Imaging the Future of Stroke: I. Ischemia

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Envisioning the future of stroke appears daunting considering the milestones already achieved in stroke imaging. A historical perspective on the developments in stroke care provides a striking narrative of how imaging has transformed diagnosis, therapy, and prognosis of cerebrovascular disorders. Multimodal imaging techniques such as CT and MRI, incorporating parenchymal depictions, illustration of the vasculature, and perfusion data, can provide a wealth of information regarding ischemic pathophysiology. Key elements of ischemic pathophysiology depicted with imaging include vascular occlusion, compensatory collateral flow, resultant hemodynamic conditions that reflect these sources of blood flow, and the neurovascular injury that ensues. The mantra of "time is brain" has been perpetuated, but this does not provide an entirely accurate reflection of ischemic pathophysiology and imaging insight shows far more than time alone. Maximizing the potential of perfusion imaging will continue to expand the nascent concept that cerebral ischemia may be completely reversible in certain scenarios. Novel modalities provide a fertile ground for discovery of therapeutic targets and the potential to assess effects of promising strategies. Beyond clinical trials, imaging has become a requisite component of the neurological examination enabling tailored stroke therapy with the use of detailed neuroimaging modalities. In this first article on ischemia, the focus is on the most recent imaging advances and exploring aspects of cerebral ischemia where imaging may yield additional therapeutic strategies. A subsequent article will review recent and anticipated imaging advances in hemorrhage. These thematic overviews underscore that imaging will undoubtedly continue to dramatically shape the future of stroke.

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Envisioning the future of stroke appears daunting when one considers the milestones already achieved in stroke imaging. A historical perspective on the developments in stroke care provides a striking narrative of how imaging has transformed diagnosis, therapy, and prognosis of cerebrovascular disorders. When the journal *Stroke* was introduced almost 40 years ago, computed tomography (CT) and magnetic resonance imaging (MRI) did not exist. Diagnostic imaging revolved around angiography, accompanied by echoencephalography, thermography, radioisotope techniques, and skull films. Clinical semiology was used to guide treatments largely supportive in nature, without targeting specific pathophysiology. CT and MRI, following shortly thereafter, revolutionized the field by providing snapshots of ischemia and hemorrhage in the brain (Fig 1). Such images inspired exhaustive efforts to establish neuroprotection to save brain, yet the next breakthrough was once again heralded by imaging and the introduction of diffusion-weighted imaging (DWI) two decades later.[1,2] As DWI and magnetic resonance angiography (MRA) made it possible to chronicle evolving infarction caused by arterial occlusion, thrombolysis provided the first effective treatment to cease this devastating process. During the past two decades, perfusion imaging and many other techniques have flourished. Stroke imaging now accounts for thousands of publications per year, and imaging has become a central facet in the management of stroke patients. In this first article on ischemia, the focus is on the most recent imaging advances and exploring aspects of cerebral ischemia where imaging may yield additional therapeutic strategies. A subsequent article will review recent and anticipated imaging advances in hemorrhage. These thematic overviews underscore that imaging will undoubtedly continue to dramatically shape the future of stroke.

Imaging the Pathophysiology of Ischemia

Multimodal imaging techniques such as CT and MRI, incorporating parenchymal depictions, illustration of the vasculature, and perfusion data, can provide a wealth of information regarding ischemic pathophysiology. Imaging goals in stroke typically address whether a stroke is the likely diagnosis, if the primary process is ischemic or hemorrhagic, where the lesion is situated, what is the likely mechanism, what treatments may be indicated, and what can be expected from prognosis. Although extensive information is available from experimental stroke models in the laboratory, knowledge of cerebral ischemic pathophysiology in humans is now readily available from what has become

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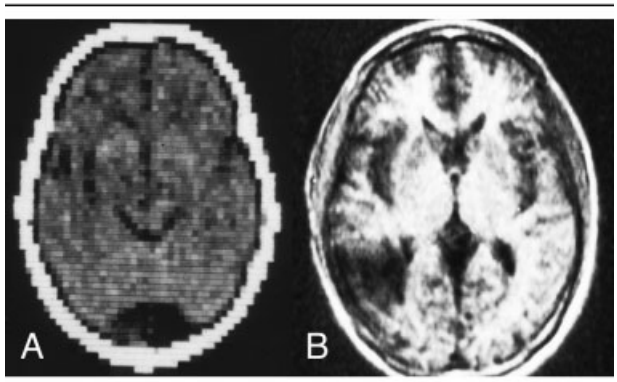

Fig 1. Noncontrast computed tomographic scan of the brain from 1974 (A) and magnetic resonance image of the brain from 5 years later (B) provided novel depictions of the human brain, albeit at limited resolution.

routine imaging of stroke patients. CT and MRI may provide slightly different information depending on specific technical parameters, yet understanding the underlying pathophysiology is paramount in optimizing care. Accurate interpretation of stroke imaging results is also critically dependent on sound knowledge of ischemic pathophysiology, because erroneous conclusions may result from incorrect assumptions about the biology. In recent years, the surge of stroke imaging has provided novel insight and led to further discovery. Key elements of ischemic pathophysiology that can be depicted with imaging include vascular occlusion, compensatory collateral flow, resultant hemodynamic conditions that reflect these sources of blood flow, and the neurovascular injury that ensues.[3]

Occlusion

Obstruction of the cerebral circulation is typically the initial event and most obvious feature of cerebral ischemia. It is important to note that such vascular obstruction can be caused by partial or subtotal luminal compromise (stenosis), or alternatively, complete blockage of the vessel lumen that limits all antegrade or forward blood flow (occlusion). Even in cases with complete occlusion of an artery, it has been noted that tram-tracking may be present with small, persistent channels of flow lining the peripheral aspects of the clot along the vessel wall.[4] These diminutive flow routes visible with transcranial Doppler ultrasound (TCD) or angiographic techniques may play an important role in allowing thrombolytic access to the clot surface. Although ischemia is typically associated with arterial occlusion, venous obstruction can also result in ischemia. For all occlusive lesions, the anatomy or structural aspects of the obstruction are likely less important than the actual flow implications.

Collateral Circulation

Vessel occlusion may be inconsequential because of the incredible redundancy of the circulatory system and existence of rich collateral networks.[5] Collateral circulation in the arteries and veins of the brain provides numerous alternative routes for blood flow in the setting of obstruction. Because of the complex configuration and often diminutive caliber of collateral vessels, illustration of collaterals has often relied on conventional angiography. Progressive refinements in noninvasive imaging approaches over the last decade have made it possible to depict such features with CT angiography (CTA) and MRA.[6] Noninvasive imaging of collateral flow patterns at the circle of Willis have been validated with respect to conventional angiography using several techniques including CTA, phase contrast and time-of-flight MRA, and TCD.[6,7] Timing of such studies, however, is critical as such flow patterns may rapidly change. In contrast with traditional descriptions of Willisian anatomy that include explicit definitions for fetal or persistent posterior cerebral artery (PCA) supply from the posterior communicating artery, serial angiographic studies demonstrate that flow in such segments can rapidly alter such appearances.[8] For instance, the posterior communicating artery is typically dilated in the setting of acute middle cerebral artery (MCA) occlusion and often diminishes in caliber once the occlusion recanalizes.

