 (anterior insular cortex-salience network), 17 (primary visual cortex-visual network), and 31 (posterior cingulate-default mode network) based on a predefined/standard ROI file in Talairach space.

**Postprocessing and Statistical Analysis.** To localize significant ROIs within the HIV and control groups, we performed a seed-based correlation for each of the 6 mentioned resting-state networks. On the basis of subject-specific correlation maps, an independent *t* test was performed to show up the differences between the HIV and control groups. All statistical analysis was performed with SPSS (Version: 1.2; IBM, Armonk, New York).

**Inclusion of External Covariates**

A single composite neurocognitive *z* score was generated through 2 steps. First, CogState normative data raw scores were converted to age-corrected *z* scores (*M* = 0, *SD* = 1) with CogState normative data, and raw scores on other tests were converted to age-adjusted scaled scores with published normative data before being transformed into *z* scores. (*Z* scores are standardized scores, ie, transformed to fit in a normal curve after being adjusted for variables such as age and sex. In healthy individuals, the distribution of standardized cognitive scores, after adjustments, is centered at zero [mean and median] with an SD of 1. Cognitively impaired individuals may have a cognitive score lower than that of healthy individuals, so the average *z* score for cognitively impaired individuals is much lower). Second, the average of each subset *z* score was taken to derive a composite neurocognitive score for each patient (Table 1).

The neurocognitive (NC) scores of all the 18 patients were plotted, and a median split was performed. On the basis of the median split of the NC score, a 1-way analysis of variance was performed with the seed-based resting-state data as a dependent variable.

Within the resulting *F*-maps, a contrast checking of the difference between group 2 (NC score > median) and group 1 (NC score < median) was performed. All resulting *t* maps were corrected for multiple comparison problems with the cluster-correction approach (Forman et al, 1995) based on an uncorrected threshold of *P* = .05 (a classic Forman cluster-correction approach to 3D statistical maps is implemented in BrainVoyager: http://support.brainvoyager.com/documents/Functional_Statistics/ClusterThreshPluginHelp/).21

**RESULTS**

rs-fMRI data were obtained from 27 subjects (18 seropositive and 9 seronegative controls). All the participants were included in the final analysis. The controls were of similar age, sex, and ethnicity (Table 1).

**Comparisons of Connectivity in Different Seed Region Networks**

There were significant group differences between the average intercluster correlation in the control and patient groups in the executive network (0.26 versus 0.14, *t* = 2.6978, *df* = 25, *P* = .0123) and salience network (0.52 versus 0.32, *t* = 2.2372, *df* = 25, *P* = .034), indicating that there is significantly reduced synchronicity within these 2 networks (salience and attentional networks) (Figs 1 and 2; Table 3). The difference between controls and patients was trending toward being significant in the dorsal attention network (0.37 versus 0.24, *t* = 1.83, *df* = 25, *P* = .07).

The group differences in the somatosensory network (0.29 versus 0.36, *t* = 0.179), ventral attentional network (0.37 versus 0.24, *t* = 0.06), and default mode network (0.21 versus 0.21, *t* = 0.91) did not reach statistical significance.
Correlations between Network Connectivity Analysis and Clinical Measures

We assessed whether observed changes in brain networks were associated with neuroinflammatory markers (namely CSF and plasma neopterin and β-2 microglobulin) and NC scores. None of the networks demonstrated any significant positive or negative correlations with plasma/CSF biomarkers. However, neurocognitive scores showed significant correlations with all 6 mentioned networks. Within these networks, the salience networks demonstrated the most significant correlations with reduced neurocognitive scores (Figs 3 and 4).

DISCUSSION

Our study showed that there is significant attenuation in the salience and executive networks in patients with HAND with active disease despite viral suppression in both plasma and CSF. The network changes correlated with the degree of neuropsychological impairment but not with markers of neuroinflammation in the blood or CSF.

The salience network is considered important for monitoring the salience of external inputs and internal brain events, and the central executive network is engaged in higher order cognitive and attentional control. The salience networks comprise cortical areas of the anterior insula and anterior cingulate and subcortical areas, including the amygdala, substantia nigra, and thalamus. The central executive networks connect the dorsolateral prefrontal cortex to the striatum and posterior inferior parietal areas and have subcortical networks distinct from those in the salience networks.23

Only 5 studies examined the effect of HIV and secondarily HAND on rs-fMRI. Forst et al9 in their study on HIV-positive subjects in their first year of infection showed diminished connectivity within the lateral occipital network (visual attention or visuospatial attention), but there were no patients with HAND. Ipsen et al11 had a cohort of 15 HIV-positive patients, 11 of whom were on cART. There were 4 patients with HAND. Reduced frontostriatal connectivity was noted, especially in relation to the executive network. Thomas et al10 had a heterogeneous cohort of 52 HIV-positive patients (23 were on cART but the number who were virally suppressed was not clear and only 12 had HAND). They were evaluated for the effect of aging in HIV compared with seronegative controls. They found attenuation in the default mode and salience networks, similar to that which occurs with age, and inferred that there is premature aging in HIV. This study did not find any correlation with neurocognitive scores or plasma markers.

Guha et al12 evaluated resting networks in HIV-infected individuals older than 60 years of age (HIV-positive, n = 52, and controls, n = 29). Most were on cART (94%) but not all were virally suppressed (35 of 50 patients) and 27 had HAND, though none appeared to have active disease. Those with detectable plasma HIV-RNA had reduced connectivity in the salience networks. No significant relationship between the neuropsychiatric performance and rs-fMRI was observed.

Ann et al13 tested the differences in connectivity in seropositive patients with and without HAND, using seed-based connectivity in the default mode network with seed in the precuneus, and demonstrated that there was reduced connectivity between the precuneus and prefrontal regions in the HAND group versus the non-HAND group (10 patients in HAND and 13 in non-HAND). The group separation was not based on CSF viral suppression. The whole-brain networks were not evaluated in this study. It is, therefore, a targeted deterministic seed-based study assessing 1 domain only (default mode network). It is also unclear whether there were any white matter lesions associated with age in this cohort and how much the effect of aging and vascular disease influenced the results.

As previously mentioned, none of the above-mentioned studies included patients with HAND with viral suppression in both
blood and CSF, and the activity of HAND was not mentioned. Nonetheless, in those studies with patients with HAND, 2 of 3 found a relationship to attenuation of the salience network. Ipser et al noted a relationship only with the central executive control network, but the study included patients with substance misuse and only 4 patients had HAND. Of potential additional importance is the finding by Guha et al of a reduction in the salience network with an elevated plasma viral load. This may be relevant to our findings: it suggests that active HAND, at least in our study, is associated with viral replication in the brain at a level not reflected in the blood or the CSF.

Our study also identified significant correlations between neuropsychological scores and significant attenuation in all 6 networks, but especially in the salience, default mode, and executive control networks. These could be due to global injury associated with HIV.

Our findings may have specificity for HAND. The frontostriatal networks have been found to be attenuated in Parkinson disease, and attenuation of these executive networks along with default mode networks is said to occur when there is coexistent cognitive impairment associated with Parkinson disease. However, salience network involvement is not known to occur in Parkinson disease. In healthy aging and Alzheimer disease, there is some uniformity in the involvement of default mode networks. In healthy aging, it was found that there is a decline in the connectivity in the default mode networks. It was also found that there is some evidence of increased connectivity with age, possibly as a compensatory mechanism due to changing neural strategies in most of the other networks. Similarly, in Alzheimer disease, there is a decline in connectivity in most of the networks, but this decline is exaggerated with the default mode network being affected most and much more pronounced than in individuals with healthy aging.

Studies in vascular dementia with rs-FMRI showed involvement of multiple domains, with most pronounced changes in the prefrontal posterior cingulate loop, which is not a typical feature in Alzheimer disease or HAND. Therefore, the demonstration of attenuation of both the executive and salience networks could be useful as a specific biomarker for active HAND.

There are several limitations in interpreting the results of our study. The study group only included white males. Sample sizes used in this study were small; this small size limited the power to detect between-group differences in the salience and attentional networks. Our cohort had a smaller number of controls who did not undergo formal neuropsychological testing though they were entirely asymptomatic. However, the test we used was not a factorial ANOVA and

FIG 2. A, Multiplanar depictions of group effect in subjects with HIV in the executive networks with the seed region in Brodmann area 9. Note large consistently activated voxels in the entire group, with activation in the dorsolateral frontal cortex and posterior inferoparietal regions and in the striatum. B, Multiplanar depictions of group effect in subjects with HIV in the executive networks with seed regions in Brodmann area 13. Large consistently activated voxels in the group with activation in the anterior insula, anterior cingulate, and thalamus.

Table 3: Mean Talairach coordinates of the center-of-gravity coordinates in X, Y, and Z axes and SD and number of voxels (1-mm resolution of each cluster) in Brodmann area 9 (control executive networks) and 13 (salience networks) seed region networks

<table>
<thead>
<tr>
<th>BA 9 Cluster</th>
<th>Mean X</th>
<th>Mean Y</th>
<th>Mean Z</th>
<th>SD X</th>
<th>SD Y</th>
<th>SD Z</th>
<th>Voxel No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster 1</td>
<td>5.98</td>
<td>25.50</td>
<td>34.01</td>
<td>35.43</td>
<td>23.28</td>
<td>11.16</td>
<td>78,154</td>
</tr>
<tr>
<td>Cluster 2</td>
<td>37.79</td>
<td>-39.71</td>
<td>46.68</td>
<td>6.20</td>
<td>3.33</td>
<td>1149</td>
<td></td>
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<tr>
<td>Cluster 3</td>
<td>2.67</td>
<td>7.61</td>
<td>22.38</td>
<td>9.84</td>
<td>2.31</td>
<td>824</td>
<td></td>
</tr>
<tr>
<td>Cluster 4</td>
<td>-2.32</td>
<td>-65.50</td>
<td>37.52</td>
<td>3.44</td>
<td>5.86</td>
<td>1437</td>
<td></td>
</tr>
<tr>
<td>Cluster 5</td>
<td>-32.92</td>
<td>-61.66</td>
<td>49.64</td>
<td>5.04</td>
<td>3.92</td>
<td>1540</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BA 13 Cluster</th>
<th>Mean X</th>
<th>Mean Y</th>
<th>Mean Z</th>
<th>SD X</th>
<th>SD Y</th>
<th>SD Z</th>
<th>Voxel No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster 1</td>
<td>-30.81</td>
<td>10.97</td>
<td>12.36</td>
<td>14.87</td>
<td>15.63</td>
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<tr>
<td>Cluster 2</td>
<td>42.25</td>
<td>13.22</td>
<td>8.38</td>
<td>8.56</td>
<td>11.14</td>
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<td>Cluster 3</td>
<td>-43.21</td>
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<td>12.22</td>
<td>12.70</td>
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<tr>
<td>Cluster 4</td>
<td>52.63</td>
<td>-20.30</td>
<td>12.93</td>
<td>6.53</td>
<td>17.32</td>
<td>11.82</td>
<td>6609</td>
</tr>
</tbody>
</table>

Note: BA indicates Brodmann area. The clusters are defined on the basis of conjointly activated voxels in patients and control subjects.
hence probably would have a limited effect on the results (we used a $t$ test with heterogeneous variances). In addition, the inherent ambiguities and pitfalls of rs-fMRI could have influenced the outcome of the results through residual effects of noise and inherent blood oxygenation–associated confounds. However, we think these noise effects are not significant because of preprocessing. Last, we cannot exclude the importance of neurotoxicity from cART as opposed to HIV, given that all the patients in our group were on long-term (>4 years) cART, though the effect of neurotoxicity–associated cognitive impairment appears to be inconclusive. The persistence of the minor cognitive impairment after widespread implementation of cART raised questions about the possible role of the antiretrovirals, particularly nucleoside reverse transcriptase inhibitors. However, several studies have demonstrated the neuroprotective effectiveness of the cART regimen on neurocognitive function. Using MR spectroscopy, investigators have shown that there is marked improvement in both clinical measures and metabolite concentrations. One recent study used the metrics derived from arterial spin-labeling and rs-fMRI to measure the blood flow and connectivity in HIV-negative individuals before and after using 2 common antiretroviral medications (efavirenz and ritonavir) and observed that there was no effect on either blood flow or connectivity in a small cohort.

**CONCLUSIONS**

We found significantly decreased connectivity in the executive and salience networks in active HAND, suggesting that it could be used as a biomarker. Furthermore, the association with the sal-
licence network and its relationship with HIV replication in the blood12 raises a further testable and plausible hypothesis: Active HAND in the context of viral suppression in blood and CSF is driven by very low-level brain replication. Future studies will need to validate these findings with larger patient numbers and correlate the findings with CSF single-copy assays of HIV.


REFERENCES

5. Brew BJ. Evidence for a change in AIDS dementia complex in the era of highly active antiretroviral therapy and the possibility of new forms of AIDS dementia complex. *AIDS* 2004;18(suppl 1):S75–78 CrossRef Medline
ABSTRACT

BACKGROUND AND PURPOSE: Dose reduction on CT scans for surgical planning and postoperative evaluation of midface and orbital fractures is an important concern. The purpose of this study was to evaluate the variability of various low-dose and iterative reconstruction techniques on the visualization of orbital soft tissues.

MATERIALS AND METHODS: Contrast-to-noise ratios of the optic nerve and inferior rectus muscle and subjective scores of a human cadaver were calculated from CT with a reference dose protocol (CT dose index volume = 36.69 mGy) and a subsequent series of low-dose protocols (LDPs I–IV: CT dose index volume = 4.18, 2.64, 0.99, and 0.53 mGy) with filtered back-projection (FBP) and adaptive statistical iterative reconstruction (ASIR-50, ASIR-100, and model-based iterative reconstruction. The Dunn Multiple Comparison Test was used to compare each combination of protocols (α = .05).

RESULTS: Compared with the reference dose protocol with FBP, the following statistically significant differences in contrast-to-noise ratios were shown (all, P < .012) for the following: 1) optic nerve: LDP-I with FBP, LDP-II with FBP and ASIR-50; LDP-III with FBP, ASIR-50, and ASIR-100; and LDP-IV with FBP, ASIR-50, and ASIR-100; and 2) inferior rectus muscle: LDP-II with FBP, LDP-III with FBP and ASIR-50, and LDP-IV with FBP, ASIR-50, and ASIR-100. Model-based iterative reconstruction showed the best contrast-to-noise ratio in all images and provided similar subjective scores for LDP-II. ASIR-50 had no remarkable effect, and ASIR-100, a small effect on subjective scores.

CONCLUSIONS: Compared with a reference dose protocol with FBP, model-based iterative reconstruction may show similar diagnostic visibility of orbital soft tissues at a CT dose index volume of 2.64 mGy. Low-dose technology and iterative reconstruction technology may redefine current reference dose levels in maxillofacial CT.

ABBREVIATIONS: ALADA = As Low As Diagnostically Achievable; ALARA = As Low As Reasonably Achievable; ASIR = adaptive statistical iterative reconstruction; CNR = contrast-to-noise ratio; CTDIvol = CT dose index volume; FBP = filtered back-projection; HU = Hounsfield unit; IRM = inferior rectus muscle; LDP = low-dose protocol; MBIR = model-based iterative reconstruction; ON = optic nerve.
Furthermore, dose reduction may not significantly influence registration and navigation accuracy for computer-aided surgery. However, the associated increase in noise may significantly influence the diagnostic image quality of soft-tissue structures such as the optical nerve and orbital muscles. The recent implementation of iterative reconstruction techniques such as adaptive statistical iterative reconstruction (ASIR) and model-based iterative reconstruction (MBIR) may improve image quality with reduced radiation doses compared with the traditionally used filtered back-projection (FBP) technique.

The aim of the present study was to evaluate the influence of various low-dose protocols and iterative reconstructions on the visualization of orbital soft tissues.

**MATERIALS AND METHODS**

We used 1 cadaver head preserved with an arterial injection of a formaldehyde-phenol solution/an alcohol-glycerin solution and immersion in phenolic acid in water for 1–3 months. The bodies were donated by individuals who had given their informed consent before death for their use for scientific and educational purposes.

The entire cadaver head including the mandible was scanned by using the Discovery CT750 HD (GE Healthcare, Milwaukee, Wisconsin) and the following protocols: the standard emergency protocol of the head (as used during initial cranial CT in the emergency setting), a high-resolution reference dose protocol (as used for surgical planning and navigated surgery), and a subsequent series of low-dose protocols (LDPs) with various iterative reconstruction techniques and bone and standard kernels (protocol details can be found in Table 1). The images were exported in a DICOM format with Impax EE (Agfa-Gevaert, Mortsel, Belgium) PACS.

### Dose Estimation

CT dose index volume (CTDI<sub>vol</sub>) and dose-length product were obtained from the DICOM tags. In addition, CT-Expol, Version 2.1 (Medical University Hannover, Hannover, Germany), an Excel (Microsoft, Redmond, Washington) application for assessing the radiation doses delivered to patients undergoing CT examinations based on the scan parameters of the used scanner type, was used to calculate effective doses (International Commission of Radiation Protection: ICRP 103; http://apps.snm.org/docs/CME/PresenterItems/EventID_85/PresenterItemTypeID_1/3.%20Eckerman%20-%20%201050.pdf) (Table 1).  

### Analysis of Hounsfield Unit Values and Contrast-to-Noise Ratios of Orbital Soft Tissues

All images were evaluated by 2 readers with AW Server 2.0 (GE Healthcare). The readers were trained for image reformation and volumetric segmentation.

Images were reformatted in axial, coronal, and sagittal views. The window/level was adjusted to obtain the best subjective contrast. The paint-on-slices tool of the AW Server 2.0 software was used to segment the optical nerve (ON) and inferior rectus muscle (IRM) on both sides.

