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Stroke Wars: Episode IV *CT Strikes Back*

Robert D. Zimmerman

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Diffusion-Weighted Imaging Parameters to Track Success of Pyogenic Brain Abscess Therapy

The fundamentals of successful treatment of any disease include early diagnosis, timely treatment, and vigilant monitoring of response to treatment. To accomplish this sometimes-difficult process, it is crucial to employ the means that provide important disease markers, including laboratory parameters and imaging characteristics, in addition to clinical symptoms and signs. A brain abscess, for instance, demonstrates the value of improved medical imaging. Before cross-sectional imaging, the diagnosis of a brain abscess depended heavily on clinical history (usually a history of otitis media) and the presenting symptoms (nonspecific headache, fever, or both). Mortality from abscess decreased dramatically to nearly zero in the post-CT era. One may ask how CT has influenced the treatment of brain abscesses. To answer this question, a thorough understanding of the evolution of a brain abscess is essential.

The formation of a brain abscess follows a typical evolution that can be divided into four contiguous stages: early cerebritis (days 1–3), late cerebritis (days 4–9), early capsule (days 10–14), and late capsule (day 14 or later). The evolution involves the inflammatory responses of the brain to restrain microorganisms from spreading by eliciting local inflammatory cell infiltration and edema, and later, by the formation of a distinct collagenous capsule. A typically mature abscess consists of a thick collagenous capsule and an acidic medium inside the abscess that hinders effective treatment with intravenous administration of antimicrobials.

Conservative treatment of a brain abscess is most effective at the early stage of cerebritis, and surgical intervention using image-guided burr hole aspiration or excision after craniotomy is usually chosen for the disease management at the capsular stage. Although other factors such as size, location, number (multiple vs single), and type (multiloculated vs uniloculated or pyogenic vs nonpyogenic) may change the treatment of choice for brain abscesses, the general concept of the management is well understood: the selection of treatment methods depends on the evolution of the disease. Hence, it is desirable that a reliable imaging tool is available to reveal the stage of the abscess and to follow progression after treatment. CT and conventional MR imaging have served this purpose well for decades. The evolution of a brain abscess can be subdivided into three distinct radiological stages: early cerebritis shows local edema without contrast enhancement; late cerebritis, an ill-defined capsule of enhancing rim; and capsule, a distinctly enhancing capsule. However, because other diseases share similar imaging features, improved imaging strategies are desirable.

Until recently, diffusion-weighted (DW) imaging has proved useful in the diagnosis of pyogenic brain abscesses by showing a low apparent diffusion coefficient (ADC) in the abscess cavity. Although the cause of ADC decrease may be controversial, there is no doubt that this imaging sequence is helpful in differentiating brain abscesses from necrotic brain tumors and in establishing the diagnosis of the disease at the capsular stage when pus accumulates in the center of the lesion. More recently, a limited number of case reports have shown that DW imaging can depict the disease even earlier at cerebritis. If this could be further validated by experimental or larger-cohort studies, more patients could be conservatively treated with good outcomes.

In this issue of the *AJNR,* Cartes-Zumelzu and colleagues extend the use of DW imaging in seven patients undergoing therapy for confirmed brain abscesses. They found the reaccumulation of pus in the abscess cavity can be reliably depicted by DW imaging by showing decreased ADC 1 week after the initial normalization or increase of ADC following aspirations. The important implications of the study are twofold: first, DW imaging increases the specificity for the detection of pus reaccumulations compared with that of other MR imaging sequences and laboratory parameters for inflammation; second, it changes the clinical management of the disease and possibly shortens the course of therapy, thanks to the highly accurate CT-guided aspiration technique that can be easily repeated. On the other hand, it has long been known that contrast-enhanced CT and conventional MR imaging are not specific, although highly sensitive as compared with other clinical indices, for the detection of pus reaccumulation. In other words, they do not show changes of abscess contents over time after treatment. The typically rimlike enhancement of a mature abscess may not show improvement on CT scans or MR images for up to 5 weeks or longer after antibiotic treatment or aspiration. Other imaging parameters such as decrease of brain edema, abscess size, and improvement of inflammatory laboratory indices therefore have to be taken into account for possible alternative therapy if the patient does not improve. In Thurnher's study, the reaccumulated pus appeared hyperintense on follow-up DW images (with low ADC values), but the contrast-enhanced T1-weighted MR images remained unchanged, as shown in pretreatment study. This highlights the merit of DW imaging in the evaluation of the brain abscess during therapy.