Collaterals are recruited at the onset of ischemia because of intraluminal pressure gradients. The small size of collateral anastomoses that has evaded many imaging approaches may be viewed as illogical for this critical adaptive response to ischemia, but in recent years, we have learned that such features serve as the perfect sensing mechanism to upregulate arteriogenesis.[9] In fact, increased flow across these small flow routes causes marked elevation in fluid shear stress, a key variable in vascular homeostasis. Increased fluid shear stress and mechanical stimulation of the vessel wall causes cytokine release and vascular remodeling to dilate the vessel. These processes may be evident as early as the first few hours after acute stroke onset and continue into subacute or chronic stages of ischemia. The cerebral venous system also adapts by retaining blood volume to maximize oxygen and nutrient exchange.

Recent correlative imaging studies of collateral circulation in acute and chronic ischemia have demonstrated that the occlusive lesion may be incompletely characterized without consideration of collaterals. For instance, internal carotid artery (ICA) occlusion may have dramatically different effects on downstream perfusion depending on collaterals. The traditional designation of a stenosis or occlusion as either asymptomatic or symptomatic must also account for collaterals. Until recently, strokes contralateral to an ICA occlusion have been overlooked, yet mechanistic studies suggest that

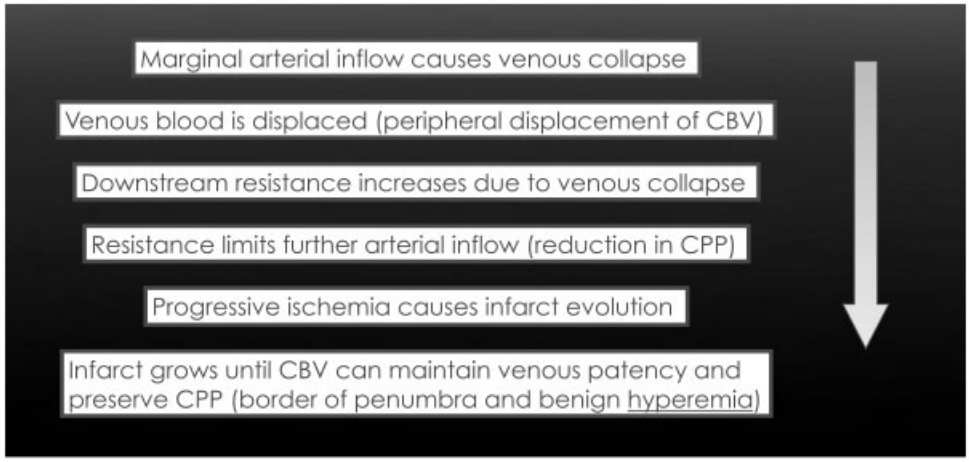

*Fig 2. Hypothetical model of progressive changes in ischemic pathophysiology (*arrow *from top to bottom), including venous factors that affect cerebral blood volume (CBV) and cerebral perfusion pressure (CPP). Peripheral zones are spared from infarction because of benign* hyperemia, *characterized by* increased *CBV.*

hypoperfusion and emboli are closely intertwined.[10] Collateral flow visible at angiography is a potent determinant of tissue fate, even beyond measures of downstream perfusion evident on noninvasive techniques.[11]

Hemodynamics

The balance of occlusion and collaterals determines the hemodynamic milieu or blood flow changes that challenge the brain. Depending on the time course, such changes may have radically discrepant effects. Longstanding hemodynamic compromise may elicit collateral development and preconditioning to adapt to recurrent ischemia. Alternatively, abrupt cessation of flow may initiate a complex series of hemodynamic sequelae that precipitate extensive tissue damage.

Despite extensive investigation on stroke hemodynamics several decades ago, the advent of CT and MRI led to increasing attention centered on neurological targets. Decreased reliance on diagnostic angiography and the protracted crusade to realize neuroprotection detracted from hemodynamic investigations until perfusion imaging was introduced. In recent years, perfusion imaging has been able to validate in humans what was known of blood flow in ischemic animal models. Low perfusion hyperemia, the rapid expansion of the venous circulation in response to reduced arterial inflow, has been illustrated in acute stroke cases.[12] Venous collapse in the ischemic core and peripheral displacement of blood volume caused by venous diversion have also been studied.[13] The decline in local cerebral blood volume (CBV) and venous collapse results in increased downstream resistance that further aggravates the marginal inflow pressure of arterial collaterals. Progressive ischemia after initial increases in CBV may be explained by this moving wavefront of hemodynamic instability originating in the core and moving toward the boundary of what has been termed *benign oligemia* (Fig 2). Notably, by strict definition, oligemia refers to *volume,* not flow, and such areas peripheral to the penumbra typically have increased or normal CBV. Perfusion imaging may show such dynamic features, yet it has been most often used in various incarnations of mismatch, where differences between the surrounding perfusion abnormality and the underlying ischemic core may be used as a surrogate for salvageable penumbra. This dynamic perspective where hemodynamics in the territory are constantly evolving within the early hours of ischemic onset is radically different from prior conceptions where specific ischemic thresholds measured by perfusion parameters dictate inevitable tissue damage from the onset.

Neurovascular Injury

Tissue injury has been of prime interest as it relates to neurological outcome, yet imaging has provided some important lessons. Identification of irreversible ischemic injury in the brain has repeatedly been proposed as a potential surrogate measure of clinical outcome. The timing of such lesion measurements is extremely important as many stages ensue from the initial appearance of early ischemic changes to subacute edema and subsequent resolution as an area of encephalomalacia. After more than 35 years of discerning early ischemic changes on CT as a manifestation of evolving infarction, recent correlation with CT perfusion has demonstrated that some increased water content may be caused by increased CBV, not intracellular swelling.[14] These findings may be markers of ischemia but do not carry the same prognostic implications. DWI provides rapid delineation of cytotoxic edema, yet lesion patterns are probably most informative about underlying mechanisms (Fig 3). Punctate lesions within an arterial

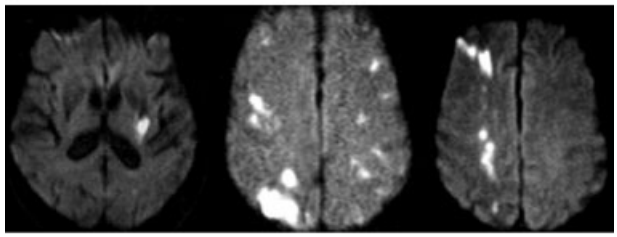

Fig 3. Diffusion-weighted imaging lesion patterns in acute ischemic stroke, including isolated lenticulostriate infarction (left), bilateral middle cerebral artery lesions caused by cardioembolism (middle), and borderzone ischemia caused by right internal carotid artery hypoperfusion (right).

territory may point to a particular source of emboli, yet attempts to separate hypoperfusion and emboli have proved difficult.[15] Reflexive interpretation of DWI findings has often prompted a narrow-minded search focused solely on arterial emboli and resultant occlusions. Complex patterns of blood flow, however, may also result in such lesions. Simply stated, small, discrete lesions do not necessarily reflect distal emboli alone because hypoperfusion may cause borderzone ischemia.