The anterior border of the segmented structures was the horizontal line at the posterior margin of the orbital bulb, and the posterior border was the horizontal line at the foramen of the posterior ethmoid artery. Average Hounsfield units (HUs) and SDs of the segmented volumes were recorded.

In addition, the average Hounsfield unit and SD of the orbital fat lateral to the optic nerve posterior to the horizontal line at the posterior margin of the orbital bulb was measured with a spheric ROI with a 6-mm diameter.

The contrast-to-noise ratio (CNR) for each anatomic structure (ON and IRM) was calculated with the following formula:

\[
CNR = \frac{|MHU_a - MHU_{on}|}{\sqrt{SD_a^2 + SD_{on}^2}}
\]

with MHU indicating the mean Hounsfield unit value, and SD, the standard deviation of Hounsfield unit values.

<table>
<thead>
<tr>
<th>Dose Protocol</th>
<th>Reconstruction Technique</th>
<th>Kernel</th>
<th>kV</th>
<th>mAs</th>
<th>Pitch</th>
<th>Rotation Time (s)</th>
<th>CTDI&lt;sub&gt;vol&lt;/sub&gt; (mGy)</th>
<th>DLP (mG × cm)</th>
<th>Effective Dose (mSv)</th>
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<tbody>
<tr>
<td>Emergency protocol head</td>
<td>ASIR-50</td>
<td>Bone</td>
<td>120</td>
<td>314–488</td>
<td>1</td>
<td>0.6</td>
<td>47.55</td>
<td>1141.26</td>
<td>4.9</td>
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<td>FBP</td>
<td>Bone, std</td>
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<td>100</td>
<td>0.5</td>
<td>1</td>
<td>36.69</td>
<td>930.78</td>
<td>3.5</td>
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<tr>
<td>Low-dose protocol I</td>
<td>FBP</td>
<td>Bone, std</td>
<td>100</td>
<td>35</td>
<td>0.5</td>
<td>0.5</td>
<td>4.18</td>
<td>106.18</td>
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<td>2.64</td>
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<td>Bone, std</td>
<td>80</td>
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<td>0.5</td>
<td>0.5</td>
<td>0.99</td>
<td>25.13</td>
<td>0.1</td>
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<tr>
<td></td>
<td>MBIR</td>
<td>Bone, std</td>
<td>80</td>
<td>10</td>
<td>0.5</td>
<td>0.4</td>
<td>0.53</td>
<td>13.39</td>
<td>0.1</td>
</tr>
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</table>

Note:—DLP indicates dose-length product; std, standard.
Analysis of Subjective Image Quality

Subjective image quality of the orbital soft tissues was assessed by consensus of 3 readers with a 5-scale system: 1, very poor/not sufficient; 2, suboptimal but sufficient; 3, average = equal to reference; 4, above average; and 5, excellent. As a “reference,” the image of the reference dose protocol with FBP and the bone kernel was used, which referred to images usually provided by maxillofacial and sinus CT. Subjective scores were evaluated for each combination of dose, reconstruction technique, and kernel.

Statistical Analysis

Data analysis and descriptive statistics were performed with PASW Statistics (Version 15.0; IBM, Armonk, New York). Interobserver agreement was assessed with weighted $\kappa$ statistics. The Dunn Multiple Comparison Test and the Bonferroni-corrected test were used to compare each combination of protocols ($\alpha = .05$). The analysis of variance for dependent variables was used to test between-subject effects: protocol, reconstruction, and kernel.

RESULTS

Using the 6 protocols, 4 reconstruction techniques, and 2 convolution kernels, we generated 36 CT datasets. CTDIvol, dose-length product, and effective doses can be found in Table 1.

Compared with the reference dose protocol, LDP I–IV showed dose reductions of about 88.7%, 92.8%, 97.3%, and 98.6%. The effective doses for LDP I–IV, which include the scan of the entire head and mandible, were 0.4, 0.3, 0.1, and 0.1 mSv.

Figure 1 shows images including the reference dose protocol with FBP using the bone and standard kernels, and all low-dose protocols with FBP, ASIR-50, ASIR-100, and MBIR with the standard kernel. The mean CNR and SDs of the ON and IRM for each protocol and reconstruction technique can be found in Table 2.

Influence of Dose

With the bone kernel, the reference dose protocol showed statistically significantly better CNR than all LDs for both the ON and IRM (all $P < .001$). Compared with the reference standard, no statistically significant difference from the emergency protocol head ($P = 1.00$) for the ON, $P = .951$ for IRM) was found. LDP-I was statistically significantly better than LDP II–IV for the ON ($P = .011$, $P < .001$, and $P < .001$), and LDP-III and IV, for the IRM (all, $P < .001$).

Table 2: Mean CNR and SD of ON and IRM for each combination of protocol and reconstruction technique

<table>
<thead>
<tr>
<th>Dose Protocol</th>
<th>Reconstruction Technique</th>
<th>ON CNR (SD)</th>
<th>ON SD (SD)</th>
<th>IRM CNR (SD)</th>
<th>IRM SD (SD)</th>
<th>Score Bone Kernel</th>
<th>Score Std Kernel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ref. Dose protocol head</td>
<td>ASIR-50</td>
<td>2.75 (0.62)</td>
<td>0.26</td>
<td>1.82 (0.26)</td>
<td>1.00</td>
<td>4.0</td>
<td>5.0</td>
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<tr>
<td>Reference dose protocol</td>
<td>FBP</td>
<td>3.80 (2.07)</td>
<td>1.22</td>
<td>2.39 (1.22)</td>
<td>1.00</td>
<td>4.0</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>ASIR-50</td>
<td>4.28 (2.04)</td>
<td>1.24</td>
<td>2.71 (1.24)</td>
<td>1.00</td>
<td>4.0</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>ASIR-100</td>
<td>4.37 (1.39)</td>
<td>1.01</td>
<td>2.99 (1.01)</td>
<td>1.00</td>
<td>4.0</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>MBIR</td>
<td>5.68 (0.17)</td>
<td>0.54</td>
<td>3.60 (0.54)</td>
<td>1.00</td>
<td>5.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Low-dose protocol I</td>
<td>FBP</td>
<td>1.57 (1.07)</td>
<td>0.79</td>
<td>1.11 (0.79)</td>
<td>2.00</td>
<td>3.0</td>
<td>4.0</td>
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<tr>
<td></td>
<td>ASIR-50</td>
<td>2.15 (1.27)</td>
<td>0.81</td>
<td>1.22 (0.81)</td>
<td>2.00</td>
<td>3.0</td>
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<td>ASIR-100</td>
<td>2.49 (0.98)</td>
<td>0.59</td>
<td>1.65 (0.59)</td>
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<td>3.0</td>
<td>4.0</td>
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<tr>
<td></td>
<td>MBIR</td>
<td>4.12 (0.85)</td>
<td>0.46</td>
<td>3.05 (0.46)</td>
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<td>3.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Low-dose protocol II</td>
<td>FBP</td>
<td>1.05 (0.75)</td>
<td>0.46</td>
<td>0.74 (0.46)</td>
<td>1.00</td>
<td>2.0</td>
<td>4.0</td>
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<tr>
<td></td>
<td>ASIR-50</td>
<td>1.41 (0.94)</td>
<td>0.43</td>
<td>0.91 (0.43)</td>
<td>1.00</td>
<td>3.0</td>
<td>4.0</td>
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<tr>
<td></td>
<td>ASIR-100</td>
<td>2.16 (1.15)</td>
<td>0.40</td>
<td>1.34 (0.40)</td>
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<td>3.0</td>
<td>4.0</td>
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<tr>
<td></td>
<td>MBIR</td>
<td>4.11 (0.66)</td>
<td>0.77</td>
<td>2.81 (0.77)</td>
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<td>4.0</td>
<td>4.0</td>
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<td>Low-dose protocol III</td>
<td>FBP</td>
<td>0.63 (0.44)</td>
<td>0.30</td>
<td>0.23 (0.30)</td>
<td>1.00</td>
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<td></td>
<td>ASIR-50</td>
<td>0.87 (0.57)</td>
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<td>0.50 (0.44)</td>
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<td></td>
<td>ASIR-100</td>
<td>1.29 (0.65)</td>
<td>0.60</td>
<td>0.92 (0.60)</td>
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<tr>
<td></td>
<td>MBIR</td>
<td>3.08 (0.63)</td>
<td>0.44</td>
<td>2.32 (0.44)</td>
<td>1.00</td>
<td>2.0</td>
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<tr>
<td>Low-dose protocol IV</td>
<td>FBP</td>
<td>0.44 (0.36)</td>
<td>0.16</td>
<td>0.10 (0.16)</td>
<td>1.00</td>
<td>2.0</td>
<td>4.0</td>
</tr>
<tr>
<td></td>
<td>ASIR-50</td>
<td>0.52 (0.57)</td>
<td>0.34</td>
<td>0.31 (0.34)</td>
<td>1.00</td>
<td>2.0</td>
<td>4.0</td>
</tr>
<tr>
<td></td>
<td>ASIR-100</td>
<td>0.93 (0.63)</td>
<td>0.56</td>
<td>0.62 (0.56)</td>
<td>1.00</td>
<td>2.0</td>
<td>4.0</td>
</tr>
<tr>
<td></td>
<td>MBIR</td>
<td>2.62 (0.52)</td>
<td>2.71</td>
<td>3.14 (2.71)</td>
<td>1.00</td>
<td>2.0</td>
<td>4.0</td>
</tr>
</tbody>
</table>

Note: — Std indicates standard.

* Subjective scores are given separately for images with a bone and standard kernel: 1 indicates very poor/not sufficient; 2, suboptimal but sufficient; 3, average = equal to reference; 4, above average; and 5, excellent.

b Statistically significant difference compared with the reference dose protocol with FBP ($P < .05$).
LDP-I was not statistically significantly better than LDP-II for the IRM (P = 1.000). LDP-II was statistically significantly better than LDP-III and IV for the ON (P = .010, P < .001) and IRM (all P < .001). LDP-III did not show statistically significant differences from LDP-IV for the ON (P = .112) and IRM (P = .126).

With the standard kernel, the reference dose protocol showed statistically significantly better CNR than all LDPs (all P < .001). LDP-I was statistically significantly better than LDP-III–IV for the ON (all, P < .001) and IRM (all P = .004). LDP-I was not statistically significantly better than LDP-II for the ON (P = .057) and IRM (P = .611). LDP-II was statistically significantly better than LDP III and IV for the ON (all, P < .001) but not for the IRM (P = .676, P = .759). LDP-III did not show statistically significant differences compared with LDP-IV for the ON (P = .565) and IRM (P = 1.000).

**Influence of Reconstruction**

With the bone kernel, ASIR-50 and ASIR-100 showed statistically significantly better CNR than FBP for the ON and IRM (all P < .001). ASIR-100 had a statistically significantly better CNR than ASIR-50 for the ON (P = .007) and IRM (P < .001).

With the standard kernel, ASIR-50 had a statistically significantly better CNR than FBP for the ON (P = .037) but not for the IRM (P = 1.000). ASIR-100 and MBIR showed statistically significantly better CNR than FBP for the ON (all, P < .001) and IRM (P = .036, P < .001). ASIR-100 did not show a statistically significantly better CNR than ASIR-50 (P = .745). MBIR showed a statistically significantly better CNR than both ASIR-50 and ASIR-100 for the ON (all P < .001) and IRM (P < .001, P = .001).

**Influence of the Convolution Kernel**

The standard kernel showed a statistically significantly higher CNR than the bone kernel for the ON and IRM (all P < .001). The convolution kernel influenced the effect of iterative reconstructions (see previous sections).

**Interobserver Agreement**

Interobserver agreement between both readers showed a Pearson correlation coefficient of 0.638 for the CNR measurements of the ON and 0.914 for the CNR measurements of the IRM. The Test of Between-Subjects Effects showed no statistically significant difference (P = .950).

**Comparison with the Reference Dose Protocol with FBP**

Compared with the reference dose protocol with FBP, statistically significant differences of the CNR for the ON were shown with LDP-I with FBP (P = .010); LDP-II with FBP (P < .001) and ASIR-50 (P = .003); LDP-III with FBP (P < .001), ASIR-50 (P < .001), and ASIR-100 (P = .001); and LDP-IV with FBP (P < .001), ASIR-50 (P < .001), and ASIR-100 (P < .001) (Table 2).

For the IRM, statistically significant differences from the reference dose protocol with FBP were shown with LDP-II with FBP (P = .012); LDP-III with FBP (P < .001) and ASIR-50 (P < .001); and LDP-IV with FBP (P < .001), ASIR-50 (P < .001), and ASIR-100 (P = .004) (Table 2).

**Subjective Scoring**

Compared with the reference dose protocol with FBP bone, which was given the reference score of 3 (average = equal to reference), scores decreased progressively during dose reduction (see Table 2 and the comparison of the images in Fig 1). Images with a standard kernel showed a higher score than with the bone kernel. The reference dose protocol with FBP standard showed a score of 4. In LDP-II, the standard kernel could retain a score of 2 (suboptimal but sufficient) in contrast to the bone kernel, which was insufficient. ASIR-50 had no remarkable effect over FBP on subjective scores. ASIR-100 showed a small effect. MBIR showed the best subjective score in all images. MBIR obtained a score of 4 for LDP I and II and retained a score of 2 for LDP III and IV. ON showed better subjective visibility then IRM.

**DISCUSSION**

Various iterative reconstruction technologies have been implemented to reduce image noise and improve the quality of low-dose images.20,21 Adaptive statistical iterative reconstruction uses information obtained from the FBP algorithm but integrates a comparison of the pixel values with an ideal value to selectively identify and then subtract noise from an image at adaptive blend levels freely selectable typically from 10% to 100%.22 Model-based iterative reconstruction does not rely on the FBP as a starting point but instead uses a more complex system of prediction models, including noise and the spatial and geometric features of the x-ray beam and detector technology.23 In a cadaver, ASIR-100 at a CTDIvol = 3.48 and 2.19 mGy and MBIR at a CTDIvol = 0.82 mGy provided similar subjective cross-sectional and 3D bone image quality compared with the FBP reference at CTDIvol = 30.48 mGy.24 At a CTDIvol = 2.19 mGy, ASIR-50 reduced noise by 22%; ASIR-100, by 35%; and MBIR, by 67%.24 When we compared contrast-to-noise ratios of the different reconstructions using a reference dose protocol at a CTDIvol = 36.58 mGy and several ultra-low doses in a phantom study with a customized polymethyl methacrylate phantom, MBIR demonstrated the highest CNR throughout, followed by ASIR-100, ASIR-50, and FBP.25 With MBIR, ultra-low-dose protocols at CTDIvol = 4.14 and 2.63 mGy may show comparable scores for spatial resolution, which may allow a dose-reduction potential of up to 93%.26 Compared with FBP, ASIR was not able to significantly improve spatial resolution.26 In a more recent human cadaver study evaluating the influence of various low-dose protocols and IRTs on the detectability of midfacial fractures, ultra-low-dose protocols at CTDIvol = 1.0 and 2.6 mGy were diagnostic for dislocated and nondislocated fractures, respectively.14 However, due to smoothing effects, ASIR and MBIR could not improve fracture detection.14 MBIR does not evaluate thin bony structures well; this evaluation may be important in surgical planning and postoperative evaluation. Unfortunately, MBIR cannot be reconstructed in bone kernels.14,27

Following the fracture study, the aim of the present study was to evaluate the variability of the CNR of orbital soft tissues with low-dose protocols and IRTs. The measures were based on 3D volume-segmented HU evaluations of the ON, IRM, and orbital fat. Compared with the reference dose protocol (CTDIvol = 36.69 mGy), LDP I–IV (CTDIvol = 4.18, 2.64, 0.99, and 0.53 mGy) showed a dose reduction of up to 98.6%. For comparison, the
current reference dose of the German Federal Office for Radiation Protection for diagnostic sinus CT is $\text{CTD}_{\text{vol}} = 9 \text{ mGy}$. The presented doses described above were equal or lower than those of previous CT techniques and also most dentomaxillofacial conebeam CT devices. Unlike CT, an important limitation of conebeam CT is the insufficient soft-tissue contrast from which orbital soft tissues cannot be discriminated.

As expected, the reference dose protocol showed a statistically significantly better CNR than all LPDs for both the ON and IRM. The standard kernel had a statistically significantly higher CNR than the bone kernel, and the convolution kernel influenced the effect of iterative reconstructions. LDP-I showed a statistically significantly higher CNR than LDP-III and IV with both kernels. However, with a standard kernel, the CNR of LDP-I did not significantly differ from that of LDP-II. ASIR-50 showed significantly better CNR than FBP for both the ON and IRM with the bone kernel but only for the ON with the standard kernel. ASIR-100 was statistically significantly better than ASIR-50 with the bone kernel but not if the standard kernel was used. Schulz et al reported that iterative reconstructions with a soft-tissue kernel were more efficient at 120 kV than the 100-kV series, and at the lowest dose settings, use of the soft-tissue kernel reduced the benefit of iterative reconstructions. In the present study, MBIR achieved a statistically significantly better CNR compared with other reconstruction techniques, which is in line with previously published results with a phantom. Foxworth et al reported a significant improvement in the evaluation of soft-tissue structures with MBIR. Compared with the reference dose protocol with FBP, CNR of both the ON and IRM showed a statistically significant difference from the following: 1) LDP-I with ASIR-50, ASIR-100, and MBIR; 2) LDP-II with ASIR-100 and MBIR; 3) LDP-III with MBIR; and 4) LDP-IV with MBIR.