Although DW imaging appears promising in the follow-up of evolution of brain abscesses during treatment, questions surrounding the sensitivity and specificity of DW imaging in the detection of pus accumulation remain to be answered. It has been reported

that small abscesses could be falsely negative at diffusion-weighted imaging. This has been attributed to the different intrinsic contents the small abscess has as compared with the larger abscesses. Abscesses caused by nonpyogenic pathogens such as fungus or parasites (eg, toxoplasmosis) may show increased ADC in the abscess cavity. Another important question is whether the hyperintense diffusion-weighted signals actually represent trauma-related accumulation after surgical aspiration. To exclude the possibility of blood accumulation in the previous abscess cavity, a T2*-weighted gradient echo imaging technique may be useful to make the differentiation.

Antibiotic treatment of brain abscesses generally takes from weeks to months because of the extended time needed for brain tissue to repair and close the abscess space. Therefore, it is worthwhile knowing the time course of DW imaging signal intensity change with respect to the dosage and duration of antibiotic treatment. This may help in establishing the medical treatment strategy and the DW imaging follow-up protocol. In Thurnher's series, one patient (patient 4) was treated with only antibiotics. The DW imaging signal intensity returned to normal 1 week following treatment. It is not known whether patient 4 underwent a shorter-than-average treatment regimen or whether the patient received a smaller-than-normal antibiotic dose. On the other hand, the treatment decision for patients 3 and 6 are worth mentioning. Patient 3 showed relatively few changes in ADC from 0.53 to 0.81 $\times$ 10^{-3} mm2/s on the first follow-up image; thus, a surgical drain was placed. However, similarly stable ADCs for both abscesses in patient 6 from initial to follow-up imaging (from 0.36 to 0.60 and 0.41 to 0.51 $\times$ 10^{-3} mm2/s 1 week after drainage) led to a continuous follow-up without aggressive intervention. Such an inconsistency prompts the need for a large-cohort, prospective study in which, ideally, a threshold for ADC evolution considered with clinical status and laboratory data would indicate further alternative therapy.

In addition to the issues raised, what would be pertinent about DW imaging features of the response to brain abscess therapy would be the parameters from which an appropriate treatment course could be suggested. In particular, is it the absolute ADC value or its relative temporal change that reflects the reaccumulation of pus? This question could be addressed if a proper choice of the *b* value existed or even if high-*b*-value DW imaging was used. Likewise, is it the ADC value or the DW imaging signal intensity that is clinically important for abscesses? Thurnher et al's data from the first follow-up images obtained in patients 3 and 6 showed that DW imaging signal intensity correlated with ADC. Although it is unclear whether ADC or DW imaging findings were considered by Thurnher et al to be most important threshfold for determining the success of surgical drainage, these results certainly emphasize the importance of examining both parameters rather than focusing on either one alone. DW imaging or ADC by themselves might not be specific enough to measure therapeutic response, particularly since it is unclear whether artifactual ADC values might arise from echo planar susceptibility effects when the abscesses are located near the skull base. All these unsolved issues remain to be answered by further investigation.

SANDY CHEN-YU CHEN
Guest Editorialist
Taiwan, Republic of China
HSIAO-WEN CHUNG
Guest Editorialist
Taiwan, Republic of China

Stroke Wars: Episode IV
CT Strikes Back

At the end of *Episode III*, upstart MR had seemingly vanquished CT as the imaging procedure of choice for detection of hyperacute infarction. Diffusion-weighted (DW) imaging has proved to be more sensitive than CT for detection of infarction and the combination of fluid-attenuated inversion recovery (FLAIR) and gradient echo sequences were shown to be superior to CT for detection of hemorrhagic transformation of infarction as well as other types of intracranial hemorrhage, including subarachnoid hemorrhage. But, as we begin *Episode IV*, a new threat has arisen. CT has returned with new technological weapons. The combination of multirow scanners and advanced easy-to-use 3D workstations has led to the development of the "Anti-Death Star" (well, okay, it is really a "multi-modal CT stroke protocol," but I think Anti-Death Star sounds more dramatic). Non-enhanced CT followed by CT angiography (CTA) and CT perfusion (CTP) can be performed within 5 minutes and provides information on the status of the extra- and intracranial circulation, the amount of brain that has been infracted, and the tissue at risk. This technique has swept through academic practices formerly in the MR camp and spread to many clinical practices. Tragically, in some centers, MR advocates and CT promoters, formerly trusted colleagues, now war for patients. (I exaggerate. No one really wars; we just scowl at each other at faculty meetings and social events.)