The focus on DWI has reinforced traditional descriptions of the ischemic cascade that commence with ion pump failure in membranes of the neuron that facilitate cytotoxic edema, but earlier sequelae may affect vascular structures such as endothelia. Ischemic endothelium may limit tissue perfusion by obliterating effective luminal flow because of swelling and loss of regulatory function. Oxygen and other strategies may provide vasoprotection, and thereby enhance neuroprotection.[16] Recognition of the neurovascular unit as a therapeutic target may encourage development of other imaging techniques as well.

After collateral failure or increasing ischemic severity, infarct growth may extend to the limits of the vascular territory or stop at a point where flow is sufficient to meet metabolic demands. Ischemic lesion volume has been used as a potential surrogate in past studies, yet patients may have excellent outcomes despite extensive tissue injury. Lesion location also appears to be critical, as some ischemic strokes may even be "silent" in certain areas of the brain. Refinement of the neurological examination may demonstrate the importance of such lesions, yet atlas-building will undoubtedly improve clinical-radiographic correlation in the future. Most commonly, areas of ischemic injury may be intermixed with reperfusion. This may be associated with hemorrhagic transformation (HT), vasogenic edema, or inflammation. Imaging of subacute stroke may therefore show complex and myriad patterns of injury. Detailing restoration or repair within a certain region of the brain may be quite difficult with even the most advanced imaging techniques. Overall, the time course of neurovascular injury varies widely from individual to individual.

Time Is Brain?

The mantra of "time is brain" has been perpetuated throughout the stroke community, but this does not provide an entirely accurate reflection of ischemic pathophysiology. Undoubtedly, ischemic injury in the brain may evolve quite rapidly within only the first hours or minutes in select cases, but the time course varies markedly across individuals. Time is measured from symptom onset in almost all cases, yet this does not reflect stroke onset. In fact, symptoms will become manifest only once collaterals fail to compensate for hypoperfusion. Transient symptoms may reflect the brief transition from dependence on antegrade to ret-

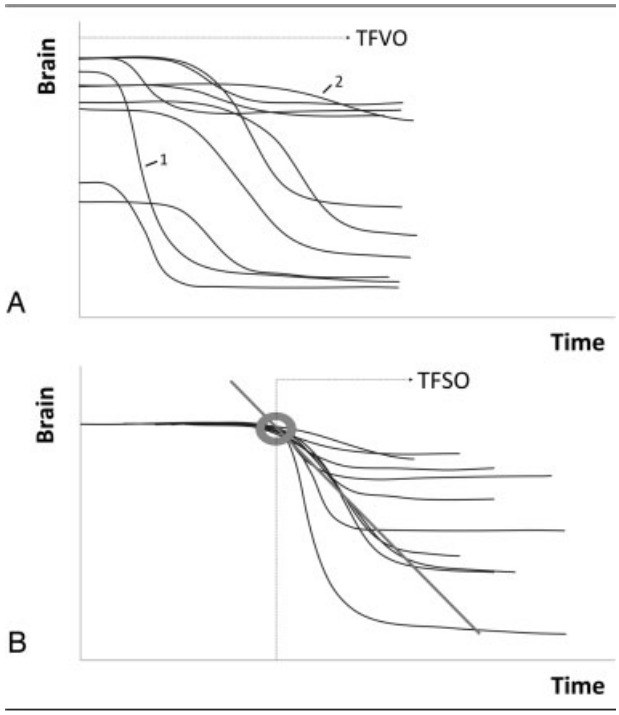

Fig 4. Schematic illustrating the relation between time and brain lost, noting marked dissimilarity between (A) pathophysiology measured from time from vascular occlusion (TFVO) and (B) measures utilizing time from symptom onset (TFSO). Each individual curve represents unique temporal features of a particular case, including baseline brain volume, time to symptom onset or collateral failure, degree of collateral dependence influenced by lesion location, and resultant infarct volume. Rapid decompensation caused by poor collaterals in abrupt cardioembolic occlusion (A, 1*) may lead to large infarcts at very early time points, whereas progressive ischemia and robust collateralization in intracranial atherosclerosis (A,* 2*) may be manifest with a long time window and smaller infarct volumes. In the absence of imaging, time alone measured from symptom onset (B,* circle*) is often used to group these identical curves and calculate brain lost based on a linear, rather than a biologically plausible sigmoid, model.*

rograde, collateral flow in a vascular territory. In most cases, the time of vascular occlusion is never known and may have occurred hours, days, or weeks in advance. At the most extreme example, asymptomatic MCA occlusion demonstrates that time may be altogether irrelevant.

It remains important to encourage patients, the public, and everyone potentially involved in the triage of a stroke patient to demonstrate the "need for speed" and rapidly intervene; however, imaging insight shows far more than time alone.[17–19] The amount of brain lost or burden of ischemic injury can be averaged based on time from symptom onset to any standard time point, yet this dynamic process is not linear and defies such calculations in any particular case. Hour to hour and even minute to minute, the evolution of ischemic injury may vary dramatically. When one averages across a population, summary statistics can be generated, but predicting CT or DWI lesion growth at the bedside defies such models. When time from symptom onset is measured, we are essentially resetting relative times to collateral failure, demarcating the initial downward inflection in sigmoid curves of time versus brain (Fig 4). Even when measured from symptom onset, *why does a time window even exist*?[20] Some have speculated that tissue vulnerability to withstand specific ischemic injury can be marked by time. Alternatively, time may be important because the hemodynamic process continues to evolve during this critical period. For instance, intravenous or intraarterial thrombolysis may be most effective early on because collateral perfusion is adequate. Several hours later, venous collapse and hemodynamic failure may limit reperfusion even if clot disruption is achieved. This would suggest that effective thrombolysis may be limited by hemodynamics, not evolving clot composition. This may explain why some cases may benefit from recanalization many hours later in MCA occlusion or why basilar occlusions can be treated up to 24 hours from symptom onset.[21] Even within the restricted time window of 3 hours for intravenous thrombolysis, time may not be on one's side as poor collateral flow and extensive hypodensity on CT may occur within the first hour or two after symptom onset (Fig 5). The time course of hemodynamic failure and window for reperfusion may vary across vascular territories as well. When looking at imaging results, it may be impossible to distinguish timing altogether (Fig 6). From a therapeutic standpoint, even "late" cases with mismatch pose a dilemma because these cases may not be prone to failure, thereby altering the risk/benefit ratio. Furthermore, time constraints for thrombolysis may differ from windows for other therapeutic strategies. If one utilizes hemodynamic augmentation rather than thrombolysis, time restrictions may vary.[22] Altogether, time to imaging remains paramount, because without rapid imaging, one must act rapidly based on time alone.