The CNR change was also supported by the subjective scoring. Scores were lower with a decreasing dose and higher for the standard kernel than for the bone kernel. The ON showed better subjective visibility than the IRM. On maxillofacial CT, images are usually provided in only the bone kernel. With the bone kernel, the orbital soft tissues were highly visible with the reference dose. However, they were blurred and invisible with ultra-low doses. The standard kernel, which is typically used only for soft-tissue imaging, such as in oncology, significantly improved visibility. ASIR-50 had no remarkable effect over FBP on subjective scores, and ASIR-100 showed only a small effect. In agreement with other researchers, an insufficient number of photons may not be compensated for by simply increasing the iterative reconstruction strength. MBIR showed the best subjective score in all images. Compared with the reference dose protocol with FBP bone, which was given a score of 3 (average = equal to reference) and the reference dose protocol with FBP standard, which obtained a score of 4 (above average), use of MBIR obtained a score of 4 for LDP-I and II and was able to retain a score of 2 (suboptimal but sufficient) for LDP-III and IV. Previous studies also indicated the high subjective image quality with iterative reconstructions in low-dose protocols, which may reach equivalent or even superior levels compared with non-dose-reduced CT scans with conventional FBP.

The study has several limitations. It was performed with a human cadaver. The results may thus not be comparable in living humans. Only 1 cadaver head was used; however, the relative differences in CNR may be very similar. Intraorbital bleeding may impair the CNR of orbital soft tissues. The influence of artifacts from surgical screws and plates has not been investigated.

CONCLUSIONS
Application of optimally tailored CT protocols with the lowest acceptable diagnostic dose is imperative in modern radiology. High-resolution ultra-low-dose CT protocols capable of being used for surgical planning and image-guided maxillofacial surgery may retain similar diagnostic visibility of orbital soft tissues at $\text{CTD}_{\text{vol}} = 2.64 \text{ mGy}$ with MBIR compared with a reference protocol at $\text{CTD}_{\text{vol}} = 36.69 \text{ mGy}$ with FBP. Reconstructions with a standard kernel may improve orbital soft-tissue visibility and should be provided in addition to the bone kernel. The achieved diagnostic dose levels in modern CT may be far lower than current reference levels for sinus CT. Application of low-dose technology and iterative reconstructions should be tested in clinical practice and may lead to redefinition of the ALARA/ALADA criteria for maxillofacial CT.

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REFERENCES
Does 3T Fetal MRI Improve Image Resolution of Normal Brain Structures between 20 and 24 Weeks’ Gestational Age?

G. Priego, N. J. Barrowman, J. Hurteau-Miller, and E. Miller

ABSTRACT

BACKGROUND AND PURPOSE: Stronger magnetic fields have the potential to improve fetal image resolution. Our objective was to detect whether there was better anatomic resolution of brain structures in fetuses imaged with a 3T magnet compared with a 1.5T magnet.

MATERIALS AND METHODS: Multiple cerebral and facial anatomic structures were retrospectively assessed in 28 fetal MR imaging scans with normal findings (12 at 3T and 16 at 1.5T) with a 0–3 grading score. Fetuses were assessed during the second trimesters (gestational age, 20–24 weeks). The association between the quality ratings and magnetic field strengths (1.5T versus 3T) was evaluated by a linear mixed-effects model. A quantitative assessment of the signal intensity was also performed in the different layers of the developing brain. Comparative log-ratios were calculated across the different layers of the fetal brain.

RESULTS: There was a statistically significant interaction between location and magnetic field strength (P < .001). The cerebral structures of the cerebellum, pons, venous system, semicircular canal, and cochlea showed statistically significant higher values on the 3T magnet. Similarly, statistical significance was also obtained on the quantitative assessment of the multilayer appearance of the brain; the 3T magnet had a median factor of 8.38 higher than the 1.5T magnet (95% CI, 4.73–14.82). Other anatomic structures assessed in the supratentorial compartment of the brain showed higher values on the 3T magnet with no statistical significance.

CONCLUSIONS: Both magnets depict cerebral and facial normal anatomic structures; however, our data indicates better anatomic detail on the 3T than on the 1.5T magnet.

ABBREVIATIONS: feMRI = fetal MR imaging; GA = gestational age; SAR = specific absorption rate

Since the first fetal MR imaging was performed in 1983,¹ the technique has developed vastly in the past 3 decades with the use of ultrafast sequences, which minimize motion artifacts² and improve the image quality of the mobile fetus. In addition, the higher magnet strength has already demonstrated superior anatomic contrast resolution in neuroradiology and has been an outstanding diagnostic tool.³–⁶

Recent literature has shown an advantage of 3T magnets in fetal body pathology imaging⁷,⁸ and in fetal brain resolution.⁹ Other advanced techniques such as MR spectroscopy and diffusion tensor imaging have begun to be applied in fetal imaging with promising results.¹⁰,¹¹ In addition, the use of stronger magnets has the potential to improve the SNR, which can be used to attain higher image quality, or can be traded for increased temporal resolution (decreased acquisition time) or a combination of both. In the case of fetal imaging, in which the fetus is usually very small and highly mobile, this gain can represent a substantial advantage. The gain in SNR can also allow implementation of SNR applications such as parallel imaging with multichannel coils to speed up single-shot MR imaging protocols, to reduce TE, to mitigate susceptibility, and to decrease radiofrequency heating by minimizing the number of pulses.

As could be anticipated, the main challenge when performing fetal MR imaging at 3T was imaging artifacts. With single-shot FSE sequences, the main artifacts were secondary to B1 inhomogeneity, which is noted as diffuse areas of image shading but did not limit diagnostic interpretation. On the other hand, an increase in the SNR can eliminate the image noise or interference at
1.5T, which results in improvement of the image quality at 3T. Motion artifacts were not thought to be different between the 2 magnets. The only perceptible difference is that planning between sequences in the 3T magnet took a few seconds longer, which might result in fetal motion.

Small centers with only 1 magnet may prefer to choose the higher field magnet for their clinical practice, which must then fulfill all their imaging requirements, including fetal imaging. Re-evaluation of the availability of fetal imaging with 3T magnets can be beneficial in this or other specific instances.

In this study, we aimed to compare the normal anatomy of the fetal brain in the second trimester between images acquired on 1.5T and 3T magnets. The normal anatomy reference of the fetal brain is essential for the interpretation of normal and abnormal fetal MR imaging (feMRI) findings. Our objective was to detect whether there was better anatomic resolution of brain and facial structures in fetuses between the gestational ages (GAs) of 20–24 weeks that were imaged with a 3T magnet compared with a 1.5T magnet. Improved anatomic resolution has the potential of a more detailed assessment and an accurate diagnosis and prognosis.12

MATERIALS AND METHODS

Demographic Data

This retrospective study was approved by the institutional review board of the Children’s Hospital of Eastern Ontario, Canada. All referrals for feMRI followed a dedicated fetal neurosonographic study. No written informed consent was obtained at the Medical Imaging Department, but feMRI requisitions are discussed with a multidisciplinary team prior to booking the MR imaging, as per departmental practice. A search of the Medical Imaging Department data base was performed to identify feMRI studies performed with a 3T system (Magnetom Skyra; Siemens, Erlangen, Germany) and a 1.5T MR imaging system (Sigma HD; GE Healthcare, Milwaukee, Wisconsin) from July 2010 to January 2016. Patients were identified by searching for the term "normal fetal brain" in the final report and having a gestational age between 20 and 24 weeks.

A total of 305 feMRIs (51 performed on the 3T and 254 performed on the 1.5T MR imaging scanner) were reviewed. Twenty-eight feMRI scans met the criteria for the term “normal fetal brain” in the final report and had a gestational age between 20 and 24 weeks.

Axial and coronal images needed to display a symmetric appearance of the cerebral and cerebellar hemispheres and of the ventricles. In the infratentorial region, the axial plane needed to demonstrate the entire cerebellum and the middle cerebellar peduncles. Angulated or tilted sequences were excluded. Readers were blinded to all clinical information, gestational age, selection of the sequences, and magnet strength. The MR images obtained with a 1.5T MR imaging scanner were acquired with an 8-channel phased array cardiac coil. Imaging parameters for both magnets followed our institutional standard protocol (Table 1).

Imaging Data Acquisition

Pregnant patients were positioned in the supine or lateral decubitus position. No anesthesia was used. MR images obtained with a 3T MR imaging scanner used a spine matrix coil with 24 elements in the table and a light weight 18-channel phased coil on the surface of the mother. The MR images obtained with a 1.5T MR imaging scanner were acquired with an 8-channel phased array cardiac coil. Imaging parameters for both magnets followed our institutional standard protocol (Table 1).

Image Analysis

All MR images were evaluated by 2 pediatric neuroradiologists with 16 and 10 years of experience in fetal imaging (E.M., J.H.-M.). Readers were blinded to all clinical information, gestational age, selection of the sequences, and magnet strength. Before starting to read cases, the readers interpreted 4 examinations in consensus to familiarize themselves with the qualitative grading and reach a consensus on the evaluation of the different brain structures and the planes needed for the evaluation. These 4 feMRIs were randomly chosen from both magnet strengths and outside the study group. A mini-atlas was also created for reference by the readers during the independent interpretation. The results of the readers’ interpretations were documented in a Research Electronic Data Capture (RedCap; https://catalyst.harvard.edu/services/redcap/) by each investigator.

Qualitative Assessment

The following structures were evaluated in the coronal and axial images: the multilayered appearance of the brain parenchyma, the

| Table 1: Parameters for 1.5T and 3T fetal MRIs |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Fetal Sequences** | **1.5T, 3 planes, T2WI SSFSE** | **3T, 3 planes, steady-state FIESTA** |
| **Free-breathing** | **Free-breathing** |
| **TR/TE, 3000/87.8 ms, ST = 4 mm** | **TR/TE, 3700/160 ms, ST = 4 mm** |
| **FOV, 340 × 340 mm²** | **FOV, 34 × 34 mm²** |
| **Matrix, 320 × 224 px²** | **Matrix, 320 × 224 px²** |
| **Time, 22.4 seconds** | **Time, 25 seconds** |

**Note:** SSFSE indicates single-shot FSE; px, pixel; ST, section thickness.
septum pellucidum, the cerebellar shape, optic (eye globes, optic nerves, optic chiasm) and ear structures (pinnae, cochlea, semicircular canals), and the choanae. In the sagittal plane, structures were the following: the corpus callosum, vermis and fissures, the belly of the pons, myelination of the midbrain, fastigial point, aqueduct of Sylvius, pituitary stalk, and face profile. In the axial plane, the cerebral peduncles and posterior walls of the optic globe were evaluated. The cerebral venous sinuses were assessed in all 3 planes. The qualitative assessments of the selected structures were rated as follows: 0 represented a structure that was not visible; 1 represented a partially visible structure; 2 represented an entirely visible structure, but ill-defined contour. D, GA, 20 weeks; 3T; score 3: entirely visible and sharp margins.

FIG 1. Sagittal T2 midline images of fetuses. Examples provide the qualitative assessment of the primary fissure of the cerebellum (arrows). A, Gestational age (GA), 21 weeks 1 day; 1.5T; score 0: no visible structure. B, GA, 21 weeks; 1.5T; score 1: partially visible structure. C, GA, 22 weeks; 1.5T; score 2: entirely visible structure, but ill-defined contour. D, GA, 20 weeks; 3T; score 3: entirely visible and sharp margins.

FIG 2. A coronal image was selected from each scan at the level of the third ventricle. One-millimeter ROIs were drawn in the developing brain layers: 1) germinal matrix, 2) periventricular, 3) subplate, and 4) cortical plate. These values were compared with an ROI outside the patient (air). This fetus had a GA of 20 weeks, scanned at 3T.

Quantitative Assessment
A quantitative assessment by the ROI of the supratentorial brain layers was obtained by a pediatric radiology fellow (G.P.). An ROI of 1 mm was manually placed on the different layers of the brain (Fig 2): germinal matrix, periventricular layer, subplate layer, and cortical layer. The mean signal intensity for each layer was collected, and a comparative ratio between the different layers and air was calculated. The contrast resolution of each layer was analyzed to compare the different magnet strengths.

The ratios of signal intensity between paired ROIs were compared between the 2 magnetic-field-strength groups. The ratios were log-transformed so that their distributions were approximately normal. A linear mixed-effects model was used to evaluate the association between the log-ratios and magnet strength across different ROIs. The model treated fetus as a random effect, with magnet strength and ROI treated as fixed effects.

RESULTS

Study Group
The gestational age range of the 12 fetuses in the group that underwent 3T MR imaging was 20.0 – 23.9 weeks (median, 21.8 weeks; interquartile range, 21.0 – 22.2 weeks). The gestational age range of the 16 fetuses in the group that underwent 1.5T MR imaging scans was 20.3 – 24.7 weeks (median, 21.1 weeks; interquartile range, 20.7 – 22.7 weeks). The maternal age range was 17.0 – 39.0 years (median, 32.5 years; interquartile range, 29.5 – 34.2 years).

Indications for MR imaging included mild ventriculomegaly (n = 7), body malformation (n = 11), and abnormality of a fetus in a previous pregnancy (n = 10). The cases with mild ventriculomegaly on sonography that were not confirmed on MR imaging were classified as normal feMRI studies. The remaining fetal brain cases were considered normal.

Qualitative Results
As presented in Table 2, the scores of both readers for all locations demonstrated an increased frequency of score 3 (excellent resolution of the structure with sharp margins) on the 3T
MR imaging scanner \( (n = 309, 56\%) \) compared with the 1.5T MR imaging scanner \( (n = 108, 15\%) \) and a larger number of score 0 for the 1.5T scanner \( (n = 74, 10\%) \) than for the 3T scanner \( (n = 20, 4\%) \).

In the linear mixed-effects model, the interaction among location, magnet strength, and gestational age was not statistically significant. On removing the interaction and refitting the model, all 2-way interactions were statistically significant, namely location by magnet strength \( (P < .001) \), location by gestational age \( (P < .001) \), and gestational age by magnet strength \( (P = .03) \). Confidence intervals for the interaction of location and magnet strength, adjusted for multiple testing, revealed that 12 structures had a significantly higher diagnostic quality with the 3T magnet and none had a significantly lower diagnostic quality. The 3T magnet showed significantly higher diagnostic quality ratings for the following: semicircular canal, cochlea, primary and secondary fissure of the cerebellum, pituitary stalk, fastigial point, pinnae, belly of the pons, optic chiasm, and the straight, transverse, and superior sagittal venous sinuses (On-line Table 1). The largest statistically significant difference was for the semicircular canal for which it was estimated that the 3T magnet yielded 1.6 points in higher diagnostic quality ratings \( (95\% CI, 1.0–2.2) \). Other structures had higher values on the 3T scanner than on the 1.5T scanner, but with no statistical significance: septum pellucidum, choanae, optic nerves, face, corpus callosum, globes, cerebellar shape, cerebral peduncles, posterior myelination of the pons, and the multilayer appearance of the brain. The only structure that did not show better values on 3T was the aqueduct of Sylvius (Fig 3).

The Cohen weighted \( \kappa \) for the 2 sets of readings by reader 1 was 0.75; for reader 2, it was 0.76. The Cohen weighted \( \kappa \) between readers was 0.71. The linear mixed-effects model for the diagnostic quality ratings showed a significant reader effect. Compared with the first reader, the second reader’s scores were lower by 0.35 points \( (95\% CI, 0.28–0.42) \).

Quantitative Results

Comparative ratios were calculated between germinal matrix/air, periventricular layer/air, subplate layer/air, and cortical layer/air for each fetal MR imaging scan. The median ratios were higher on the 3T scanner than on the 1.5T scanner (Table 3). Across all ROIs, compared with the 1.5T magnet, the signal-intensity ratios from the 3T magnet were higher by a median factor of 8.38 \( (95\% CI, 4.73–14.82) \) (Fig 4).

DISCUSSION

MR imaging is a noninvasive technique increasingly used to scan pregnant patients. Imaging performed with higher strength magnets has been proven superior in clinical practice\(^{3-6}\) due to their high signal intensity, resolution, reduced scanning times, and overall improved diagnostic ability. Imaging of the fetus has been evaluated with 3T, but studies were mainly focused on body imaging and not the brain and head anatomy.\(^8\) Our aim was to demonstrate the difference in spatial resolution between 1.5 and 3T magnets in fetal brain anatomy. Fetal MR images were selected between 20 and 24 weeks of gestation to ensure a similar fetal sulcation age and anatomy.\(^{14}\) This choice has resulted in a relatively homogenous sample for our trial, with similar gyration patterns. In addition, the early second trimester is a crucial time in pregnancy development, counseling, and decision-making. The second trimester feMRI has been demonstrated to be safe and helpful for the diagnosis of brain anomalies when there is a sonography concern, adding valuable information and changing management in approximately 30% of cases.\(^ {15}\)
The classification into 4 categories for each structure was carefully considered to be a good representation of the variety of qualitative imaging acquired on the scans and also an acceptable pathway for agreement between readers. The locations selected in our study are an extensive representation of the neuroanatomy in the fetus and key structures in the assessment of anomalies. The results of the analyzed brain structures demonstrated higher values on 3T magnets than on the 1.5T magnets, meaning better qualitative assessment with a stronger magnetic field. In particular, all the structures involving the auditory system showed exponential statistical significance (semicircular canals, cochleae, and pinnae). Inner ear structures have already been shown to have higher resolution on 3T than on 1.5T magnets in healthy adult volunteers.\textsuperscript{16} In addition, the 3T magnet is often chosen as the preferred technique for volumetric assessment of adult inner ear structures,\textsuperscript{17} particularly in the quantification of volumes for inner ear pathologies. The observation from the assessment with our grading also confirms that the stronger field can be used as a tool in prenatal diagnosis to reassure normal anatomic development of the major structures of the inner ear.