From my little parody, it is apparent where my sympathies lie, but it is important to realize that both imaging techniques can provide information that would have seemed impossible to obtain a few years ago. Each technique currently has a role, depending

on the clinical circumstance and local constraints (type and availability of technology, experience of staff, etc.). The future is a different story. I firmly believe that MR, with its ability to look at many aspects of the pathophysiological features of infarction rather than one parameter (perfusion), will provide information that CT will not be able to match.

Let me begin with the issue that colors this debate. A commonly stated argument against the use of MR imaging is that it is too difficult to perform these examinations in the setting of hyperacute infarction. It is claimed that patients are too unstable or that it is difficult to get the patients on an MR unit quickly enough in light frequency of use of MR imaging and length of examination. It is time that we stop using these problems as excuses and do the work necessary to overcome them. We are 4 years into the new millennium. We should be by using the most powerful tool at our disposal to deal with one of the most common and debilitating diseases we encounter. Patient monitoring has become easier with development of MR-compatible equipment and short-bore magnets. MR imaging in stroke patients can be performed within 15 minutes. New-generation magnets are easier to site, and many institutions have multiple MR systems, some deployed near acute care services. MR systems are more than money-making (or consuming) machines to be fed by healthy outpatients with damaged knees or headaches (or both). The sooner we devote ourselves to overcoming the logistical and technical problems inherent in performing MR imaging in the setting of hyperacute infarction, the sooner we will be able to take advantage of the potential of MR imaging.

Patients Who Are Not Candidates for Thrombolysis

In individuals presenting 6 hours after symptom onset or those with medical conditions that preclude use of thrombolytics, the goal of imaging is the detection of the presence and extent of infarction and the detection or exclusion of other causes of acute neurologic dysfunction, including intracranial hemorrhage, tumors, infection, posterior reversible encephalopathy syndrome, and venous thrombosis. MR imaging is clearly superior to noncontrast CT for the identification of acute infarction and the neurologic disorders that may mimic infarction. It should be the procedure of choice unless contraindicated (eg, if the patient has a pacemaker or other device incompatible with MR imaging).

It is true that CT can depict many infarcts within the first few hours of onset. Signs of hyperacute infarction include loss of gray matter density (ie, reduced gray matter–white matter differentiation), minimal mass effect, and increased density in a major artery, most often the distal internal carotid or middle cerebral artery (the "dense vessel sign") signifying an acute clot in the vessel. The loss of gray matter density is always ascribed—without, as far as I can tell, experimental verification—to the presence of edema. It seems to me that this assumption is incorrect or at least incomplete for a number of reasons, and I would like to offer an alternate hypothesis as to its etiology. First, the cytotoxic edema that dominates the early period of infarction is a shift of water from the extracellular to the intracellular space without a net increase in tissue water. Mild vasogenic edema occurs in the early phases of infarction but produces only a minimal increase in tissue water, and mass effect is usually absent. Minimal mass effect may be encountered near the end of the hyperacute phase (around 6 hours). If there really is an increase in water sufficient to cause hypoattenuated CT findings, this should cause obvious hyperintense T2-weighted and FLAIR findings. In a recent study of more than 600 infarcts evaluated within the first 24 hours of ictus, hyperacute infarcts produced T2-weighted and FLAIR findings that were either falsely negative (42%) or only slightly hyperintense (58%) (1). In my experience, these changes are always mild and often so subtle that they are appreciated only in retrospect. It seems improbable that this small change in water content would be more apparent on CT scans than on MR images. So what causes infarcts to be hypoattenuated on CT scans, and why does this have any bearing on this discussion? One needs to ask why normal gray matter is hyperattenuated relative to normal white matter in the first place. The most likely cause is intraluminal blood. Cerebral blood volume (CBV) in gray matter is twice that of white matter (2), and the intrinsic hyperattenuation of blood could account for the increased attenuation in gray matter. On contrast-enhanced CT scans, gray matter–white matter differentiation improves because of increased iodine in the gray matter compared with that in white matter, thus accentuating the effect of differential blood volume. The CT finding of hypoattenuated gray matter in acute infarction is most likely a direct consequence of decreased CBV in the infarcted brain and thus a crude sign of hypoperfusion rather than edema. Gray matter–white matter signal intensity differences at MR imaging are due to water content, not blood volume, so decreased CBV cannot be depicted on unenhanced MR images. If true, this hypothesis implies that CT depicts alteration with a single parameter, perfusion. Perfusion is important but surely it is not the only variable of interest in acute infarction.