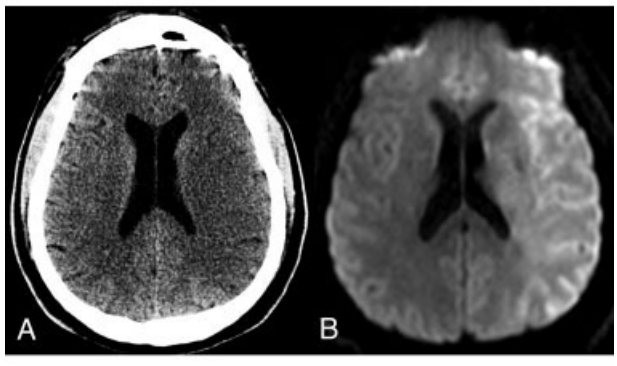

Fig 5. Extensive computed tomographic hypodensity (A) and diffusion-weighted imaging evidence of ischemia (B) in the left middle cerebral artery territory in a 40-year-old man within 75 minutes of witnessed onset of right hemiparesis and aphasia.

Vessel Imaging

Vascular Pathology

Atherosclerosis is the primary culprit of most ischemic strokes, but many types of vascular abnormalities may be identified with recent advances in imaging. From the venous circulation to the most proximal sites of arterial emboli in the heart, CT and MRI can provide detailed information. Cardiac imaging with visualization of all proximal arteries to the cerebral circulation in one acquisition will likely become routine in the next few years. Wall motion abnormalities and other functional lesions such as patent foramen ovale can be studied with cine techniques.[23] Hemodynamic evaluation of cardiac function may also be assessed with evolving techniques. Enhanced resolution and proper gating will be required to thoroughly evaluate the possibility of intracardiac thrombi at risk for embolization. Similarly, the utility of noninvasive modalities such as CT and MRI to evaluate aortic arch atheromatous disease will require further refinement.

Recent work on imaging of the proximal cervicocephalic arteries has rapidly expanded to address several key questions regarding identification of vulnerable or high-risk lesions. Intimal-medial thickness has been studied for many years with ultrasound as a marker of vascular risk and now increasingly with CT and MRI.[24] Plaque characterization may be achieved with CTA, black-blood MRI, T1 MRI, and with various novel contrast agents such as iron oxide particles that may delineate active inflammation or instability.[25–27] In parallel, prominent calcifications signifying potentially stable yet chronic disease is easily visualized as well. Calcified plaque on carotid CTA may be associated with reduced risk for subsequent stroke possibly

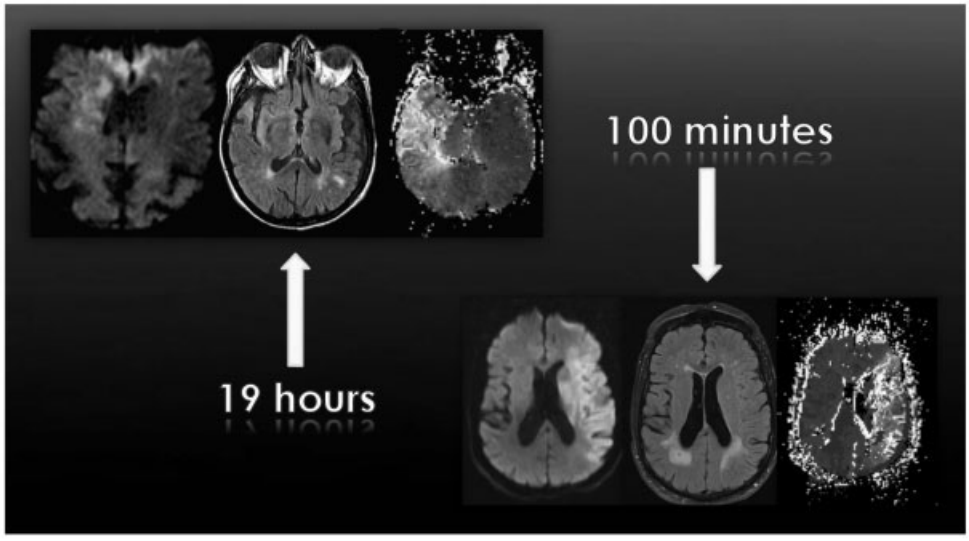

Fig 6. Detailed imaging of acute middle cerebral artery stroke (left to right: diffusion-weighted imaging, fluid-attenuated inversion recovery, time-to-peak perfusion magnetic resonance imaging) shows that one cannot tell time from images because marginal tissue damage may be present at 19 hours (left) compared with more extensive injury at 100 minutes (right).

because of reduced emboligenic potential.[28] Many studies have embarked on detecting lipid-laden plaque at the carotid bulb that may be prone to rupture or hemorrhage. Similar techniques for evaluation of the intracranial circulation await further development. In the future, one may expect to differentiate risk for intracranial atherosclerotic disease based on direct imaging of such plaques in the arteries at the base of the brain. Recent work has highlighted the potential role of MRI to characterize vasculitis in the intracranial vasculature, manifest as frank enhancement of the vessel wall.[29] These approaches may complement the current role of conventional angiography for vasculitis where only luminal irregularities may be seen with no information about the vessel wall itself. Intramural lesions such as dissection have been easily identified with such noninvasive techniques for many years now. Aside from predilection for certain sites in the circulation and guidance from classic clinical features to suggest this diagnosis, dissection is readily identified by the spiraling crescent of intramural hematoma on fat-saturation T1-weighted MRI or other noninvasive techniques. Often subtle lesions with this highly specific configuration of dissection can be seen on other sequences such as fluid-attenuated inversion recovery images (Fig 7). Small-vessel disease remains elusive, often identified only by the ischemic lesions in subcortical zones. Although direct imaging of small vessels in the brain cannot be reliably achieved, associated findings such as cerebral microbleeds and the newly recognized pathological role of Virchow–Robin spaces is expanding current knowledge.[30] Previously considered nor-