On the other hand, the optic chiasm and many of the posterior fossa structures such as the belly of the pons, fastigial point, and primary and secondary fissures of the vermis revealed statistically significant differences in the qualitative assessment. Because a normal biometry of posterior fossa structures rules out many of the concerning anomalies in neurofetal imaging, it is essential to appropriately visualize and assess these structures. These structures are often critical and an area of challenge when performing neurofetal sonography; therefore, the feMRI becomes a tool of trustworthiness.\textsuperscript{18}

The flow void of cerebral venous vessels, including the superior sagittal, transverse, and straight venous sinuses, also revealed better resolution on the 3T magnet than on the 1.5T magnet with statistical significance. Anomalies of the cerebral venous sinuses in the fetus are very rare but may present as congenital anomalies, such as the persistence of the falcine sinus or agenesis of the straight sinus, or as acquired disorders, most commonly a thrombotic occlusion.\textsuperscript{19} Prenatal sonography is an effective method for diagnosing and monitoring thrombosis, but feMRI serves as a complementary technique to evaluate the full extent of the cerebral venous sinuses and extension of thrombus and to rule out cerebral parenchymal lesions secondary to hypoperfusion of the associated malformation.\textsuperscript{20}

The remainder of the evaluated structures did not show statistically significant values, but the multilayering appearance of the brain on a 3T magnet demonstrated higher comparative quantitative ratios than on the 1.5T magnet. These quantitative differences in the signal intensity of the brain layers has been demonstrated to reflect different histologic patterns.\textsuperscript{21} The visualization of a normal transient laminar organization in the fetal brain is a relevant finding related to the normal development of the white matter in the neonate.\textsuperscript{21} Detection and characterization of malformation of cortical development have already been demonstrated to be better with a 3T than with a 1.5T magnet.\textsuperscript{22} The lack of statistical significance in our study group might be because only fetal studies with normal findings were included in this trial. Future studies with a combination of normal and pathologic fetal cases might enhance differences in the multilayered appearance of the fetal brain and could demonstrate the better image resolution of stronger magnets when pathology is present.

FeMRI has shown no reproducible harmful effects on pregnant women and their fetuses at a magnetic field strength of ≤3T.\textsuperscript{7,8} The major concern of feMRI is thermal exposure to the mother and

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### Table 3: Median IQR signal intensity ratio by location and magnet

<table>
<thead>
<tr>
<th>Location</th>
<th>1.5T (IQR)</th>
<th>3T (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germinal</td>
<td>7.3 (4.8–19.4)</td>
<td>72.3 (49.5–100.6)</td>
</tr>
<tr>
<td>Periventricular</td>
<td>10.7 (6.2–21.1)</td>
<td>103.8 (54.9–181.7)</td>
</tr>
<tr>
<td>Subplate</td>
<td>12.0 (8.4–25.4)</td>
<td>165.2 (97.2–270.1)</td>
</tr>
<tr>
<td>Cortical</td>
<td>9.7 (5.5–19.5)</td>
<td>90.1 (61.7–119.4)</td>
</tr>
</tbody>
</table>

Note: —IQR indicates interquartile range.

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FIG 4. The ratio between signal intensity and air at each location for each magnet. Each estimated ratio is shown as a small circle. Each superimposed box indicates the 25th percentile (lower part of the box), median (heavy horizontal line), and 75th percentile (upper part of the box). Note that the vertical axis has a logarithmic scale.
fetus because of the potential biologic damage. In fact, the main reason to avoid fMRI during the first trimester is the thermal risk. The heating caused by the radiofrequency energy is measured by the specific absorption rate (SAR), which is fixed by the appropriate authorities. In the United States, the Food and Drug Administration mandates that the SAR not exceed 4 W/kg of the mother’s body weight for all magnet strengths.7 The SAR is also limited by manufacturers to ensure that the increase in body temperature is <0.5°C. Experimental evidence proposes that SAR deposition to the fetus in utero is higher at 3T but remains within accepted limits for clinical practice. There are recommendations to reduce the fetal SAR between 2 and 3 times with circularly polarized B1 fields instead of linear-horizontal polarization mode 2-port radiofrequency shimming.23 The ability to decrease magnet time with faster sequences at 3T also has the potential to decrease the SAR. In addition, the acoustic effect has also been raised as a hypothetic concern, but the literature has shown it to be a theoretic risk rather than a real practical issue.4–7

The advantages of a stronger magnet are primarily an increase in the signal-to-noise ratio,2,5 meaning a higher image quality, with an increased spatial-temporal resolution and a decreased acquisition time per sequence. The principal disadvantage is artifacts from a higher magnet strength (On-line Figure) (ie, susceptibility and magnetic field heterogeneity) because there is stronger radiofrequency penetration, which results in unpaired hydrogen proton spin-up.

Limitations of this study include the small sample size, the retrospective design, and the lack of prospective follow-up to ensure that each fetus is entirely neurologically normal in childhood. Another limitation is the difference between the technique and parameters applied on the 3T and 1.5T magnets, including the difference in section thickness between the 1.5T magnet (4 mm) and the 3T magnet (3 mm), particularly important in the assessment of small structures. The combination of T2-weighted single-shot FSE and steady-state FIESTA was used on the 1.5T magnet compared with single T2-weighted single-shot FSE on the 3T magnet. The 3D and 2D FIESTA sequences have been useful in the assessment of brain and body abnormalities in the second trimester, primarily because the FIESTA sequence provides better motion artifact-free imaging.24–25 Motion artifacts of the images were also eliminated from the sample by selectively including the best sequence from each study in the 3 different planes.

CONCLUSIONS

Both magnet strengths can examine brain and facial anatomic structures for diagnostic purposes. However, our research demonstrates a better qualitative and quantitative resolution of the evaluated structures and images with the 3T magnet. This seems especially noticeable in the posterior fossa structures, venous system, and inner ears. Future studies comparing normal and abnormal fetal brains at different gestational ages may enhance the practical impact of using higher strength magnets as long as the safety of the fetus and mother are guaranteed or assured.

ACKNOWLEDGMENTS

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REFERENCES


MR Imaging Diagnosis of Diencephalic-Mesencephalic Junction Dysplasia in Fetuses with Developmental Ventriculomegaly


ABSTRACT
SUMMARY: Diencephalic-mesencephalic junction dysplasia is a rare malformation characterized by a poorly defined junction between the diencephalon and the mesencephalon, associated with a characteristic butterfly-like contour of the midbrain (butterfly sign). This condition may be variably associated with other brain malformations, including callosal abnormalities and supratentorial ventricular dilation, and is a potential cause of developmental hydrocephalus. Here, we have reported 13 fetuses with second-trimester obstructive ventriculomegaly and MR features of diencephalic-mesencephalic junction dysplasia, correlating the fetal imaging with available pathology and/or postnatal data. The butterfly sign can be clearly detected on axial images on fetal MR imaging, thus allowing for the prenatal diagnosis of diencephalic-mesencephalic junction dysplasia, with possible implications for the surgical management of hydrocephalus and parental counseling.

ABBREVIATION: DMJ = diencephalic-mesencephalic junction

Diencephalic-mesencephalic junction (DMJ) dysplasia is a rare malformation characterized by a poorly defined junction between the diencephalon and the mesencephalon and associated with a characteristic butterfly-shaped contour of the midbrain on axial sections on MR imaging.1-3 This condition is included in a larger spectrum of DMJ anomalies, comprising forms that are recognizable in the axial (type A-DMJ anomalies, including DMJ dysplasia) or sagittal planes (type B-DMJ anomalies).3 DMJ anomalies may be variably associated with other brain malformations, including callosal abnormalities and supratentorial ventricular dilation. In the original report, massively enlarged lateral ventricles were appreciated in 2 patients with DMJ dysplasia.1 Thereafter, partial aqueductal stenosis was identified in 1 patient with DMJ dysplasia and prenatal onset of severe ventriculomegaly, suggesting a mixed obstructive and malformative cause of the hydrocephalus.3 The prenatal imaging features of DMJ have not been reported. Moreover, the relationship between DMJ anomalies and early developmental hydrocephalus remains unclear.

Several causes of developmental hydrocephalus have been described in fetuses and children, mostly associated with myelomeningocele, aqueductal obstruction, posterior fossa crowding, and cysts or cephaloceles.4-6 To the best of our knowledge, no imaging features of DMJ dysplasia have been described in fetuses with developmental ventriculomegaly. Here, we have reported the second-trimester prenatal MR imaging of 13 fetuses with moderate-to-severe obstructive ventriculomegaly presenting unequivocal features of DMJ dysplasia, and we correlated the imaging with available pathology and/or postnatal data.

CASE SERIES
This case series included 13 fetuses, referred to 3 pediatric institutions over a 10-year period (2005–2015) for fetal MR imaging because of second-trimester ultrasound findings of obstructive ventriculomegaly, in whom clear MR features of DMJ dysplasia were retrospectively detected. These cases were found by searching the fetal MR imaging data bases of the 3 centers for reports indicating obstructive ventriculomegaly, defined as bilateral atrial width > 12 mm with the hemisphere convexity reaching or almost reaching the skull inner surface, and with downward displacement of the fornix, without enlargement of the fourth ventricle. The DMJ dysplasia was not detected in the sonography examinations.
The MR imaging studies were performed for clinical purposes on 1.5T scanners (Achieva, Philips Healthcare, Best, the Netherlands; Ingenia, Philips Healthcare; Magnetom Avanto, Siemens, Erlangen, Germany) with a phased array abdominal or cardiac coil after an expert neurosonography study. All studies included 3 mm–thick single-shot fast spin-echo multiplanar T2-weighted images. The mothers had signed a specific consent form for fetal MR imaging, and the study complied with the internal guidelines for retrospective studies of the 3 institutions.

The On-line Table summarizes the clinical radiologic data of all fetuses. The mean gestational age at first fetal MR imaging was 23.8 weeks (range, 20–31 weeks). All fetuses were males. The mean maternal age was 32.9 years. Congenital infections and alcohol abuse were excluded in all pregnancies. No karyotype anomalies were reported in the 11/13 cases with available testing.

The mean atrial width was 20.6 mm (range, 12–38 mm). Supratentorial brain mantle thinning was noted in all fetuses, with the brain surface reaching or almost reaching the inner skull surface. Complete or partial agenesis of the corpus callosum was noted in 9/13 fetuses, and marked callosal thinning caused by the underlying ventriculomegaly was seen in the remaining 4 cases. In all cases, on prenatal MR imaging, the butterfly sign was detected on axial sections, and on sagittal images, a poorly defined DMJ was noticeable, with the thalamic mass sitting in an abnormal anterior position with respect to the midbrain (Fig 1 and On-line Figure).

On coronal sections, a merger between the midbrain and thalami was detected in all cases. Ventral dislocation of an enlarged interthalamic adhesion was noted in 9/13 fetuses, and the aqueduct was poorly defined in 10/13 cases. Pontine hypoplasia was identified in 6/13 fetuses and cerebellar hypoplasia in 3 cases. A moderate brain stem kinking was present in 11/13 cases.

In 9/13 cases, the parents elected for termination of pregnancy after prenatal counseling. Two fetuses had a second antenatal MR imaging performed 1 and 10 weeks after the first examination, respectively. Postnatal MR imaging was available in 4 patients (Fig 2), and MR autopsy was performed in 1 fetus. DTI was performed in 2 patients on a 1.5T scanner along 34 noncollinear directions by using an axial single-shot spin-echo echo-planar sequence, with b-values of 0 and 1000 s/mm²; TR, 9203 ms; TE, 71 ms; section thickness, 2 mm; FOV, 240 × 240 mm; matrix size, 128 × 128. The corticospinal tracts were reconstructed with a deterministic algorithm by using the IntelliSpace Portal 8.0 (Philips Healthcare). Interestingly, no tracking of corticospinal tracts was obtained below the level of the midbrain (Fig 3). Neuropathologic data were available in 2 fetuses, confirming the altered DMJ segmentation with deep ventral midbrain cleft and the level and etiology of the obstruction. In 1 fetus, there was a trifurcation of the cerebral aqueduct, and the olivary nuclei were small and anteriorly dislocated. Moreover, an incomplete lobulation of the right lung and right-sided moderate hydronephrosis were noted. Overall, the prenatal diagno-
sis of DMJ dysplasia was confirmed postnatally or ex vivo in 6/13 cases of this series.

DISCUSSION

We described a relatively large series of fetuses with second-trimester obstructive ventriculomegaly associated with clear features of DMJ dysplasia. Our cohort demonstrates that DMJ dysplasia could already be detected before gestational week 24 and that it has to be included among the causes of early developmental hydrocephalus. Fetal ventriculomegaly is a relatively common finding, occurring in approximately 1% of fetuses on sonography and in 1 of 1000 live born neonates. Conversely, DMJ dysplasia is probably rare, though it may be underestimated in cases without ventriculomegaly. The role of MR imaging in detecting brain anomalies in fetuses with ventriculomegaly is well established. Griffiths et al demonstrated a 17% risk of finding other brain abnormalities in fetuses with a confident sonography diagnosis of isolated ventriculomegaly. More recently, Barzilay et al showed that in fetuses with ventriculomegaly, the MR detection rate of minor and major brain findings increases with each millimeter increase in ventricle width. Various etiologies of fetal ventriculomegaly have been demonstrated, including acquired causes such as intraventricular hemorrhage, infection, or neoplasms. When these have been excluded, radiologists must carefully assess MR images to identify additional brain abnormalities that may suggest a developmental/ malformative cause of the hydrocephalus.

DMJ dysplasia is a rare malformation first described in 6 children born from 3 consanguineous Egyptian families, with facial dysmorphisms, severe cognitive impairment, axial hypotonia, spastic quadriaparesis, vasomotor instability, unexplained fever, and seizures. So far, no causative genes have been linked to this condition. On imaging, DMJ dysplasia is characterized by a poorly defined junction between the diencephalon and the mesencephalon and by a ventral cleft contiguous with the third ventricle, producing a characteristic butterfly-shaped contour of the midbrain on axial images. Notably, MR imaging identified the butterfly sign and the abnormal relation between the midbrain and thalamic mass already at 20–21 gestational weeks in 6 fetuses of this series. Nonetheless, if not carefully sought, this finding may be overlooked, especially in the early gestational weeks. Therefore, to improve the detection rate of DMJ anomalies in earlier gestational stages, fetal MR imaging must be technically adequate, with perfectly oriented axial planes, and should not be hampered by fetal motion artifacts.

Developmental forms of hydrocephalus often have multiple points of obstruction. In the present series, cerebral aqueduct stenosis was confirmed in all cases with postnatal MR imaging or autopsy. Moreover, the cerebral aqueduct was scarcely visible in most fetuses of our series, suggesting that aqueductal stenosis could be the main cause of obstructive ventriculomegaly. Of note, the identification of the lumen of the cerebral aqueduct on MR imaging may not always be reliable in the early gestational weeks, often requiring follow-up studies for confirmation. Interestingly, in most of the present fetuses, the interthalamic adhesion was additionally enlarged and caudally displaced. The location of the interthalamic adhesion is highly variable in humans, but in most people, it lies at the center or in the anterior upper quadrant of the third ventricle, whereas it is located in the posterior inferior quadrant in fewer than 1% of cases. A recent computational study on CSF dynamics demonstrated that pressure in the third ventricle is higher when the interthalamic adhesion is located close to the cerebral aqueduct. Partial or complete aqueductal stenosis associated with alterations of CSF flow dynamics within the third ventricle and abnormal WM development might thus explain the ventriculomegaly in these fetuses. In addition, the interthalamic adhesion hypertrophy is an important dysmorphic feature reported in several brain malformations, including Chiari II malformation, L1 syndrome with X-linked hydrocephalus, and 6q terminal deletion syndrome. Notably, marked interthalamic adhesion hypertrophy may overlap with diencephalosynapsis, a rare malformation designating a complete or partial fusion of the thalami associated with secondary reduction of the lumen of the third ventricle, and with rhombencephalosynapsis.

Interestingly, all our presented fetuses were males, suggesting a possible X-linked inheritance pattern. Neuropathologic data from 138 fetuses and neonates genetically tested for X-linked...
hydrocephalus showed that 56 subjects (42%) harbored L1CAM gene mutations, and the remaining fetuses (58%) were classified into 4 distinct subgroups: 1) “L1-like” syndrome, including fetuses with no L1CAM mutations, but exhibiting characteristics of L1 syndrome (20%); 2) aqueductal atresia/forking spectrum, often associated with midbrain-hindbrain dorsoventral patterning defects (27%); 3) hydrocephalus associated with polymalformative syndromes, such as VACTERL-H (9%); and 4) hydrocephalus associated with isolated CNS malformations (44%).16 The L1CAM gene (Xq28) encodes a highly conserved type 1 transmembrane protein of the immunoglobulin superfamily that plays important roles in neuronal adhesion, neuronal migration, axonal growth, pathfinding, and fasciculation as well as in the development of the ventricular system and cerebellum. On imaging, L1 syndrome with X-linked hydrocephalus is usually characterized by bi- or triventricular dilation, aqueductal stenosis, enlarged quadrigeminal plate, interthalamic adhesion hypertrophy, and vermian hypoplasia.12,17 Intriguingly, most of the fetuses in our series showed phenotypic and imaging characteristics similar to L1CAM-mutated fetuses. Moreover, postnatal MR imaging with DTI revealed corticospinal tract abnormalities in 2 cases, likely corresponding to the agenesis/fragmentation of the corticospinal tracts described in neuropathology cases of L1 and L1-like syndromes. Unfortunately, because of the lack of L1CAM genetic analysis in the present cases, we cannot establish whether DMJ dysplasia is caused by L1CAM mutations or if it belongs to the L1-like spectrum. Moreover, data on fetal MR features of L1 or L1-like syndrome are not available in the literature. DMJ features are likely to occur on a different genetic basis, and studies on genotype-phenotype correlation are definitively needed.