How good is CT? Many studies have addressed this issue with variable results. Sensitivity has been reported to be as high as 85% in patients who are candidates for intraarterial thrombolysis and are imaged within 6 hours. This detection rate is deceptively high for several reasons. First, high rates of detection are usually seen in studies that are dominated by large middle cerebral artery–distribution infarcts, the easiest lesions to detect (3). In a large retrospective study of more than 600 patients examined at Harvard University, the detection rate for CT in the first 24 hours for all infarcts was only 40%, whereas detection with DW imaging was 97%. Several studies have documented a detection rate with DW imaging of more than 90% (1, 4, 5). Second, two other factors have

been identified that affect detection with CT but not MR imaging; namely, the experience of the reader and clinical information (4, 5). Expert readers do better than novices, and if one knew that the patient was having a stroke, it was easier to find it by using CT. This confirms what all of us know about detection of hyperacute infarction with CT. It is hard. Scans must be of high quality. Loss of gray matter density is subtle and can be difficult to detect even for the experienced reader. Gyri that curve in and out of the imaging plane may be hypoattenuated because of partial volume effects from adjacent CSF. Vessels may be dense because of calcification and may appear asymmetrically attenuated because of patient angulation or partial volume effects or both. Because of this, experienced neuroradiologists do much better than novices at detecting subtle infarcts and differentiating them from artifacts. The stroke neurologist at my hospital has an uncanny knack for correctly identifying acute infarcts on the basis of one hyperattenuated middle cerebral artery branch in the sylvian fissure and one image with a smudged gray white interface. But, of course, he is "cheating." He has already examined the patient and cannily knows exactly where to look on the CT scan to identify the infarct he knows is present. Thus, in academic centers with experienced neuroradiologists and stroke neurologists, CT detection is good. Most patients with hyperacute infarcts, however, do not present to academic centers. In community hospitals, radiologists and neurologists interpreting CT findings often do not have this degree of expertise or clinical skill. The European thrombolysis trial (ECAS) was initially deemed to have failed, but evaluation of the data revealed that this failure was due to misinterpretation of CT findings by the treating physicians. In routine clinical practice, one should not expect to see even the modest detection rates reported in the Harvard study (1). Alternatively, detection of hyperacute infarction on MR images is easy and requires little experience with either image interpretation or clinical neurology. Medical students can identify the "light bulb" sign on a DW image after 2 days of a neurology or neuroradiology rotation. I find it ironic that, after my talk promoting emergent MR imaging, experienced radiologists often say that they do not like to use MR imaging in these circumstances because it is complex, whereas CT is simple. CT is simple to perform, but MR findings are simple to interpret.