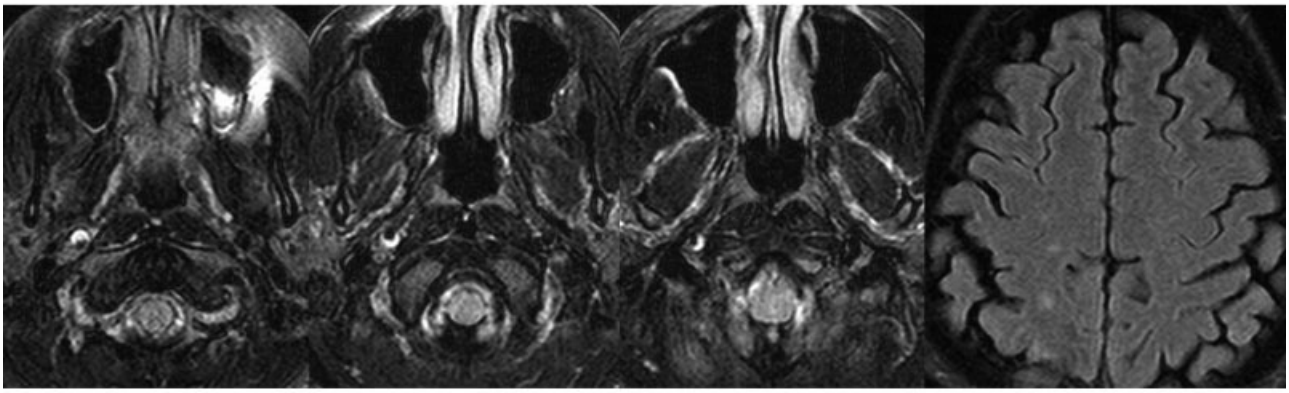

Fig 7. Fluid-attenuated inversion recovery images showing the hyperintense, spiraling crescent sign of dissection in the right petrous internal carotid artery (three sequential axial images from left) and associated borderzone infarction in downstream right parietal region (far right).

mal, Virchow–Robin spaces are now being revisited as a possible marker of small-vessel disease.

In coming years, detailed imaging of such vascular pathology may help stratify risk, allowing more informed decisions about potential therapeutic interventions. Adding this imaging data may help identify unstable or symptomatic lesions, revising the standard definitions that have been used in carotid disease for decades. These techniques may also be used to monitor treatment, as in the case of statin therapy for carotid plaque regression.

Stenosis and Occlusion

A broad array of imaging modalities from ultrasound and angiography to CTA and MRA now make it possible to characterize focal narrowings or stenoses in the cerebral circulation. The most common measure of grading stenoses, measurement of luminal caliber reduction, has principally relied on the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method in the extracranial carotid artery and the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) method in the intracranial circulation. Most noninvasive technologies have been validated against the gold standard of conventional angiography, and a plethora of reports have included multiple modalities evaluated at once. Simple correlations between angiographic techniques are often reported, yet proper evaluation requires elimination of bias and rigorous trial design as in the Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis (SONIA) study.[31–33] Rough correlations across modalities have been substantiated, but exact agreement is almost never achieved. Aside from other methodological issues, the inherent nature or physical basis of the technique must be considered. For instance, CTA utilizes relatively prolonged acquisition after contrast injection, thereby providing maximal anatomic detail of the lumen. MRA techniques generally accentuate flow features; therefore, a moderate stenosis based on luminal caliber may show poor distal flow caused by hemodynamic effects. Inaccuracy of stenosis measures on time-of-flight MRA may simply be caused by pronounced flow reduction. Even global reductions in cerebral blood flow may limit MRA depiction, as often seen on time-of-flight MRA in elderly patients (Fig 8). In short, CTA accentuates anatomy and MRA emphasizes flow. Dynamic, phase contrast and quantitative MRA all capitalize on this aspect. Although the management of extracranial and now intracranial stenoses has revolved solely around single measures of percentage luminal reduction, noninvasive and conventional angiography may better define how tandem stenoses, lesion length, tortuosity, and other morphology may influence downstream flow.

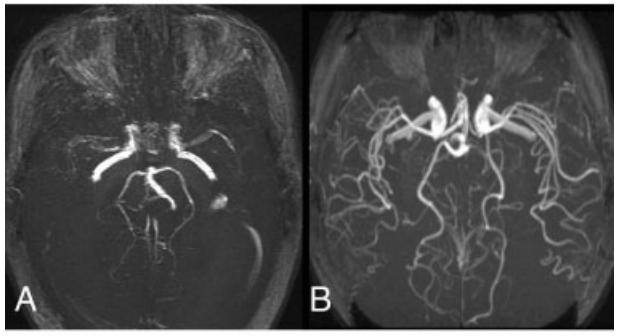

Fig 8. The effects of global cerebral blood flow may be evident in the perceived quality of time-of-flight magnetic resonance angiography, with limited depiction of distal vessels in a 90-year-old man (A) compared with detailed illustration of the intracranial circulation in a 26-year-old woman with migraine (B).

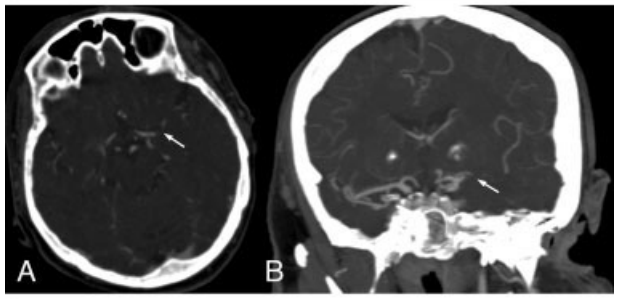

Fig 9. Axial source image (A) and coronal maximal intensity projection (MIP) view (B) of computed tomographic angiography in acute left middle cerebral artery (MCA) occlusion (arrows). *Opacification in more distal segments of the proximal MCA on axial source images (A) because of collaterals may be mistaken for patency of the MCA unless MIP views (B) are viewed.*