Finally, we observed pontine hypoplasia and small cerebellar vermis in most of the present fetuses, variably associated with moderate brain stem kinking. The differential diagnosis of prenatal ventriculomegaly and brain stem kinking has been recently widened to include several brain malformations, such as congenital muscular dystrophies, X-linked hydrocephalus caused by L1CAM mutations, microcephaly with lissencephaly and mid-hindbrain involvement, and tubulopathies.18,19 Taken together, these data indicate that a kinked brain stem is not a pathognomonic finding, but more likely an indicator of severe neurodysgenesis arising early in gestation and often associated with developmental hydrocephalus.18

The main limitation of our report is the lack of extensive genetic testing and histology investigation in all cases with pregnancy termination. Moreover, the possibility that fetal DMJ dysplasia cases without developmental obstructive ventriculomegaly may have been missed in our prenatal imaging search has to be taken into account.

In conclusion, a butterfly-shaped contour of the midbrain along with an abnormal spatial relation between the midbrain and thalamic mass may be detected on axial and sagittal sections, respectively, thus allowing an early prenatal diagnosis of DMJ dysplasia in fetuses with proximal obstructive ventriculomegaly. Among the rare causes of developmental hydrocephalus, DMJ dysplasia is likely to be an underestimated condition and seems to share several phenotypic features with the L1 and L1-like syndromes. Further studies on larger fetal populations with genotype-phenotype correlations are needed to clarify the causes, pathophysiology, and prevalence of DMJ dysplasia in the fetal population.

Disclosures: Andrea Rossi—UNRELATED: Consultancy: Bracco Imaging Italia Srl.

REFERENCES

10. Samra KA, Cooper HS. Radiology of the massa intermedia. Radiology 1968;91:1124–28 CrossRef Medline
Temporal Evolution of Disc in Young Patients with Low Back Pain and Stress Reaction in Lumbar Vertebrae

A. Sharma, K. Sargar, and A. Salter

ABSTRACT

BACKGROUND AND PURPOSE: Although stress-induced bony changes often resolve with conservative treatment, the long-term effects of such mechanical stresses on intervertebral discs have not been studied. We aimed to assess the differences in the temporal evolution of disc in segments of the lumbar spine with and without signs of increased mechanical stresses.

MATERIALS AND METHODS: Using MR imaging performed ≥6 months apart, 2 radiologists evaluated lumbar intervertebral discs for degenerative changes affecting the annulus fibrosus, the nucleus pulposus, and the endplates in 42 patients (22 male, 20 female; mean age, 16.0 ± 3.7 years [range, 7–25 years]) with low back pain and imaging evidence of stress reaction/fracture in the lumbar spine. Data were analyzed for differences in the presence and progression of disc degeneration in stressed versus nonstressed segments.

RESULTS: At baseline, stressed discs had a higher burden of annular fissures, radial fissures, herniation, and nuclear degeneration. Endplate defect burden was comparable in stressed and control discs. At follow-up, the burden of new annular fissures and endplate defects was comparable for stressed and control discs. However, a higher proportion of stressed discs showed worsening nuclear signal intensity grade (14.3% versus 0% control discs; P = .008) and worsening nuclear degeneration grade (11.9% versus 0% control discs; P = .02). An increased risk of progressive nuclear degeneration of stressed discs was observed irrespective of the outcome of bony changes.

CONCLUSIONS: Stressed discs exhibit a higher burden of nuclear and annular degeneration at baseline. These discs have a higher risk of progressive nuclear degeneration irrespective of improvement or worsening of stress-related bony changes.

S

stress reaction in posterior elements of the lumbar spine is a common cause for low back pain in young athletes.1-11 Whereas ongoing mechanical stresses can cause overt stress fractures and eventually spondylolisthesis, an initial microtrabecular bony injury within an affected pedicle or pars interarticularis manifests either as edema on MR imaging or as increased uptake on a bone scan.2-5,12,13 Intervertebral discs attached to stressed vertebrae experience higher mechanical stresses, and even at a young age, these stressed discs demonstrate a higher burden of annular fissures, herniation, and loss of normal hyperintensity of the nucleus pulposus on T2WI.14 The stressed bone often heals with conservative management, allowing patients to resume their athletic activities.12,15,16 In contrast to the ability of bone to heal itself, there is little evidence to support disc regeneration after the initiation of the degenerative cascade, wherein an insult to the disc may initiate a chain of chemical or inflammatory events that can further damage the disc.17 Although cross-sectional studies have highlighted a higher prevalence of disc degeneration in patients with spondylolysis and spondylolisthesis in adults,18-21 there is a paucity of information about the risk of progressive disc degeneration in young patients presenting with clinical and imaging evidence for bony stresses in the lumbar spine. We aimed to study the longitudinal evolution of degeneration in the individual components of stressed discs, hypothesizing that the stressed discs would demonstrate a higher burden of progressive degeneration relative to control discs.

MATERIALS AND METHODS

Our institutional review board at Washington University School of Medicine approved this retrospective longitudinal observational study, waiving the need for consent.

Patient Selection

We identified consecutive patients diagnosed with a stress reaction or fracture in the posterior elements of the lumbar spine over
an 8-year period ending in 2015. Inclusion criteria were age <25 years and the availability of lumbar spine MR images obtained first at presentation and then >6 months later. All patients presented with low back pain without any history of acute injury. Diagnosis was confirmed by the senior author, a board-certified neuroradiologist with >15 years of experience. Patients with spinal infection and neoplasms were excluded. Forty-two patients (22 male, 20 female; mean age, 16.0 ± 3.7 years [range, 7–25 years]) were included. Bony stresses involved the L5 segment in 29 (69.0%) patients and the L4 segment in 9 (21.4%). Four patients (9.6%) had bony stresses at 2 segments (L3 and L4 in 2; L4 and L5 in 2). Thirty-nine of 46 (84.8%) stressed segments showed bilateral changes. Anterior fusion (grade 1 in all) was present in 15 (35.7%) cases. The mean duration between 2 studies was 19.8 months (range, 6–51 months). On the Hollenberg grading system, which categorizes stress injury into grades 1 through 4 (corresponding to edema without fracture line, incomplete fracture, complete fracture with edema, and fracture nonunion without associated edema, respectively), 18 of 42 (42.9%) patients were graded 1 or 2, indicating a lack of complete fracture.

### Imaging Analysis

MR imaging was performed on 1.5T or 3T scanners (Sonata, Vision, Avanto, Magnetom Aera, and Trio; Siemens, Erlangen, Germany) and included sagittal T1WI (TR, 448–640 ms; TE, 11–29 ms; thickness, 3 mm), sagittal T2WI (TR, 3110–5390 ms; TE, 99–164 ms; thickness, 3 mm), sagittal STIR (TR, 4300–6359 ms; TE, 18–100 ms; TI, 135–160 ms; thickness, 3 mm), and axial T2WI (TR, 2280–4820 ms; TE, 102–120 ms; thickness, 3–4 mm).

Two radiologists (K.S., a neuroradiology fellow, and A. Sharma, the senior author) evaluated MR images in a consensus read. Each component of the intervertebral discs between the T12 and S1 segments was evaluated on baseline scans as reported previously. The annulus fibrosus was assessed for annular fissure, radial fissure (annular fissure with its hyperintensity in continuity with that of the nucleus pulposus), and herniation. The nucleus pulposus was graded according to the Pfirrmann scale. The baseline degenerative burden in stressed discs demonstrated annular fissure, the burden of annular fissures in stressed discs was 0.5. Similarly, if the only control disc had nuclear degeneration, the burden of nuclear degeneration for the control disc was 1. For meeting the binary definition of nuclear degeneration, the disc had to be graded III or higher on the Pfirrmann scale. The baseline degenerative burden in stressed and control discs was compared. Differences between stressed and control discs for various parameters were assessed by using a non-parametric paired test, the Wilcoxon signed rank test, and the McNemar test. Correlation was sought between baseline disc degeneration, the presence of spondylolisthesis, and the grade of bony stress. Differences between scans were used to assess the burden of new degeneration by using similar tests. In cases where no new changes were observed in the discs of all patients, a binomial test of proportions was calculated. The Fisher exact test was used to test differences between patients with persistent bony stresses and those with improvement. A P-value <.05 was considered significant. All tests were 2-sided.

### RESULTS

At baseline, the burdens of annular fissures, radial fissures, and herniation were higher in stressed discs compared with control discs (P < .0001, P < .0001, and P = .024, respectively) (Table 2; Fig 1). Median [25th, 75th percentiles] signal intensity rating for stressed discs was 1.39 [1, 2], significantly higher than control discs (1 [1, 1]; P < .0001 [Table 2]). A higher percentage (52.4%) of patients showed at least 1 stressed disc with signal intensity grade >1 compared with those with a similar change in control discs (11.9%; P < .0001). Although the mean Pfirrmann grade in the 2 groups was comparable, a higher percentage of patients had nuclear degeneration (Pfirrmann grade >II) in stressed segments (19.1% versus 4.8% for control segments; P = .031). The endplate defect burden in stressed and control discs was comparable (Table 2).

No significant Spearman correlation was observed between various parameters of disc degeneration in stressed discs and spondylolisthesis at baseline. No significant Spearman correlation was present between annular fissure or radial fissure burdens in stressed discs and bony stress reaction grade (Wilcoxon signed rank, P = .37 and P = .29). However, there was a significant difference in the median stress grade for stressed discs showing nuclear degeneration compared with those without such indications (Wilcoxon signed rank, P = .034). For control discs, none of the parameters demonstrated any correlation with the grade of bony stress reaction.

At follow-up, the burdens of new annular fissures, new radial

<table>
<thead>
<tr>
<th>Location of Bony Stress Changes</th>
<th>Stressed Discs</th>
<th>Control Discs</th>
</tr>
</thead>
<tbody>
<tr>
<td>T12</td>
<td>T12–L1</td>
<td>L1–L2</td>
</tr>
<tr>
<td>L1</td>
<td>T12–L1, L1–2</td>
<td>L2–3</td>
</tr>
<tr>
<td>L2</td>
<td>L3–2, L2–3</td>
<td>T12–L1</td>
</tr>
<tr>
<td>L3</td>
<td>L2–3, L3–4</td>
<td>T12–L1, L1–2, L4–5, L5–S1</td>
</tr>
<tr>
<td>L4</td>
<td>L3–4, L4–5</td>
<td>L5–S1</td>
</tr>
<tr>
<td>L5</td>
<td>L4–5, L5–S1</td>
<td>L3–4</td>
</tr>
<tr>
<td>S1</td>
<td>L5–S1</td>
<td>L3–4, L4–5</td>
</tr>
</tbody>
</table>
Table 2: Disc degeneration in stressed and nonstressed segments of lumbar spine

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline Degeneration</th>
<th>Progressive Degeneration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stressed Discs</td>
<td>Control Discs</td>
</tr>
<tr>
<td>Annular fissure ab</td>
<td>0.76 ± 0.35</td>
<td>0.07 ± 0.18</td>
</tr>
<tr>
<td></td>
<td>37 (88.1)</td>
<td>6 (14.3)</td>
</tr>
<tr>
<td>Radial fissure ab</td>
<td>0.59 ± 0.43</td>
<td>0.07 ± 0.38</td>
</tr>
<tr>
<td></td>
<td>30 (71.4)</td>
<td>6 (14.3)</td>
</tr>
<tr>
<td>Herniation</td>
<td>0.07 ± 0.20</td>
<td>0.01 ± 0.08</td>
</tr>
<tr>
<td></td>
<td>8 (19.1)</td>
<td>2 (4.9)</td>
</tr>
<tr>
<td>Nuclear degeneration abc</td>
<td>0.13 ± 0.30</td>
<td>0.10 ± 0.28</td>
</tr>
<tr>
<td></td>
<td>5 (11.9)</td>
<td>2 (4.9)</td>
</tr>
<tr>
<td>Nuclear SI loss c</td>
<td>0.39 ± 0.42</td>
<td>0.12 ± 0.33</td>
</tr>
<tr>
<td></td>
<td>8 (19.1)</td>
<td>2 (4.9)</td>
</tr>
<tr>
<td>EPD ab</td>
<td>0.11 ± 0.24</td>
<td>0.00 ± 0.00</td>
</tr>
<tr>
<td></td>
<td>8 (19.1)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Note: EPD indicates endplate burden; SI, signal intensity.

* Burden (mean ± SD) of degenerative parameter calculated on per disc basis.
* Number (%) of patients with specified degenerative parameters in stressed or control segments of lumbar spine.
* Baseline Degeneration refers to changes on MR scan obtained at the time of presentation and “Progressive Degeneration” refers to appearance of new changes noted on a follow-up MR scan obtained ≥6 months later.
* Defined as discs graded higher than 2 on Pfirrmann grading system.
* Discs graded higher than 1 on a 6-point scale based on SI on T2-weighted images indicating any loss of normal hyperintense signal.

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Burden of Baseline Degeneration

![Bar diagram demonstrating the baseline burden of degenerative parameter in individual components of the lumbar intervertebral discs of patients <25 years old and presenting with low back pain caused by stress reaction in the posterior elements of the lumbar vertebrae. Stressed discs refer to intervertebral discs attached to the vertebrae with increased bony stresses. Control discs refer to discs not in contact with stressed vertebrae, but with otherwise equivalent axial loading.](image)

Burden of Progressive Degeneration

![Bar diagram demonstrating the burden of new degenerative changes in stressed and control discs as observed on follow-up MR imaging acquired ≥6 months after the baseline scan.](image)

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Fisher exact test did not reveal any differences in the parameters of progressive disc degeneration in patients with improved (8 patients; Fig 5) and those with persistent/worsening bony stress reaction (34 patients) on follow-up imaging.

DISCUSSION

Previous studies have reported a high prevalence of disc degeneration in adults with spondylolysis, with or without spondylolysis. It has also been demonstrated that early degenerative changes in the form of annular fissures, radial fissures, and nuclear degeneration can be seen around stressed vertebral segments in young patients with a stress reaction detected on MR imaging before complete stress fracture. By showing a relatively higher overall rate of worsened disc degeneration in stressed discs in follow-up studies, our results demonstrate, for the first time, the progressive nature of degenerative changes initiated in association with bony stress reaction fractures at a young age.

Although disc degeneration progresses relatively slowly, the long life expectancy of patients included in our study makes these results particularly noteworthy. It should be noted that most outcome studies in this patient population are limited to 1–3 years of follow-up, a rather short time span compared with the life expectancy of these patients. Based on the progressive disc degeneration seen in our study, it is likely that the advanced disc degeneration documented in many adults with spondylolytic spondylolisthesis reflects the sequela of a mechanical process that initiated degenerative cascade in discs at the same time it induced stress fractures in the vertebral elements.

Outcome studies in young patients with back pain caused by stress reaction have focused on either clinical symptoms or the evolution of stressed bone, with relatively few studies exploring the effects of such stresses on associated intervertebral discs. and new herniation in stressed discs (0.06 ± 0.17, 0.07 ± 0.18, and 0.01 ± 0.08, respectively; Table 2; Fig 2) and control discs (0.05 ± 0.22, 0.05 ± 0.22, and 0.00 ± 0.00, respectively; Table 2; Fig 2) were not significantly different. Similarly, the percentages of stressed and control discs demonstrating new annular fissure, radial fissure, or herniation were also comparable (P = .375, P = .219, and not available). Worsened signal intensity and Pfirrmann grade were present in 6 (14.3%) and 5 (11.9%) stressed discs, respectively (Figs 3–5). Control discs had no shift in their signal intensity or Pfirrmann rating. The binomial test of proportions indicates that stressed discs had a statistically different proportion with signal intensity (P = .008) and Pfirrmann rating (P = .017). No new endplate defects were found for either stressed or control discs (Table 2; Fig 2).
Progressive degeneration was observed in stressed discs irrespective of bone healing on follow-up imaging. It implies that in some patients, long-term sequelae of high segmental spinal stresses may be left in the form of disc degeneration rather than a stress fracture (Fig 5). Studies in asymptomatic athletes have demonstrated a high prevalence of both bony stress reaction and disc degeneration in the lumbar spine, indicating that mechanical stress–induced bony fractures as well as accompanying disc degeneration can take place in the absence of overt pain. The role of mechanical factors in disc degeneration is well established.

The previously reported higher burden of degeneration in stressed discs on both sides of the stressed vertebral segment suggests that in patients with a bony stress reaction, increased mechanical stresses are conveyed to the disc through the vertebral body to whichever disc components are attached. Whether, and to what extent, a similar mechanism may be responsible for initiating disc degeneration in the general population is unclear. Our results do suggest that in patients with advanced disc degeneration, intact posterior vertebral elements in the vertebrae around the degenerated disc do not exclude the possibility of a similar mechanism for the initiation of disc degeneration.

At baseline, the pattern of disc degeneration observed was similar to what has been previously reported, with a higher burden of annular fissures, radial fissures, and herniation as well as nuclear degeneration. Previous studies have highlighted the association between radial annular fissures and progressive nuclear degeneration. Therefore, it is to be expected that some stressed discs with annular pathology at baseline would undergo progressive nuclear degeneration on follow-up imaging irrespective of how the bony changes evolve, likely explaining the progressive disc degeneration in patients with improved bony stress reaction.