If MR imaging is to be used in these patients, how is it to be performed? We use different protocols in different clinical situations. In emergent circumstances, we use a fast protocol consisting of sagittal T1-weighted and axial DW, gradient echo, FLAIR, and MR angiography (MRA) sequences. The sequences are performed in this order to ensure that the most critical information is obtained if the examination must be prematurely terminated. The sequences are optimized for shortest acquisition time allowable for diagnostic-quality images. The sagittal T1-weighted image acts as the localizer image and allows for the detection of herniation and hyperintensity secondary to subacute hemorrhage. The axial DW sequence provides diffusion information and images obtained at a *b* value of 0 act as T2-weighted and susceptibility-weighted sequences in case the examination must be terminated after only 3 minutes. The gradient echo sequence is, next to DW imaging, the most critical sequence. It is the most sensitive technique available for detection of hyperacute hemorrhage. Several studies have documented that gradient echo images are at least as sensitive as CT for detection of hemorrhagic infarction (6, 7). Animal studies, case reports (8), and my own experience make me believe that gradient echo imaging is more sensitive than CT in detecting subtle hyperacute hemorrhage. Acute hematomas are easily identified on the DW images obtained at a *b* value of 0, but these images are inadequate for detection of subtle hemorrhage encountered in some acute infarcts (9). Gradient echo imaging can also be used to detect acute embolic occlusion of major vessels, the MR equivalent of the "dense vessel sign." Differentiation between hypointensity due to flow and hypointensity due to acute intraluminal clot is difficult with T2-weighted or FLAIR images. Spatially displaced flow-related enhancement is encountered on gradient echo images in most large patent major vessels producing hyperintensity adjacent to the dark lumen. Absence of this hyperintensity is highly suggestive of clot rather than flow. Gradient echo images also allow for detection of microbleeds that are seen as small punctate foci of hypointensity in patients with hypertensive cerebrovascular disease and cerebral amyloid angiopathy (9). FLAIR imaging allows for adequate assessment of brain parenchyma and for detection of subarachnoid hemorrhage. It is thus particularly useful in identifying stroke mimics such as inflammatory processes, mass lesions, and point-resolved spectroscopy. MRA is the least important sequence. It is, of course, helpful to know the status of the intracranial vessels, but this is not critical in the diagnosis of infarction. The neuroradiologists and stroke neurologists at our hospital are happy with this protocol, but many of our clinical colleagues prefer complete MR and MRA examinations of the head and neck when the patient's status and system availability allow.

Patients Who Are Candidates for Thrombolysis

The current criteria for use of intravenous thrombolytics are 1) symptom onset not exceeding 3 hours; 2) involvement of less than one-third the middle cerebral artery distribution; and 3) no CT evidence of hemorrhage. Most patients presenting with acute infarction fail to meet these criteria and therefore are not candidates for thrombolysis. It is important to note that thrombolysis is successful in approximately 75% of patients treated within 3 hours of onset of symptoms (10). Successful, that is, in the sense that there is dissolution of the clot. Success in terms of improved outcome is another matter. Thrombolysis will improve outcome only if there is salvageable brain that is critically underperfused, and the treat-

ment does not produce hemorrhage. If we add this additional inclusion criterion, presence of salvageable brain, it would at first glance appear to shrink the pool of patients who are candidates for thrombolysis even further. But this may not be the case. The current criteria reflect the balance between the benefit of reperfusion and the risk of hemorrhage in the general population. The goal of imaging is to gain sufficient information to "customize" these general criteria to the individual patient. For instance, if we eliminate the patients who are at greatest risk for hemorrhage or those who will not benefit from reperfusion regardless of other criteria, we may find that thrombolysis on balance aids patients treated at 4 or 5 hours, thus dramatically increasing the number of patients who are candidates for thrombolysis. Perfusion imaging identifies the tissue at risk and is thus critical to management. Bolus chase perfusion imaging can be performed with either CT or MR imaging in about 30 seconds (the time it takes the blood to circulate through the brain). There is still uncertainty as to the significance of various perfusion parameters but there is a growing consensus that CBV is a good indicator of initial infarct volume while mean transit time (MTT) and cerebral blood flow (CBF) and possibly loss of flow heterogeneity are more predictive of final stroke volume. Therefore, MTT and CBF are better indicators of brain at risk than CBV.

With MR imaging, the perfusion examination is added to the end of the fast stroke study. Perfusion data are obtained for virtually the entire brain. The ischemic penumbra is the brain tissue with normal diffusion and decreased perfusion surrounding the core region of infarction (defined as the region that is hyperintense on DW images) that is likely to go on to infarction if hypoperfusion is not rapidly corrected. An additional region of mild hypoperfusion or normal perfusion with decreased hemodynamic reserve may surround the zone of abnormal perfusion. The MR perfusion maps are easy to generate and interpret. Parametric maps of cerebral blood volume, time to peak, and relative cerebral blood flow are typically produced. These maps are usually adequate for assessment of perfusion in acute infarction, but they can be inaccurate when there is diffuse or multifocal hypoperfusion, because they document differences between portions of the brain rather than absolute perfusion measurements. In addition, it is difficult to evaluate changes in perfusion on serial examinations. In patients with acute infarction, this is not an issue but in patients with spasm secondary to subarachnoid hemorrhage relative perfusion data are inadequate.