The complex configuration of the intracranial circulation and limited capacity to reliably discern flow in small, distal vessels without conventional angiography has limited our understanding of key mechanisms in stroke caused by intracranial atherosclerosis. Although combinations of noninvasive techniques including TCD with embolus detection, angiographic studies, and perfusion imaging may be used to serially evaluate these cases, such an intensive battery has not been analyzed to date.[34] Current therapeutic approaches, including angioplasty and stenting, have been based solely around presence of symptoms and solitary measures for degree of stenosis.[35] Recent work has demonstrated that asymptomatic intracranial stenoses have low risk for stroke, and that angiographic collateral flow beyond a stenosis remains the most potent predictor of recurrent ischemia.[36,37] Future research will define the role of collaterals, arterial emboli, perforator

compromise, and in-stent restenosis utilizing the latest imaging technology. Severe intracranial disease may exist without hemodynamic impairment, as chronic MCA occlusions may show no abnormalities on positron emission tomography.[38] Such compensated lesions are often seen with moyamoya syndrome, the ultimate model of acute-on-chronic ischemia in humans. Recurrent ischemia eventually stabilizes after gradual occlusion of multiple proximal arteries. The progressive compensation in CBV allows such patients to avoid major strokes, despite extensive mismatch on perfusion imaging.[39] Recurrent ischemia in MCA stenosis typically results in small infarcts along the borderzones.[40] These lesions may be caused by emboli or hypoperfusion, which typically coexist.[15] After surgical revascularization, perfusion patterns and arterial territories may completely shift.[41,42]

Complete occlusion can be illustrated with most modalities. More dramatic flow effects evident on TCD or MRA may focus attention on a particular vessel, whereas the exquisite anatomic detail of CTA must be carefully inspected to avoid missing an occlusion. As the entire vascular circuit may be visualized with CTA, including enhancement of collaterals at the distal end of the occlusion and the deep middle cerebral vein, proper evaluation on thin maximum intensity projection images may be required (Fig 9). CTA is extremely valuable for rapid evaluation of potential occlusion in most stroke patients.[43] For more than two decades, the presence of a hyperdense artery on noncontrast CT has been used as a sign of MCA occlusion. More recently, this finding has been described in the ICA and PCA.[44,45] Others have demonstrated that, although this finding is a marker of poor outcome, intravenous thrombolysis may be effective with such lesions.[46] Hyperdense arteries on CT associated with clot are often mistakenly described as early ischemic findings, and various mimics exist as well. Increased use of gradient-recalled echo (GRE) MRI has stimulated interest in blooming artifact or hypointensity in and around a vessel containing thrombus. Age of the clot, amount of thrombus, location, and local flow conditions all affect appearance of this finding. Only recently has radiographic-pathological correlation investigated how clot composition affects appearance on CT and MRI. The first descriptive series of clots extracted from humans with acute ischemic strokes noted that thrombi rich in red cell content appear hyperdense on CT and hypointense on GRE.[47] It was also noted that clots may be obtained from vessels that do not manifest such findings indicative of thrombosis. Further development of thrombolysis and thrombectomy devices will likely spur further work on imaging of clot composition in vivo.

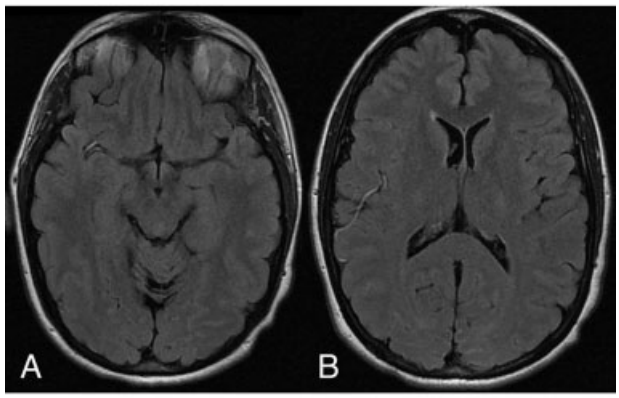

Fig 10. Fluid-attenuated inversion recovery of M2 segmental occlusion of the middle cerebral artery demonstrates vascular hyperintensity immediately proximal to the occlusion (A) caused by slow flow and serpiginous vascular hyperintensity distal to the occlusion (B) from slow, retrograde collateral flow.

Collaterals and Other Flow Routes

An overwhelming focus on arterial obstruction by clots or stenoses has detracted from imaging of actual ischemia and related flow phenomena. Slowing of flow immediately upstream from an occlusion may be seen as hyperintensity on fluid-attenuated inversion recovery (Fig 10A). Diversion of flow into adjacent territories to provide collateral support may also be evident, either as ipsilateral prominence of the PCA in MCA occlusion or as conspicuous flow voids on GRE in collateral vessels. These MRI findings reflect flow diversion manifest on TCD.[48] Other indicators of flow abnormalities include absence of flow voids downstream from an occluded vessel. On GRE, phase mismapping that is normally present with robust flow may disappear.[49] This bright stripe or hyperintensity at the margin of the vessel is an artifact that is produced by relatively faster flowing blood being "mismapped" by the MRI to the edge of the vessel also indicating the direction of flow. On rare occasion, flow reversal or retrograde collateral flow in the MCA may be discerned by the flipped phase-mismapping artifact in vessels entering the Sylvian fissure from the PCA. Slow, retrograde flow beyond an occlusion is frequently seen as fluid-attenuated inversion recovery vascular hyperintensity (see Fig 10B).[50] Other conspicuous vessel findings include deoxygenation seen as hypointensity on GRE in draining veins of the ischemic territory, either over the hemispheric convexity or through the basal venous circuit.

Perfusion

The perfusion status of downstream regions in the setting of ischemia determines tissue injury, shapes recanalization, influences effective reperfusion, and importantly, mitigates HT. Limited hypodensity, or a high Alberta Stroke Program Early CT Score (ASPECTS),

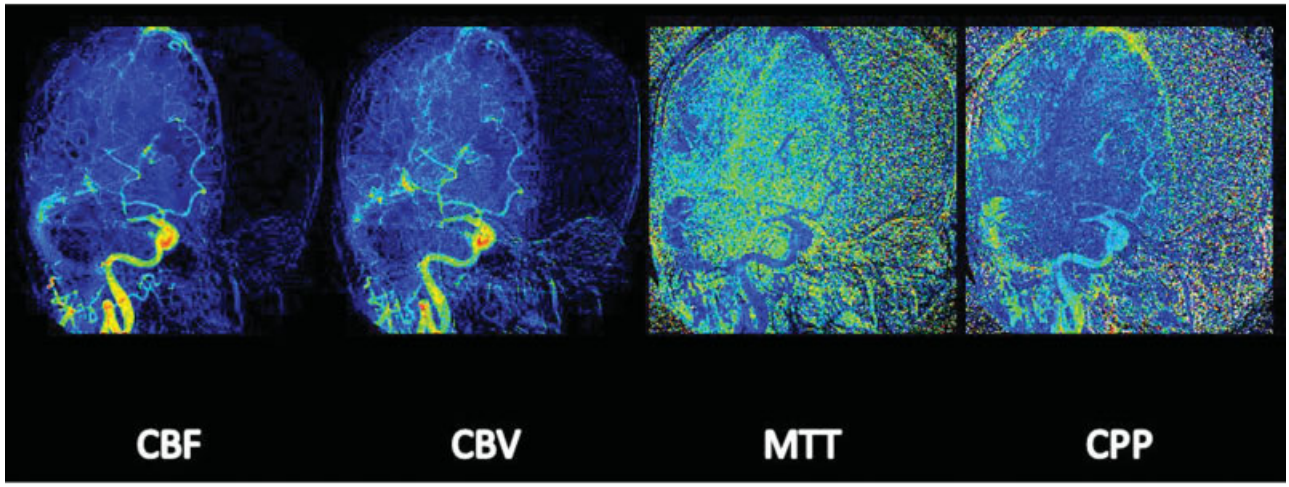

Fig 11. Perfusion angiography images generated from an oblique projection of right internal carotid artery injection at angiography shows blood flow changes in standard perfusion parameters beyond a right middle cerebral artery occlusion. CBF = cerebral blood flow; CBV = cerebral blood volume; MTT = mean transit time; CPP = cerebral perfusion pressure.