Although stressed discs showed a higher baseline burden of both annular and nuclear degeneration, progressive changes were mainly seen in the nucleus pulposus. Lack of a higher burden of new annular fissures in stressed discs could potentially be attributed to activity modifications induced by persistent symptoms in our patients. Alternatively, because the annulus may be the first component of the intervertebral discs to

Discs around the time of presentation. Conservative treatment is often successful in alleviating patients’ symptoms, allowing a high proportion of these patients to resume the offending physical activity. Follow-up imaging in our patients was done based on clinical need, and thus, our study fails to document the evolution of disc degeneration in patients who become asymptomatic. However, given the propensity of disc degeneration to remain asymptomatic and a higher baseline burden of annular pathology that is associated with progressive nuclear degeneration, it is possible that progressive disc degeneration also occurs in some patients despite their becoming asymptomatic.

**FIG 3.** Sequential MR images of the lumbar spine showing the evolution of lumbar disc degeneration in a 16-year-old female patient presenting with low back pain and evidence for stress reaction in both L5 pedicles (not shown) at the time of presentation. Both intervertebral discs (L4–5 and L5–S1) also shown in magnified images) around the stressed segment demonstrated the presence of annular fissures (arrows), disc herniation, and nuclear degeneration at baseline. The control disc in the lower half of the lumbar spine (L3–4) had an intact annulus and preserved nuclear signal intensity at baseline. Follow-up MR imaging 10 months later reveals stability in the appearance of the control disc, but interval loss of signal intensity, signifying progressive nuclear degeneration of both stressed discs. The annular fissure at the L4–5 level has become less conspicuous, but one at the L5–S1 level is more easily recognizable on a follow-up scan.

**FIG 4.** Sequential lumbar MR imaging over a 47-month period in a 12-year-old female patient presenting with low back pain caused by a partial L4 stress fracture as indicated by edema in the right pedicle (arrow) on a parasagittal STIR image. Initial and follow-up midsagittal T2-weighted images highlight marked progressive nuclear degeneration in the inferior stressed disc at the L4–5 level, but preserved appearance of a more caudally located control disc at the L5–S1 level.
be affected in the degenerative process, it is possible that patients in whom the annulus was prone to stress-induced injury had already developed annular fissures by the time of presentation. A similar explanation could also be used to explain why only nuclear degeneration correlated with the bony stress grade. The Hollenberg grading system progressing from bony edema to fracture nonunion can be viewed as an indirect proxy for the duration and/or the degree of mechanical stresses. Accordingly, even the baseline imaging in these patients may provide a sense of the timeline of associated disc degeneration. Again, it is possible that any annulus fibrosus predisposed to rupture in the face of increased mechanical stresses did so early in the process, thereby inciting ongoing nuclear degeneration that became more evident as the disease progressed.

Stressed discs did not exhibit a higher burden of endplate defects. These results are concordant with those previously reported. Apparent discordance from other studies showing a strong association between Schmorl nodes and disc degeneration may simply reflect differences in the population being studied and the hypothesis being tested. Despite a strong correlation between endplate defects and nuclear degeneration, their segmental distributions differ. Endplate defects are more prevalent at the thoracolumbar junction with inherently weaker endplates, whereas nuclear degeneration preferentially affects caudal segments of the lumbar spine. Stressed discs in our study were mainly seen in the caudal half of the lumbar spine, likely explaining a low burden of endplate defects in both stressed and control discs.

The retrospective nature of our study imposes some limitations. Very few segments from the upper lumbar spine were represented in our study. We did not take into consideration the weight of patients or activity level between the 2 studies. Although both of these factors can influence the risk of disc degeneration, these factors would have affected both the stressed and control discs. A longer follow-up duration could have further exaggerated the differences in the progression of disc degeneration of stressed versus control discs. Similarly, the overall burden of disc degeneration could have been different had we restricted the study to higher-strength MR imaging. Despite these limitations, the selection of stressed and control discs from the same patients allowed us to conclusively demonstrate a higher burden of both the baseline and the progressive degeneration of discs in lumbar spinal segments experiencing higher mechanical stress.

CONCLUSIONS
Intervertebral discs in stressed segments of the lumbar spine demonstrate a higher burden of disc degeneration at baseline and an increased risk of progressive degeneration irrespective of the outcome of bony changes. The progression of disc degeneration occurs mainly in the form of worsening nuclear degeneration.

REFERENCES


ABSTRACT

BACKGROUND AND PURPOSE: Despite the growing use of percutaneous ablation therapy for the treatment of metastatic spine disease, several issues have yet to be fully addressed. Our aims were to determine whether the vertebral body cortex protects against ablation-induced spinal cord injury; correlate radiofrequency, cryo-, and microwave ablation parameters with resulting spinal ablation zone dimensions and describe normal spinal marrow postablation changes on MR imaging.

MATERIALS AND METHODS: Ten thoracolumbar vertebrae in 3 sheep were treated with radiofrequency ablation, cryoablation, or microwave ablation under fluoroscopic guidance. Technique parameters were chosen to produce ablation zones that exceeded the volume of the vertebral bodies in sheep 1 and were confined to the vertebrae in sheep 2 and 3. Expected ablation zone dimensions were based on data provided by the device manufacturers. Postablation MR imaging was performed at 48 hours (sheep 1) or 7 days (sheep 2 and 3).

RESULTS: In sheep 1, cryoablation and microwave ablations extended into the spinal canal and caused histologically confirmed neurologic injury, but radiofrequency ablation did not. The mean difference between the lengths of the radiofrequency ablation zone dimensions measured on gross pathology compared with those expected was 9.6 ± 4.1 mm. The gross pathologic cryo- and microwave ablation zone dimensions were within 1 mm of those expected. All modalities produced a nonenhancing ablation zone with a rim of enhancement, corresponding histologically to marrow necrosis and hemorrhagic congestion.

CONCLUSIONS: An intact cortex appears to protect against radiofrequency ablation-induced spinal cord injury, but not against non-impedance-based modalities. Ablation dimensions produced by microwave and cryoablation are similar to those expected, while radiofrequency ablation dimensions are smaller. Ablation of normal marrow produces a rim of enhancement at the margin of the ablation zone on MR imaging.

ABBREVIATIONS: MWA—microwave ablation; RFA—radiofrequency ablation

Percutaneous, image-guided ablation is a minimally invasive therapy for metastatic spine disease. Several ablation modalities are commercially available, including radiofrequency ablation (RFA), cryoablation, and microwave ablation (MWA). RFA and MWA heat the tumor to temperatures above 60°C, at which point protein denaturation, immediate cell death, and coagulative necrosis occur.1 Mechanisms of cryoablation-induced cell death include osmotic bursting, intracellular ice formation, coagulative necrosis, free radical release and apoptosis in response to biochemical stress, and stimulated immunologic targeting of tumor cells.2 For patients with painful spinal metastases who do not respond or have a contraindication to radiation therapy, ablation may produce clinically significant pain palliation.3–7 Additionally, Wallace et al8 recently reported a 1-year radiologic local control rate of 70% (21/30) after RFA of spinal metastases, and Tomasian et al5 achieved a 97% (30/31) radiologic local control rate of spinal metastases treated with cryoablation after a median follow-up of 10 months (range, 1–24 months). As a result, recent treatment algorithms for metastatic spine disease have incorporated ablation as an alternative option for pain palliation and local tumor control.9

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The authors received ablation probes from DFINE, Galil Medical, and Medtronic for this study.

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Despite the growing use of percutaneous ablation therapy for the treatment of metastatic spine disease, several important issues have yet to be fully addressed. First, most spinal metastases involve the posterior vertebral body where complete tumor ablation is essential to prevent localized epidural invasion and spinal cord compression.10,11 However, it is unclear whether intact cortex acts as a protective barrier for the spinal cord and exiting nerve roots during ablation of the posterior vertebral body.12,13 Second, adequate tumor ablation requires accurate correlations between technique parameters and the resulting ablation zone dimensions. However, existing correlations derived from the manufacturers’ preclinical data are based on soft-tissue and artificial models that have different thermal and electrical conductive properties to bone.14 Last, although MR imaging is typically used to assess for local tumor control after ablation of spinal metastases,15 diagnosis of residual tumor is limited by a paucity of literature describing ablation-induced MR imaging findings in normal spinal marrow.

The purposes of this study were to determine whether intact posterior vertebral body cortex protects the spinal cord against radiofrequency-, cryo-, or microwave ablation-induced injury, to correlate the technical parameters of each ablation technique with the resulting dimensions of the ablation zone, and to describe normal spinal marrow postablation changes on MR imaging.

**MATERIALS AND METHODS**

The protocol of this study was approved by our institutional animal care and use committee.

**Ablation Technique**

Ablations were performed under fluoroscopic guidance by 4 radiologists (A.N.W., T.J.H., M.V.F., J.W.J.) with 1–9 years of experience performing musculoskeletal tumor ablation. Ten vertebral bodies in 3 healthy living adult female sheep (weight range, 55–60 kg) were ablated. All 3 sheep were sedated by a veterinarian staff member with an intramuscular injection of ketamine hydrochloride (2–10 mg/kg) and xylazine (0.2 mg/kg), intubated, and maintained under inhaled isoflurane (1%–5%) for general anesthesia. Mechanical ventilation was used throughout the procedure. The target vertebral bodies were localized by using a single-plane fluoroscopy unit, and the planned skin entry sites were sterilized with betadine scrubs and draped. Five- to 10-mm incisions were made at each skin entry site with a No. 11 blade to accommodate the percutaneous instruments. Unilateral transpedicular osseous channels into the vertebral bodies were created for ablation probe placement by using the OnControl system (Vidacare, Shavano Park, Texas), which consists of a 10-ga outer can-

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**FIG 1.** Fluoroscopic documentation of ablation probe placement in sheep. Anteroposterior (A, C, and E) and lateral (B, D, and F) fluoroscopic images show transpedicular placement of the cryoablation probe within the T4 vertebra (A and B), the radiofrequency ablation probe within the L3 vertebra (C and D), and the microwave ablation probe within the L6 vertebra (E and F).

**Table 1:** Technical parameters used for radiofrequency ablation, expected minor-axis diameter of the ablation zones based on nonanimal models, and measured ablation zone diameters on MRI and gross pathology.

<table>
<thead>
<tr>
<th>Watts</th>
<th>Thermocouple Temperatures (°C)</th>
<th>Ablation Time (sec)</th>
<th>Diameter of Ablation Zone Orthogonal to Ablation Probe (mm)</th>
<th>Expected MRI Gross Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Proximal</td>
<td>Distal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>72</td>
<td>51</td>
<td>92</td>
<td>20.0</td>
</tr>
<tr>
<td>5</td>
<td>58</td>
<td>42</td>
<td>107</td>
<td>16.6</td>
</tr>
<tr>
<td>5</td>
<td>51</td>
<td>40</td>
<td>42</td>
<td>13.0</td>
</tr>
</tbody>
</table>

**Table 2:** Technical parameters used for cryoablation, expected minor-axis diameter of the ablation zones based on nonanimal models, and measured ablation zone diameters on MRI and gross pathology.

<table>
<thead>
<tr>
<th>Probe</th>
<th>Intensity (%)</th>
<th>Freeze Cycles (min)</th>
<th>Thaw (min)</th>
<th>Diameter of Ablation Zone Orthogonal to Ablation Probe (mm)</th>
<th>Expected MRI Gross Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>IceSphere</td>
<td>60</td>
<td>6.0</td>
<td>7.0</td>
<td>20.0</td>
<td>19.2</td>
</tr>
<tr>
<td>IceSeed</td>
<td>50</td>
<td>5.0</td>
<td>5.0</td>
<td>6.0</td>
<td>6.6</td>
</tr>
<tr>
<td>IceSeed</td>
<td>50</td>
<td>3.5</td>
<td>5.0</td>
<td>6.0</td>
<td>6.4</td>
</tr>
<tr>
<td>IceSeed</td>
<td>50</td>
<td>3.0</td>
<td>5.0</td>
<td>5.0</td>
<td>5.5</td>
</tr>
</tbody>
</table>
and the craniocaudal dimension of the ablation zone is perpendicular to the ablation probe in the axial plane, respectively, and anteroposterior dimensions of the ablation zone are parallel and perpendicular to the ablation probe in the axial plane, respectively, and the craniocaudal dimension of the ablation zone is perpendicular to the ablation probe in the sagittal plane.

Ablation Parameters
The technical parameters and expected dimensions of each ablation zone based on preclinical data provided by the manufacturers are detailed in Tables 1–3. In sheep 1, cryoablation, RFA, and MWA were performed in the T14, L3, and L6 vertebral bodies, respectively. Sheep most commonly have 14 rib-bearing thoracic and 6 lumbar vertebrae, and the spinal cord terminates caudal to the sacrum. Each ablation probe tip was placed 5 mm from the posterior vertebral body cortex on a true lateral fluoroscopic projection. The parameters of radiofrequency, cryo-, and microwave ablation were chosen to produce an ablation volume that would be confined to the vertebral body cortex. The orientation of each dimension of the ablation zone with respect to the ablation probe was defined as depicted in Fig 2. Thus, for each ablation, the radius of the ablation zone extending from the probe tip toward the posterior vertebral body cortex was expected to be 10 mm. Every third vertebra was treated to ensure correct localization of histologic ablation-induced spinal cord injury.

In sheep 2 and 3, each ablation probe was placed in the center of the vertebral body, and the parameters of each ablation were chosen to produce an ablation volume that would be confined to the vertebra on the basis of preclinical data provided by the manufacturers. In sheep 2, RFA was performed at T14; MWA, at L3; and cryoablation, at L6. In sheep 3, RFA was performed at T14; MWA, at L2; and cryoablation, at L4 and L6.

RFAs were performed with the STAR Tumor Ablation System (Medtronic, Minneapolis, Minnesota). Ablations were performed at a power setting of 100 W for 10, 15, and 50 seconds. Power settings of 45 and 75 W are also available. The expected diameter of each MWA zone was based on an ex vivo porcine kidney model.

MR Imaging
In sheep 1, MR imaging was performed 48 hours after treatment owing to clinical signs of spinal cord injury and the ethical necessity for euthanasia earlier than the planned 7-day time point. MR imaging was performed 7 days after treatment of sheep 2 and 3. Images were obtained on a Magnetom Trio 3T scanner (Siemens, Erlangen, Germany) using the spine coil within the table of the scanner. The protocol included T1-weighted conventional spin-echo images (TR, 783 ms; TE, 10 ms), T2-weighted fast spin-echo images with fat suppression (TR, 3500 ms; TE, 94 ms), and postcontrast conventional spin-echo T1-weighted images with fat suppression obtained after the intravenous bolus administration of 0.1 mmol/kg of gadoversetamide (Optimark; Coviden, Irvine, California). All images were acquired with a 2.5-mm section thickness with 1-mm intersection spacing, 30 × 30 cm FOV, and 288 × 384 matrix. On MR imaging, the ablation zone was defined as the volume of nonenhancement on contrast-enhanced T1-weighted images with fat suppression. The measurements of MR imaging ablation zones were performed on high-resolution MR imaging workstation monitors. The anteroposterior, transverse, and craniocaudal ablation zone dimensions were measured for sheep 2 and 3. Only the transverse and craniocaudal dimen-

### Table 3: Technical parameters used for microwave ablation, expected minor-axis diameter of the ablation zones based on nonanimal models, and measured ablation zone diameters on MRI and gross pathology

<table>
<thead>
<tr>
<th>Watts</th>
<th>Ablation Time (sec)</th>
<th>Diameter of Ablation Zone Orthogonal to Ablation Probe (mm)</th>
<th>Expected</th>
<th>MRI</th>
<th>Gross Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>50</td>
<td>20.0</td>
<td>17.4</td>
<td>20.0</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>15</td>
<td>9.5</td>
<td>7.9</td>
<td>9.0</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>10</td>
<td>6.0</td>
<td>5.9</td>
<td>6.5</td>
<td></td>
</tr>
</tbody>
</table>

FIG 2. Anteroposterior (A) and lateral (B) CT images of a normal lumbar vertebra. The thick black line represents the unilateral transpedicular trajectory of the ablation probe. By definition, the transverse and anteroposterior dimensions of the ablation zone are parallel and perpendicular to the ablation probe in the axial plane, respectively, and the craniocaudal dimension of the ablation zone is perpendicular to the ablation probe in the sagittal plane.

FIG 3. Measurement of the expected diameter of each ablation zone orthogonal to the craniocaudal and transverse ablation zone dimensions were measured. Sheep most commonly have 14 rib-bearing thoracic and 6 lumbar vertebrae, and the spinal cord terminates caudal to the sacrum. Each ablation probe tip was placed 5 mm from the posterior vertebral body cortex on a true lateral fluoroscopic projection. The parameters of radiofrequency, cryo-, and microwave ablation were chosen to produce ablation zones with anteroposterior, transverse, and craniocaudal dimensions of 30 × 20 × 20 mm, 25 × 20 × 20 mm, and 20 × 20 × 20 mm, respectively. The orientation of each dimension of the ablation zone with respect to the ablation probe was defined as depicted in Fig 2. Thus, for each ablation, the radius of the ablation zone extending from the probe tip toward the posterior vertebral body cortex was expected to be 10 mm. Every third vertebra was treated to ensure correct localization of histologic ablation-induced spinal cord injury.