The workup of hyperacute stroke with multimodal CT provides most of the information obtained from MR imaging. Noncontrast CT is followed by CTP and CTA of the cervical and cranial vessels (11, 12). CTA allows for accurate assessment of both extra- and intracranial circulation. CTP is currently limited to four sections, although the introduction of 16-row scanners should make it possible to obtain greater brain coverage. The core area of irreversible infarction is the region of hypoattenuation identified on the source images from the CTA examination. (The extent of the core infarct identified on the CT source images has been shown to correlate with core infarct identified on DW imaging [12]). Normally perfused brain enhances after contrast material administration more than hypoperfused brain, which accentuates the hypoattenuation seen on nonenhanced CT scans. If hypoattenuation on noncontrast CT scans is a reflection of hypoperfusion, the findings on multimodal CT can be viewed as a continuum. Profoundly hypoperfused infarcted brain is visible on noncontrast scans. Hypoperfusion visible on CT source images is less severe but still sufficient to cause infarction. Hypoperfusion that can be identified only on perfusion maps represents salvageable brain at risk for infarction. CTP has an advantage over MR perfusion, because it is possible to obtain absolute rather than relative perfusion values. CBF and MTT measurements are therefore more accurate with CT than MR imaging. Absolute perfusion measurements are obtained with CT by performing deconvolution computations that subtract attenuation contributions from small arteries and veins. Deconvolution is more difficult to achieve with MR imaging, in part, because susceptibility effects of contrast material in small vessels alter signal intensity in the adjacent brain. It is likely that some of the technical issues involved in generating absolute perfusion data from MR imaging will be overcome in the near future; but for the moment CTP, is superior in this regard. The multimodal CT examination provides all essential information for making therapeutic decisions (intravenous or intra-arterial thrombolysis or both), including extent of infarction, location of vascular occlusion, presence of gross hemorrhage, and status of perfusion in brain surrounding the infarct. Advocates of CT point out that the examination is faster, more easily obtained, and less expensive than MR imaging.

On the other hand, there are practical and theoretical difficulties with CT. It is true that the CT examination is faster than the MR examination (5 minutes versus 20 minutes), but at the end of acquisition the MR study can be made ready for interpretation in about 5 minutes (the time it takes to generate the perfusion maps). Much more time and expertise are required for CT. Construction of CTA images from source images has become much easier and faster in the past few years, but it still takes an experienced radiologist or specially trained technologist at least 5–10 minutes. MRA images are automatically generated and instantaneously available. Despite the theoretical advantage that absolute perfusion measures obtained with CT have over the relative perfusion measures obtained with MR imaging, it is unclear how these absolute measures aid in therapeutic decisions. The parametric maps take time to produce and quantitative interpretation is a tedious process. (At our institution, it takes a minimum of 15 minutes to construct and evaluate the perfusion maps.) Therefore the time it takes to perform the examination and generate angiograms and perfusion maps is actually longer and much more labor intensive with CT than

MR imaging. In practice, the initial CT interpretation is made by evaluating the source images from both the CTA and the CTP examinations. If there is time, the parametric perfusion maps are visually inspected. Careful quantitative assessment of perfusion is frequently performed after the clinical decision has been made. Evaluation of source images requires experience and expertise. This approach works well in academic centers, but I suspect it will be less successful in the community hospital setting. The addition of CTA and CTP has not changed the fact that CT is more easily performed but MR imaging more easily interpreted.

Despite these practical limitations, it is clear that multimodal CT can be used to make therapeutic decisions concerning thrombolysis, and therefore at present it is an effective tool for assessment of hyperacute infarction. Over the next 5 years, we can expect CT to improve with of the introduction of scanners with even more detectors. (I fully expect to see a 128-row scanner described as "faster-than-light speed," causing Albert Einstein to rise from his grave and strike us all down.) Workstation hardware and software advances will make it possible to generate high-quality CTA and CTP data with greater speed and ease. Research will determine which perfusion measures are most useful, but I suspect that these advances will not lead to a dramatic improvement in stroke outcome.