on CT facilitates recanalization with thrombolysis.[51] Even when CTA source images are used to judge the extent of injury at baseline, CTA may predict good functional outcome if the ASPECTS is preserved. Similar correlates have been demonstrated with DWI ASPECTS.[52] Collateral perfusion beyond an occlusion, therefore, not only preserves tissue at risk for infarction, but aids recanalization. This concept that downstream flow influences what happens upstream is an important facet that underscores the dynamics and interrelated aspects of ischemia, a radically different approach than solely considering mismatch or the elusive penumbra as a target to be salvaged only by removing the arterial occlusion. For the last decade, perfusion imaging in ischemic stroke has been equated with mismatch and the identification of the vulnerable region of brain. The penumbra, aptly termed as a shadow cast on the brain by vascular physiology, has been described as residing or emanating from brain parenchyma itself. Selective neuronal loss in the penumbra may occur, yet one should not forget that, in acute ischemic stroke, the primary process is vascular. Mismatch is, therefore, a moving target that may be largely influenced by hemodynamics, including preconditioning and factors that alter blood flow immediately after occlusion. The focus on arterial occlusion and extensive use of CT and MRI perfusion imaging has largely eliminated consideration of specific vascular structures that may be evident on angiography. For instance, arterial collaterals or venous drainage patterns cannot be identified with perfusion imaging, yet these are important features visible at angiography. Recent development of a novel postprocessing technique now makes it possible to generate perfusion parameter maps directly from conventional angiography (Fig 11), allowing feeding or draining vessels to be simultaneously identified.[53]

Perfusion information is often inferred from infarct patterns or summarily described by a single parameter, rather than delving into the mathematics of flow or underlying biology. For instance, DWI lesion patterns such as borderzone infarcts may implicate hypoperfusion, and cause is often inferred.[54] This may be misleading without further confirmatory diagnostic studies as a transient ischemic attack (TIA) ascribed to embolism because of a small punctate lesion on DWI may be caused by hypoperfusion downstream from large-artery stenosis. The presence of DWI lesions in TIA has received much attention, yet the biological determinants have been neglected as opposed to the emphasis on revising clinical definitions and prognostication.[55–58] Furthermore, infarct size has not always been an accurate predictor of outcome.[59] Monitoring treatment with DWI or diffusion tensor imaging and evolution of such lesions will be fruitful in coming years.[60,61] Consideration of perfusion in further detail, such as multiparametric analyses, may provide insight on lesion evolution.[62] Many perfusion algorithms have been used, yet most predictive models have been based on finding a single optimal parameter.[63,64] Perfusion imaging data obtained from first-pass contrast bolus techniques (including CT, MRI, and angiography) are always described by a curve of contrast concentration over time, with specific measurements yielding distinct blood flow parameters. Technical differences, including accounting for delay and dispersion, may alter calculation of parameters such as CBV.[65] Multiparametric models of infarct prediction have also failed to consider the bidirectional nature of CBV changes that evolve over time. Interestingly, substantially more information is provided by current multiparametric perfusion data

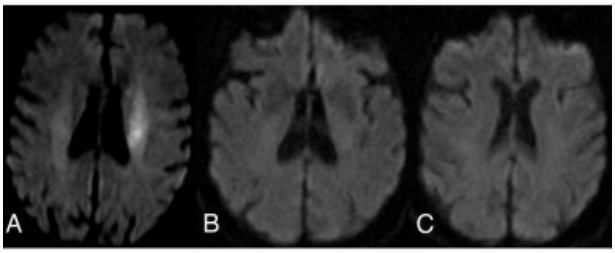

Fig 12. Serial diffusion-weighted imaging of acute left middle cerebral artery occlusion shows an initial subcortical abnormality (A) and complete reversal (B, C) 5 days after treatment with intravenous thrombolysis.

compared with older techniques focused solely on CBF measurement in animal models. Similarly, arterial spin labeled MRI focusing on CBF measures may miss other important aspects. CBF may be the least dramatic change during earlier stages of ischemia. Perfusion must be considered as flow involving arteries, microcirculation, and veins. Flow is only partially determined by pressure, and resistance has a prominent role. Multiparametric analyses may better characterize such individual features. For this reason, time-to-peak on MRI cannot be compared with CBV on CT. Even when specific measures are obtained with identical technical specifications, mathematical errors cannot be overlooked.[66] Ultimately, understanding the biology of perfusion patterns will be critical in developing novel treatments.[64,67,68] Even at baseline, one must consider variables such as hydration status, head positioning, and serial changes caused by increasing downstream resistance that influence perfusion imaging patterns. These studies will also clarify the potential and limitations of collateral therapeutic strategies such as induced hypertension or augmentation of pressures in collapsible veins to reduce downstream resistance.[22,69–71]

Reperfusion

Reversing Ischemia

Maximizing the potential of perfusion imaging will continue to expand the nascent concept that cerebral ischemia may be completely reversible in certain scenarios. During the earliest epochs, DWI lesions may be reversible (Fig 12), and even extensive perfusion abnormalities can be eradicated without arterial recanalization. These features that have been demonstrated with venous ischemia may also occur with arterial occlusion if imaged early. Most stroke imaging studies in the past focused on infarction and others on later stages of repair.[72] When an arterial occlusion is identified early, the goal should be to improve perfusion converting potential strokes to TIA. Even when CBV appears collapsed because of failure to detect low flow with severe delays, prompt intervention may lead to reversal in isolated cases.