In sheep 2 and 3, each ablation probe was placed in the center of the vertebral body, and the parameters of each ablation were chosen to produce an ablation volume that would be confined to the vertebra on the basis of preclinical data provided by the manufacturers. In sheep 2, RFA was performed at T14; MWA, at L3; and cryoablation, at L6. In sheep 3, RFA was performed at T14; MWA, at L6. In sheep 3, MWA was performed at L6. In sheep 2, cryoablation, RFA, and MWA were performed in the T14, L3, and L6 vertebral bodies, respectively. Sheep most commonly have 14 rib-bearing thoracic and 6 lumbar vertebrae, and the spinal cord terminates caudal to the sacrum. Each ablation probe tip was placed 5 mm from the posterior vertebral body cortex on a true lateral fluoroscopic projection. The parameters of radiofrequency, cryo-, and microwave ablation were chosen to produce ablation zones with anteroposterior, transverse, and craniocaudal dimensions of 30 × 20 × 20 mm, 25 × 20 × 20 mm, and 20 × 20 × 20 mm, respectively. The orientation of each dimension of the ablation zone with respect to the ablation probe was defined as depicted in Fig 2. Thus, for each ablation, the radius of the ablation zone extending from the probe tip toward the posterior vertebral body cortex was expected to be 10 mm. Every third vertebra was treated to ensure correct localization of histologic ablation-induced spinal cord injury.

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RFAs were performed with the STAR Tumor Ablation System (DFINE, San Jose, California). Ablations can be performed at power settings of 5 or 10 W. Two thermocouples located on the shaft of the probe enable real-time monitoring of temperatures 10 and 15 mm from the center of the ablation zone, and the dimensions of the ablation zone are estimated from these maximum temperature readings. The expected diameter of each RFA zone orthogonal to the probe is based on the manufacturer’s thermal distribution curves derived from ex vivo porcine liver models.

Cryoablations were performed with the Visual-ICE Cryoablation System (Galil Medical, Arden Hills, Minnesota) with either the IceSeed 1.5 or IceSphere 1.5 cryoprobe. For a given cryoprobe, the volume of the ablation zone is controlled by changing the intensity (percentage maximum) and the duration of the freeze cycle. In the present study, 2 freeze cycles were performed and the probe was actively heated to thaw the tissue between cycles. The expected diameter of each ablation zone orthogonal to the cryoprobe was based on the −40°C isotherm dimensions produced in a 37°C gel bath.

MWAs were performed by using the Emprint Ablation System (Medtronic, Minneapolis, Minnesota). Ablations were performed at a power setting of 100 W for 10, 15, and 50 seconds. Power settings of 45 and 75 W are also available. The expected diameter of each MWA zone was based on an ex vivo porcine kidney model.

**Postablation Evaluation**
The sheep were clinically evaluated by a veterinarian immediately after each procedure for signs of pain or ablation-induced nerve injury, including lameness or abnormal movement. Subcutaneous buprenorphine, 0.005–0.01 mg/kg, was administered every 10–12 hours, and carprofen, 2–4 mg/kg, was administered every 12–24 hours for 2 days postoperatively. The sheep were then periodically monitored by veterinary staff before sacrifice for evidence of procedure-related complications.
sions of each ablation zone were measured in sheep 1, because the anteroposterior dimensions was not confined to the vertebral body marrow. MR signal and enhancement characteristics of the ablation zones of each technique were also subjectively reviewed by the first and senior authors. No interpretations were discrepant.

**Pathology**

Following MR imaging, the sheep were euthanized by barbiturate overdose (intravenous pentobarbital, 150 mg/kg) and the vertebral bodies and spinal cord were harvested by senior neurosurgery residents (B.H.S., Z.S.Z.). Tissues were fixed in 10% neutral buffered formalin. After fixation, the vertebral bodies were decalcified in hydrochloric acid–ethylenediaminetetraacetic acid decalcifier (EKI, Joliet, Illinois) to permit cross-sectioning of the bones for gross examination of the ablation sites and trimming of tissues for histopathology. The diameters of the pale tan necrosis orthogonal to the transverse and craniocaudal probe tracts were measured once by the first author and a veterinary pathologist with a Westcott 6” Clear Plastic Acrylic Ruler (Acme United Corporation, Fairfield, Connecticut). Because the vertebral bodies could be sectioned in only 1 plane, only the transverse and craniocaudal diameters of the ablation zones could be measured. Tissues were then paraffin-embedded, sectioned at 5 μm, and stained with hematoxylin-eosin for histopathologic evaluation.

**RESULTS**

Immediately after recovering from anesthesia, sheep 1 demonstrated bilateral lower extremity weakness, which did not improve during 48 hours of observation. MR imaging showed intramedullary T2 hyperintensity and enhancement involving the ventral spinal cord at the level of the cryoablated vertebra consistent with ablation-induced injury. Similar findings were seen along the ventrolateral aspect of the spinal cord at the level of the microwave-ablated vertebra, likely due to a slightly more oblique angulation of the MWA probe relative to the coronal plane. Histologically, the ablation zone was characterized by white matter necrosis with cavitation and axonal swelling and degeneration (Fig 3). The RFA zone measured 13.8 mm in the craniocaudal dimension. Because the RFA probe was placed only 5 mm from the posterior vertebral body cortex, the RFA zone should have extended into the spinal canal. Yet, histologic evaluation of the spinal cord at this level showed no evidence of ablation-induced injury.

Tables 1–3 summarize the correlations between the technical parameters of each technique and the resulting dimensions of the gross pathologic ablation zones. The mean differences in millimeters among the anteroposterior, transverse, and craniocaudal ablation zone dimensions expected on the basis of the manufacturers’ preclinical data and those measured on MR imaging and gross pathology are presented in Table 4. The dimensions of the RFA zones measured on gross pathology were smaller than those expected on the basis of correlations provided by the manufacturer. The mean differences between the lengths of the transverse and craniocau-

![FIG 3. Sagittal postcontrast T1-weighted image with fat suppression (A) and a T2-weighted image (B) of the vertebral level treated with cryoablation show the ablation zone extending beyond the posterior vertebral body into the spinal canal. There is enhancement and intramedullary T2 signal hyperintensity in the ventral aspect of the edematous spinal cord (white arrowheads). There is also inflammation in the soft tissues ventral to the spine where the ablation zone extended beyond the anterior vertebral body cortex (white arrows). Sagittal postcontrast T1-weighted image (C) and axial T2-weighted image (D) of the vertebral level treated with microwave ablation similarly show extension of the ablation zone into the spinal canal (white arrowheads). E, Hematoxylin-eosin staining of the spinal cord at the level of the cryoablated vertebra at ×100 total magnification shows axonal necrosis and edema. Similar findings were seen at the microwave-ablated level (not shown). F, Sagittal postcontrast T1-weighted image with fat suppression of the radiofrequency-ablated vertebra shows the posterior margin of the ablation zone confined to the vertebral body.](image)

| Table 4: Mean differences among the anteroposterior, transverse, and craniocaudal ablation zone dimensions expected on the basis of manufacturers’ preclinical data and those measured on MRI and gross pathology* |
|-----------------|-----------------|-----------------|-----------------|
|                 | Expected vs MRI (mm) | Expected vs Pathology (mm) | MRI vs Pathology (mm) |
|                 | AP               | CC              | TV              | CC              | TV              | CC              |
| Radiofrequency ablation | 6.7 ± 0.9 | 11.0 ± 2.5 | 6.6 ± 0.7 | 13.4 ± 2.1 | 5.9 ± 0.7 | -12 ± 0.7 | -0.8 ± 0.1 |
| Cryoablation    | -0.5 ± 0.3 | 0.1 ± 0.7  | -0.1 ± 0.7 | -0.4 ± 0.6 | -1.0 ± 0.5 | -3.4 ± 0.2 | -0.9 ± 0.3 |
| Microwave ablation | 0.9 ± 0.4 | 0.3 ± 0.5 | 1.4 ± 1.0 | 0.1 ± 0.5 | 0 ± 0.4 | -0.8 ± 0.2 | -0.9 ± 0.3 |

* A positive value indicates that the value listed first in the upper row was larger than the value listed second. For example, a positive value under the “Expected vs MRI” column indicates that the expected ablation zone dimension was larger than that measured on MRI. Orientations of the ablation zone dimensions with respect to the ablation probe are defined in Fig 2.
crosis with areas of granulation tissue and edematous stroma. Ablation zones were characterized by widespread marrow ne-
revealed discrete pale tan ablation zones. Histologically, the
(Fig 4). The gross and histologic findings seen with all modal-
yes measured on gross pathology were within 1 mm of those
expected. In contrast, the cryo- and microwave ablation zone dimen-
sions measured on gross pathology compared with those expected were 13.4 ± 2.1 and 5.9 ± 0.7 mm, respec-
tively. In contrast, the cryo- and microwave ablation zone dimensions measured on gross pathology were within 1 mm of those expected.

All ablation modalities produced the same subjective signal and enhancement characteristics on MR imaging (Table 5). Relative to normal marrow, the probe tracts demonstrated T1 hyperintense soft tissue within the probe tract (black asterisk) outlined by a signal void. The surrounding ablation zone is isointense to normal marrow and outlined by a thin hyperintense rim (white arrowheads). B, T2-weighted oblique sagittal MR imaging with fat suppression shows the hyperintense probe tract (black asterisk) and slightly hypointense ablation zone surrounded by a hyperintense rim (white arrowheads). C, T1-weighted, postcontrast subtraction images show enhancement along the probe tract (black asterisk) and the nonenhancing ablation zone surrounded by a rim of enhancement (white arrowheads).

Table 5: MRI, gross, and histopathologic findings produced by all 3 ablation modalities

<table>
<thead>
<tr>
<th>Probe track</th>
<th>T1WI</th>
<th>T2WI</th>
<th>CE-T1WI</th>
<th>Histopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Center</td>
<td>Hyperintense</td>
<td>Hyperintense</td>
<td>Enhancement</td>
<td>Hemorrhage, trabecular fragments, serum exudate, granulation tissue</td>
</tr>
<tr>
<td>Rim</td>
<td>Slightly hyperintense</td>
<td>Slightly hypointense</td>
<td>No enhancement</td>
<td>Marrow necrosis, granulation tissue, intact trabeculae</td>
</tr>
<tr>
<td></td>
<td>Hyperintense</td>
<td>Hyperintense</td>
<td>Enhancement</td>
<td>Hemorrhagic congestion</td>
</tr>
</tbody>
</table>

Note: —CE indicates contrast-enhanced.

Surrounding the ablation zones were rims of hemorrhagic congestion (Fig 5).

DISCUSSION

In the present study, we used a bipolar RFA system in an attempt to produce an ablation zone with a minor-axis diameter greater than the distance from the probe tip to the posterior vertebral body cortex, but caused no histologic evidence of spinal cord injury due to the insulating effect of the posterior cortex. Previous animal experiments assessing the safety of RFA in close proximity to the spinal cord have been inconclusive. Dupuy et al 12 safely performed monopolar RFA of the posterior vertebral body for 10 minutes, but the maximum temperature generated within the bone was only 48°C, which is below the cytotoxic threshold. In a subsequent porcine study, monopolar RFA performed flush with the posterior vertebral body cortex for 10 minutes at a constant temperature of 90°C at the probe tip caused paraplegia with histologically confirmed spinal cord injury. 13 However, this latter experiment does not reflect clinical practice because adequate ablation of tumor within the posterior vertebral body only requires that the periphery of the ablation zone reach 60°C for a matter of seconds. 1

In contrast with these previous studies, the ablation system used in the present experiment has several features that facilitate its safe use in the spine. First, the distal segment of the probe articulates up to 90°, enabling accurate placement of the tip with respect to the posterior vertebral body cortex. Second, the 2 active thermocouples incorporated into the shaft of the probe allow real-time estimation of the dimensions of the ablation zone. Last, monopolar systems require placement of a skin-grounding pad, which, if placed incorrectly, can cause a skin burn. This risk is eliminated with the use of a bipolar probe. 16 The RFA zones measured on gross pathology were smaller than those predicted from the manufacturer’s preclinical data derived from a soft-tissue model. 14 Potential reasons for this discrepancy include the higher impedance and lower thermal conductivity of bone compared with soft tissue and a heat sink effect from blood flow in the vertebrae and epidural space, as well as circulating CSF. 1, 12

In contrast to RFA, when we produced a cryoablation zone with a diameter greater than the distance from the probe tip to the posterior vertebral body cortex, histologic evaluation of the spinal cord at the treated level showed white matter necrosis with cavitation and axonal swelling and degeneration consistent with ablation-induced injury. Although there are no prior studies assessing the safety of cryoablation within the posterior vertebral body, this result is expected because increased bone density does not limit the propagation of the cryoablation zone. 12 Several measures may be taken to minimize the risk of this complication clinically. First, the distance between the probe tip and the spinal...
The ablation-induced marrow changes on MR imaging, gross pathology, and histopathology were consistent across all 3 modalities. The necrotic ablation zone was depicted on postcontrast T1-weighted MR imaging with fat suppression as a nonenhancing area surrounded by a thin, enhancing rim of granulation tissue. T2 hyperintense enhancing residual tumor can appear similar to the rim of the ablation cavity. In some cases, FDG PET/CT or biopsy may be needed to differentiate residual tumor from postablation change. The ablation zone dimensions of all 3 modalities measured on gross pathology were slightly larger than those measured on MR imaging. In the absence of a plausible physiologic explanation, the discrepancy is likely related to the resolution limitations of MR imaging.

A limitation of this study is that the correlations between technical ablation parameters and ablation zone dimensions were derived in normal bone, and these correlations may be altered by the presence of tumor. Also, the derived correlations are specific to the ablation systems used in this experiment and cannot be extrapolated to other devices.

CONCLUSIONS

Intact posterior vertebral body cortex in normal sheep may protect the spinal cord from radiofrequency ablation–induced injury, but not against microwave or cryoablation injury. Ablation dimensions produced by microwave and cryoablation are similar to those expected, while RFA volumes are smaller. Postablation marrow changes in normal spinal marrow include a rim of enhancement at the margin of the ablation zone.

Disclosures: Adam N. Wallace—RELATED: Grant: Medtronic, Galil, DFINE, Comments: received donated ablation probes from these companies.* Travis J. Hillen—UNRELATED: Consultancy: Merit Medical, Comments: honorarium for proctoring physician education courses. Jack W. Jennings—UNRELATED: Consultancy: Galil, Medtronic, Merit Medical, Bard Medical; Payment for Lectures Including Service on Speakers Bureaus: Medtronic and Medtronic Speaker Panels; Travel/Accommodations/Meeting Expenses Unrelated to Activities Listed: Comments: for meetings in which Speaker Panel duties were performed. *Money paid to the institution.

REFERENCES


Is an Intact Posterior Vertebral Body Cortex Protective for Percutaneous Ablation?

After the lung and liver, bone is the most common site for metastatic disease and the spine is the most common site of bony metastases. Roughly 70% of patients with cancer will develop metastatic disease. Of these, 40% develop spinal metastatic disease and 10%–20% of these will develop metastatic spinal cord compression.

Treatment of spinal metastases is usually palliative, with the goals of therapy including timely control of pain, local tumor control to prevent neurologic deficits, and mechanical stabilization to preserve function. Traditional treatment has been noninvasive, using analgesics, chemotherapy, and radiation therapy. Surgery is considered for radiation-resistant tumors, spinal instability, symptomatic neural compression, or intractable pain unresponsive to nonoperative measures. Recent studies have demonstrated image-guided invasive techniques of radiofrequency ablation (RFA), cryoablation, microwave ablation (MWA), and vertebral augmentation to be safe and effective in treating symptomatic metastatic osseous disease. The effects of different ablation modalities on the vertebral body and spinal cord are not completely understood.

The authors presented a study showing the ablation effects of bipolar RFA, cryoablation, and MWA on a normal sheep vertebral body and the adjacent spinal cord and nerve roots. The study addressed whether an intact posterior cortex of the vertebral body will act as an insulator during ablation to prevent injury to the spinal cord. The authors showed that an intact posterior vertebral body cortex acts as an insulator when using a bipolar radiofrequency system; however, with cryoablation and MWA, this effect is not present and cord damage may occur. The results of previous animal experiments assessing the safety of RFA in proximity to the spinal cord have been inconclusive. However, these were monopolar RFA systems, whereas the current study used a bipolar system. There are no prior studies assessing the safety of cryoablation or MWA within the posterior vertebral body. This study showed that for cryoablation and MWA, the posterior vertebral body cortex does not act as an insulating barrier. For these 2 modalities, the ablation probes must be accurately placed in the vertebral body and the ablation zone must not extend past the posterior wall of the vertebral body to avoid injury to the spinal cord and nerve roots. Motor-evoked potential monitoring and peripheral motor nerve electrostimulation can be performed only with cryoablation and may prevent iatrogenic injury to the spinal cord and nerve roots.

The RFA zones measured on gross pathology were smaller than those predicted from the manufacturer’s 37°C gel bath model. However, the cryoablation and MWA zones were within 1 mm of those predicted from the manufacturer’s preclinical data derived from the gel bath model. Awareness of this information is important for operators when performing ablation of a vertebral body.

Furthermore, the authors showed that ablation-induced marrow changes were similar on MR imaging, gross pathology, and histopathology across all 3 different ablation modalities. MR imaging showed the ablation area to be slightly hyperintense on T1-weighted imaging, slightly hypointense on T2-weighted imaging, with a central area of nonenhancement and a peripheral rim of enhancement on the contrast-enhanced T1-weighted images. The ablation zone dimensions of all 3 modalities measured on gross pathology were larger than those measured on MR imaging. These findings are helpful for the diagnostic neuroradiologist and interventionalist interpreting the posttreatment images to determine whether there is residual tumor.

The main limitation of the experiment is that all ablations were performed in a normal vertebral body, which is not the same scenario as in the clinical setting. The ablation zone volumes obtained from the experiment may not correlate with vertebral bodies with tumor involvement, given the different impedance and

A
thermal conductive properties of specific tumor types versus normal bone. Furthermore, the ablation zones derived from the experiment are specific to each manufacturer and cannot be generalized to other manufacturers of similar equipment.