New therapeutic options are needed if we are to improve stroke outcome dramatically. To devise new therapies, we need more than just perfusion information. We need to know about the status of the brain itself. MR imaging already provides this information. DW and T2-weighted sequences allow for the direct and independent assessment of cytotoxic and vasogenic edema, respectively. The simple scheme of a core area of irreversible infarction surrounded by a penumbra of hypoperfusion was developed in animal models. In practice, human strokes are much more complex. The value of diffusion information is sometimes downplayed in the discussion of stroke treatment, because diffusion abnormalities usually reflect irreversible brain damage. Complete reversal of diffusion abnormalities is a rare phenomenon that occurs in fewer than 5% of infarcts, but diffusion information still may affect outcome and therefore therapy. It is common to describe DW examinations as if they were pregnancy tests, either unequivocally positive or negative, but there is a difference. Whereas a woman cannot be a "little bit pregnant," a brain *can be* a little bit infarcted. There is a continuum of diffusion abnormalities seen in patients with infarction. To be sure, most infarcts reveal severe apparent diffusion coefficient (ADC) decreases (> 70%), but in some cases ADC changes are less marked. Reversible diffusion abnormalities occur most frequently when initial ADC reductions are mild (13). The severity of diffusion changes within an infarct correlates with clinical outcome independent of infarct size. In clinical practice, serial DW examinations reveal significant variation in both the initial ADC and subsequent evolution of diffusion changes. I have found that initial signal intensity on DW images (indicative of cytotoxic edema) is variable, and over the first few days, it is not uncommon to see heterogeneous changes with increasing signal intensity in some portions of the infarct, and on occasion, rapid resolution of hyperintensity in other regions. What does it mean when an infarct has only mild diffusion changes? It probably reflects heterogeneity within the "core" infarct with a mixture of living and dead (or dying) cells. This heterogeneity explains the fact that transient ischemic attacks may produce mild but persistent decreases in ADC (undetectable on DW images) in the affected portion of the brain (14). Presumably a small number of cells are destroyed, enough to lower ADC but not enough to produce permanent neurological damage. Therefore, the "core" infarct may contain viable cells. Therapies aimed at protecting these viable cells or interrupting the events leading from cell damage to cell death could improve outcome. Hyperintensity on FLAIR images (indicative of vasogenic edema) also varies depending on time of appearance and severity. This variation depends upon restoration of flow to vessels with damaged endothelial cells. Assessment of the integrity of the endothelium (possibly by combining perfusion and T2 information) might therefore help to predict the likelihood of hemorrhagic transformation. Proponents of CT could point out that all of this speculation is very interesting, but at least for the moment it is of no clinical relevance and they would be right.

Or, would they?

The story is not quite over. In every space opera there is a hook—a "Luke, I am your father" moment—which alters everything and sets up the next installment. In our little story, that hook is hemorrhage. Gradient echo images can reveal hemorrhagic transformation of infarction not detectable on CT scans. Current criteria for thrombolysis are based on CT evidence of hemorrhage. Should those criteria be extended to include hemorrhage invisible on CT scans but depicted on MR images? Gradient echo images also reveal the presence of microbleeds, small punctate foci of chronic hemorrhage seen in patients with hypertension and cerebral amyloid angiopathy. Microbleeds imply vascular fragility and are associated with an increased risk for infarction, hemorrhagic infarction, and frank hematomas (15). It is possible that patients with microbleeds should not be candidates for thrombolysis or at least intravenous thrombolysis. This all seems like bad news, and another reason to render someone ineligible for the only treatment known to improve outcome in stroke. Although this may be true, it is possible that elimination of patients most at risk for hemorrhage will allow for more aggressive treatment of the remaining patients. We also need to develop a less defeatist attitude toward hemorrhage. Therapies aimed at limiting hemorrhage and its negative consequences (eg, edema) might allow for improved outcome. In any event, if it turns out that the detection of these

hemorrhages is therapeutically important, the debate will be over and MR imaging will have "won." Future investigations will surely ask and answer these questions.

So stay tuned for *Stroke Wars, Episode V: Attack of the Microbleeds.*

ROBERT D. ZIMMERMAN
Member, Editorial Board

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