The authors are to be commended for performing this in vitro experiment in a sheep model with the 3 most common ablation modalities. This report provides valuable information for operators performing vertebral body ablation with augmentation in patients with metastatic disease to the spine. With any palliative treatment, it is important to limit morbidity and maintain or improve quality of life. This information will help operators prevent injury to the adjacent spinal cord and nerve roots.

REFERENCES


http://dx.doi.org/10.3174/ajnr.A5235
Regarding “Differences in Hemodynamics and Rupture Rate of Aneurysms at the Bifurcation of the Basilar and Internal Carotid Arteries”

W ith great interest and appreciation, we have read the article by Doddasomayajula et al1 entitled “Differences in Hemodynamics and Rupture Rate of Aneurysms at the Bifurcation of the Basilar and Internal Carotid Arteries.” They analyzed the differences in hemodynamics at the bifurcation of the basilar and internal carotid arteries to explain why posterior circulation aneurysms have a higher rupture risk than those in the anterior circulation, and they found that higher-flow conditions in basilar tip aneurysms could explain their high rupture risk compared with internal carotid bifurcation aneurysms.

In their article, the typical inlet flow boundary conditions were used for all models. However, the inlet flow boundary conditions of the basilar artery (the posterior circulation) and internal carotid artery (the anterior circulation) could be an obvious difference for the diameter and flow of the inlet artery. Such settings with the same inlet flow boundary conditions of the basilar and internal carotid arteries may disrupt the hemodynamic results markedly in this study, and the conclusions might involve significant bias without considering this factor. To avoid such biases, mirror aneurysms may be an ideal within-patient disease model to provide an internal control for the analysis of possible factors linked to aneurysm rupture.2,3 Moreover, patient-specific inflow boundary conditions may avoid biases in the calculation of hemodynamics when using the computational fluid dynamics techniques.4

The authors should be commended for their meticulous in-study design using state-of-the-art methodology. We look forward to future research and discussion.

REFERENCES

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We appreciate the interest and comments on our paper entitled “Differences in Hemodynamics and Rupture Rate of Aneurysms at the Bifurcation of the Basilar and Internal Carotid Arteries.”

There are a few points that we would like to clarify.

In our models, we do not use the same flow conditions for all patients. The inflow boundary conditions are scaled with the size of each person’s anatomy based on a relationship determined experimentally with MR measurements and consistent with flows reported in other studies. In the absence of direct patient-specific measurements, this is, in our opinion, a reasonable approximation. In addition, our sensitivity analyses lead us to believe that relatively small variations in the boundary conditions (of approximately 30%) do not have an important effect on the conclusions drawn from the computational fluid dynamics (CFD) analysis that we are doing.

We agree that our results should be confirmed with studies that use direct patient-specific flow conditions and large sample sizes.

On the other hand, using mirror aneurysms, as suggested, would not solve the problem because in those cases, the aneurysms are located at the same anatomic location on each side. In our study, we compared basilar tip and internal carotid terminus aneurysms, which are fed by different arteries. Furthermore, even if only patients with aneurysms at the basilar tip and the internal carotid bifurcation were considered, there is still the uncertainty of the relative flow conditions in the feeding arteries. Only in ipsilateral multiple aneurysms fed by the same parent artery one can be sure that the inflow conditions are the same. In fact, we are submitting a new paper entitled “Hemodynamic Characteristics of Ruptured and Unruptured Multiple Aneurysms at Mirror and Ipsilateral Locations” that focuses on this issue. The results of that paper are consistent with the results presented in the current article.

We look forward to further discussions and exchanges of ideas.

REFERENCES
Regarding “What Is the Ideal Core Number for Ultrasonography-Guided Thyroid Biopsy of Cytologically Inconclusive Nodules?”

We read with great interest the article “What Is the Ideal Core Number for Ultrasonography-Guided Thyroid Biopsy of Cytologically Inconclusive Nodules?” by Hahn et al. In that study, the authors evaluated the correct number of core-needle specimens for patients with previously inconclusive fine-needle aspiration cytology (FNA) results and suggested that at least 2 core specimens containing intranodular and capsular tissue are necessary for a proper diagnosis. In their results, the diagnostic ability of 2 specimens was found to be higher than that of 1 specimen and was similar to that of 3 specimens. This concept is concordant with that of the recent core-needle biopsy (CNB) guidelines published by the Korean Society of Thyroid Radiology. Application of the results of Hahn et al will help patients to avoid repeated FNAs or diagnostic surgery. Thanks to the valuable results in CNB skills and pathologic evaluation of core specimens. This study explained comprehensive aspects of the number of core specimens, and this concept had not been reported to date. The authors revealed several important aspects of core biopsy after previously inconclusive FNA results: 1) CNB achieved no nondiagnostic results; 2) the rate of inconclusive results was just 6.7% (4 of 60); 3) the final surgical pathology was well correlated with the core biopsy results; and 4) CNB procedures were tolerable in all patients. Thus, CNB is an effective and safe procedure for patients with previously inconclusive results, and these findings are concordant with those of previous CNB studies.

Although the study of Hahn et al obtained informative results, there are 3 points to be considered. The first is the relationship between the number of core specimens and the size of the specimen notch of the core device. Second, capsule information is necessary, especially for diagnosing follicular neoplasm; however, a core technique including the capsule is not recommended in all patients, especially those with suspected papillary thyroid cancers. Finally, to justify 2 core specimens, the complications of the 3 groups should be compared. Regarding the relationship between the core specimen number and the size of the specimen notch of the core device, a core device with a 0.7-cm specimen notch. This obtains a core specimen of approximately 0.7 cm in length. A 1.6-cm excursion core device can obtain a 1.2-cm specimen length, whereas a 2-cm excursion device can obtain a 1.6-cm specimen length. Therefore, 2 specimens obtained by a 1.1-cm device are similar to 1 specimen obtained by a 1.6- or 2-cm core device. In addition, an 18-gauge core device can obtain larger-bore tissue than a 20- or 21-gauge core device. However, complications should be compared among devices with different lengths or thicknesses. Regarding capsule information, capsules can help to diagnose follicular neoplasms. Current CNB guidelines recommend that a nodule capsule be obtained during core biopsy. However, capsule information is unnecessary for the diagnosis of papillary thyroid cancers. Therefore, the use of an extra core biopsy should be restricted to certain types of thyroid nodules. Suh et al performed less than 2 core biopsy, but inconclusive results is not high in their factor analysis. Multiple biopsies can cause more complications; this issue should be considered during CNB procedures. To minimize complications, the operators performing CNB should understand the basic techniques and perithyroidal structures.

In conclusion, Hahn et al have reported valuable results on the number of core specimens needed for patients with previously inconclusive FNA results in thyroid biopsy. Although these data are practically important, knowledge of the core device, the relationship between specimen notch and specimen length, the type of thyroid nodule, and possible complications is essential for operators to perform thyroid CNB.

Disclosures: Jung Hwan Baek—UNRELATED: Consultancy: RFA Company, ATARmed and RF Medical, Comments: since 2017, $2700/year.

REFERENCES
3. Suh CH, Baek JH, Lee JH, et al. The role of core-needle biopsy as a

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first-line diagnostic tool for initially detected thyroid nodules. Thyroid 2016;26:395–403 CrossRef Medline


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Regarding “Measured Head CT/CTA Skin Dose and Intensive Care Unit Patient Cumulative Exposure”

We thank Nawfel and Young¹ for their thoughtful article, “Measured Head CT/CTA Skin Dose and Intensive Care Unit Patient Cumulative Exposure.” Nawfel and Young¹ have published a timely study in the midst of recent positive neurointerventional stroke trials and the resultant increased volume of CT angiographic imaging. Radiation exposure from medical imaging is always part of the risk-benefit analysis for critically ill patients. Accurate radiation dosimetry has been a topic of much debate in recent years, both from a scientific standpoint and from patient concerns sparked by the lay press. We would like to discuss the conclusions from Nawfel and Young¹ regarding radiation exposure from head CT/CTA in the context of the current medical literature and the potential future directions for research.

The authors did not find a statistically significant correlation between patient head size and peak skin dose. The peak skin dose was found to be consistently lower than the volumetric CT dose index (CTDIvol), citing the use of a “correction factor” with no additional variable. However, McCollough et al² summarized an exponential relationship between patient size (sum of anteroposterior [AP] and lateral diameters) and patient dose at other sites such as the abdomen. Perhaps the patient sample size was not sufficient to include enough variability to make an exponential relationship apparent. In addition, adult head size does not vary as widely as abdominal girth. The homogeneity of adult head size in the available cohort of patients may not sufficiently power for accurate statistical analysis. Perhaps either a much larger cohort or the inclusion of a pediatric patient population would have introduced the size heterogeneity necessary to make clear whether the exponential relationship between patient size and dose applies to head imaging as it does for the abdomen.

 Whereas the authors used the geometric mean to represent head size, other surrogates for size have been cited in the literature, such as weight, body mass index, single AP or single lateral diameter from either the localizer image or an axial cross-sectional image, summative AP and lateral diameters, and effective diameters.³ Work by the American Association of Physicists in Medicine³ has also identified water-equivalent diameter (Dw) as a surrogate for patient size in thoracic and abdominal imaging. In addition to measuring patient size, the application of Dw in the head would also take into account the variable attenuation properties ranging from air within paranasal sinuses to sclerotic calvaria. In fact, recent work by Anam et al⁴ has demonstrated an exponential relationship between a normalized size-specific dose estimate and Dw for head CT, including automation of the Dw calculation as others have previously described. Perhaps Dw or one of the other surrogates of patient size might have been useful in the study by Nawfel and Young¹ to elucidate the exponential relationship with size-specific dose estimate.

Disclosures: Michele Johnson—UNRELATED: Board Membership: Continuum Health, Comments: nonprofit board with no compensation.

REFERENCES

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We would like to thank Dr. Ikuta et al for their interest in our paper and comments on the data underlying Fig 4, which illustrates the variation in peak skin dose with patient head size.1

In our study, the effective diameter of adults undergoing head CT/CTA ranged from 14.9–18.7 cm. As Ikuta et al note, prior studies have demonstrated an exponential relationship between patient size and patient dose. McCollough et al2 demonstrated this in a study showing substantially more variation in abdomen size (20–80 cm) than the head size variation in our study. Anam et al3 reported that the normalized dose/100 mAs over a range of head sizes was only approximately 4 mGy. As such, we agree with Ikuta et al that the small range of head sizes encountered in our study, as compared with variation in abdominal girth, likely accounts for the absence of an exponential relationship between head size and dose in our data.

We believe that our use of effective diameter to represent head size, following the method of AAPM Reports 204 and 220, is appropriate because body mass index and weight are not necessarily well correlated with head size.4,5 AAPM Report 220 reports only a slight change in size-specific dose estimate when using water equivalent diameter (Dw) as compared with effective diameter as a conversion factor. Hence, we doubt that using Dw as a surrogate for head size would have changed our results significantly or demonstrated an exponential relationship between head size and peak skin dose.

To the contrary, our data provide support for the recommendation by Huda et al6 that a standard head size is appropriate for adult dose assessment because of the minimal variation in adult patient dose related to head size.

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REFERENCES

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The authors regret that in the October 2013 article “Widespread White Matter Alterations in Patients with End-Stage Renal Disease: A Voxelwise Diffusion Tensor Imaging Study” (AJNR Am J Neuroradiol 2013;34:1945–51), the MNI coordinates of brain regions shown in Tables 2–6 were incorrect. The MNI coordinates in Tables 2–6 should be corrected by shifting −20 in Y direction and +20 in Z direction. The tables are reproduced below with the corrected segments shown in bold.

Table 2: MNI coordinates of major areas with significant AD differences along with their means and standard deviations

<table>
<thead>
<tr>
<th>Brain Regions</th>
<th>MNI Coordinate (mm)</th>
<th>AD (Mean ± SD) × 10⁻³ mm²/s</th>
<th>ESRD</th>
<th>Healthy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rt. RLIC</td>
<td>25 −36 8</td>
<td>1.43 ± 0.17 1.39 ± 0.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lt. RLIC</td>
<td>−27 −34 6</td>
<td>1.66 ± 0.21 1.57 ± 0.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lt. Fmajor</td>
<td>−21 −32 8</td>
<td>1.43 ± 0.07 1.33 ± 0.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pons</td>
<td>1 −34 −36</td>
<td>1.85 ± 0.18 1.73 ± 0.11</td>
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<td></td>
</tr>
</tbody>
</table>

Table 3: MNI coordinates of major areas with significant RD differences along with their means and standard deviations

<table>
<thead>
<tr>
<th>Brain Regions</th>
<th>MNI Coordinate (mm)</th>
<th>RD (Mean ± SD) × 10⁻³ mm²/s</th>
<th>ESRD</th>
<th>Healthy</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCC</td>
<td>1 19 19</td>
<td>0.94 ± 0.2 0.86 ± 0.14</td>
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<td></td>
</tr>
<tr>
<td>SCC</td>
<td>1 −34 25</td>
<td>0.65 ± 0.15 0.56 ± 0.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rt. Fmajor</td>
<td>24 −74 12</td>
<td>0.66 ± 0.11 0.62 ± 0.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lt. Fmajor</td>
<td>−28 −62 12</td>
<td>0.67 ± 0.09 0.61 ± 0.11</td>
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</tr>
<tr>
<td>Rt. PCR</td>
<td>25 −43 27</td>
<td>0.64 ± 0.09 0.63 ± 0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lt. PCR</td>
<td>−28 −40 27</td>
<td>0.66 ± 0.09 0.65 ± 0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rt. ACR</td>
<td>17 31 14</td>
<td>0.64 ± 0.06 0.62 ± 0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lt. ACR</td>
<td>−20 −36 12</td>
<td>0.63 ± 0.06 0.59 ± 0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pons</td>
<td>3 −33 −34</td>
<td>0.82 ± 0.19 0.71 ± 0.12</td>
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Table 4: MNI coordinates of major areas with significant MD differences along with their means and standard deviations

<table>
<thead>
<tr>
<th>Brain Regions</th>
<th>MNI Coordinate (mm)</th>
<th>MD (Mean ± SD) × 10⁻³ mm²/s</th>
<th>ESRD</th>
<th>Healthy</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCC</td>
<td>1 19 12</td>
<td>1.16 ± 0.07 1.08 ± 0.05</td>
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<tr>
<td>SCC</td>
<td>1 −33 25</td>
<td>1.12 ± 0.13 1.02 ± 0.06</td>
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</tr>
<tr>
<td>Rt. SS</td>
<td>31 −51 11</td>
<td>1.27 ± 0.22 1.21 ± 0.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lt. SS</td>
<td>−39 −44 5</td>
<td>1.07 ± 0.12 1.04 ± 0.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rt. Fmajor</td>
<td>25 −62 17</td>
<td>0.96 ± 0.11 0.89 ± 0.04</td>
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<td></td>
</tr>
<tr>
<td>Lt. Fmajor</td>
<td>−30 −54 17</td>
<td>1.15 ± 0.11 0.99 ± 0.09</td>
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<tr>
<td>Rt. PCR</td>
<td>27 −45 24</td>
<td>1.07 ± 0.12 0.92 ± 0.06</td>
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</tr>
<tr>
<td>Lt. PCR</td>
<td>−29 −45 21</td>
<td>1.21 ± 0.18 1.11 ± 0.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pons</td>
<td>2 −34 −36</td>
<td>1.28 ± 0.13 1.13 ± 0.09</td>
<td></td>
<td></td>
</tr>
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</table>

Table 5: MNI coordinates of major areas with significant FA differences along with their means and standard deviations

<table>
<thead>
<tr>
<th>Brain Regions</th>
<th>MNI Coordinate (mm)</th>
<th>FA (Mean ± SD)</th>
<th>ESRD</th>
<th>Healthy</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCC</td>
<td>3 20 12</td>
<td>0.6 ± 0.06 0.67 ± 0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCC</td>
<td>3 −34 25</td>
<td>0.65 ± 0.05 0.72 ± 0.05</td>
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<tr>
<td>Rt. SS</td>
<td>31 −48 14</td>
<td>0.50 ± 0.04 0.56 ± 0.04</td>
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<tr>
<td>Lt. SS</td>
<td>−27 −59 14</td>
<td>0.46 ± 0.05 0.56 ± 0.07</td>
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<td></td>
</tr>
<tr>
<td>Rt. MCP</td>
<td>13 −38 −38</td>
<td>0.45 ± 0.03 0.53 ± 0.04</td>
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Table 6: MNI coordinates of areas with significant correlations along with their correlation coefficients

<table>
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<th>Brain Regions</th>
<th>MNI Coordinate (mm)</th>
<th>Correlation Coefficient</th>
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</thead>
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<tr>
<td>RD and duration</td>
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<tr>
<td>Lt. Pons</td>
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<td>0.7093</td>
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<td>RD and CASI</td>
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<tr>
<td>Lt. ACR</td>
<td>−28 33 39</td>
<td>−0.7442</td>
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<tr>
<td>Rt. SCR</td>
<td>31 −13 41</td>
<td>−0.6154</td>
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<tr>
<td>MD and duration</td>
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<td></td>
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<tr>
<td>Rt. RLIC</td>
<td>33 −40 14</td>
<td>0.6009</td>
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<tr>
<td>Lt. FWM</td>
<td>−21 43 15</td>
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<td>Lt. Pons</td>
<td>−12 −23 −26</td>
<td>0.6675</td>
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<td>0.7067</td>
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<td>Lt. PCR</td>
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<td>Rt. SCR</td>
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