No Reflow

Now that arterial revascularization strategies abound, the greatest enigma has been recanalization without reperfusion. One may expect that removing the arterial occlusion should allow pressure to adequately perfuse downstream reaches, yet resistance has been neglected. Such resistance is not necessarily mediated by arteriolar autoregulation, but by the microcirculation and dynamic changes in the venous circulation in the hours that ensue after arterial occlusion.[13] No reflow has been known in the heart and observed in animal stroke models many years ago, yet only recently recognized in the brain. After arterial recanalization, angiography often shows poor distal perfusion with tapered arteries, yet no evidence of distal embolic occlusion. Plugging of the microcirculation has been previously implicated, and reperfusion injury remains largely unexplored despite concern that this remains a critical issue in acute stroke.[73] Imaging of animal models has shown that the postischemic blood flow response to functional activation is severely attenuated for several hours.[74] Future studies will be able to explore the role of other factors such as age, sex, and hyperglycemia influencing reperfusion in the microcirculation and the concept of cerebral ischemic postconditioning.[75–77] Postconditioning suggests that gradual reperfusion may be more effective than sudden revascularization. Most importantly, imaging can improve medical decision making by providing enhanced estimates that balance risk and benefit of attempted reperfusion.

Hemorrhagic Transformation

Hemorrhagic conversion of an ischemic lesion remains the most feared complication of reperfusion. Numerous imaging studies have correlated baseline imaging features with subsequent HT.[78,79] HT is known to result from severe ischemia exacerbated by reperfusion.[80] Leukoaraiosis and associated perfusion abnormalities have been studied in this context.[81,82] Progressive ischemia over time caused by impaired perfusion, permeability derangements in the blood–brain barrier, and ineffective reperfusion after recanalization may all be studied with imaging.[67] Discussion of these imaging approaches is included in the companion article on hemorrhage.

Innovative Dimensions

Vessel Imaging

The growth of endovascular therapy has increased the use of conventional angiography, providing an ideal opportunity to perform correlative studies with nonin-

vasive angiographic techniques and perfusion imaging. Continued refinement of CTA and enhanced MRA will likely yield improved resolution and detection of increasingly subtle vascular changes. In diminutive vessels, endothelial imaging may show ischemic changes as well.[83] Further validation of quantitative MRA across a spectrum of clinical scenarios will finally move characterization beyond isolated measures of stenosis, probing the amount of flow beyond such lesions.[84] Detection of emboli with TCD offers advantages that no other modality can address, and increased use of this approach in conjunction with other modalities will undoubtedly grow in coming years. Such monitoring proximal and distal to specific lesions may disclose the culprit emboligenic lesion with certainty (Fig 13).

Perfusion

Numerous aspects of perfusion imaging await further development, although routine use of CT and MRI techniques is already widespread. Several modifications in CT perfusion imaging are being explored including progressively increased spatial coverage with higher resolution, reduced contrast requirements, and minimized radiation effects.[85–89] Whole-brain CT perfusion is being developed with several approaches, including up to 256 detector rows.[85,86] The effects of different biological factors on CT or MRI perfusion such as proximal stenoses and baseline differences in regional blood flow are also under study.[90,91] Selective arterial spin labeling will also be able to show regional differences in perfusion.[92] Of particular interest is the variation of perfusion in white matter and different ischemic thresholds.[93,94] Regional variation in blood flow abnormalities and topography is already under investigation with the development of perfusion atlases.[95] Because of the practical constraints of acute stroke image acquisition, maximal use of perfusion data is a key priority. Currently, permeability maps that denote regions of contrast leakage in the blood–brain barrier and flow in the microcirculation with flow heterogeneity maps can be generated from routine perfusion acquisitions (Fig 14). Recent postprocessing modifications allow identical mathematical approaches to be applied to both CT and MRI techniques to provide these maps. Prediction of hemorrhage and arteriogenesis can be studied with these approaches.

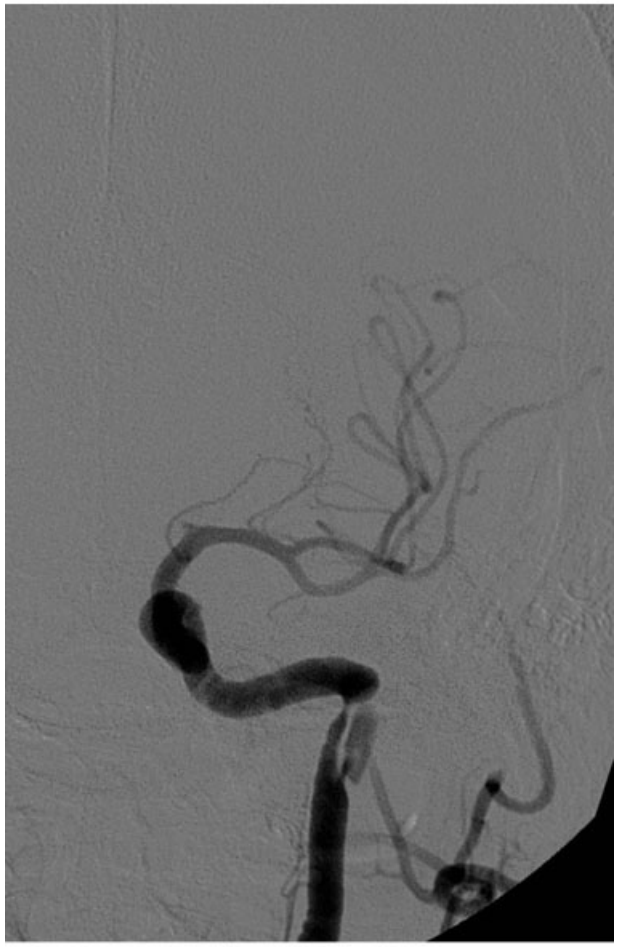

Fig 13. Transcranial Doppler ultrasonography with embolus detection in proximal and terminal segments of the left internal carotid artery confirmed that emboli were emanating from this dissection illustrated on angiography.

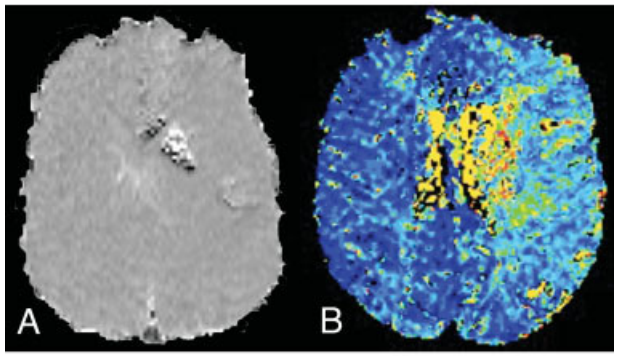

Fig 14. Permeability image (A) showing blood–brain barrier disruption in the basal ganglia and flow heterogeneity map (B) showing slowing of microcirculatory blood flow in subcortical regions derived from standard perfusion imaging data set acquired in acute ischemic stroke.

Parenchyma

Detection of tissue abnormalities associated with ischemia is also advancing with improved image acquisition and postprocessing. An adaptive smoothing filter of unenhanced CT images may aid recognition of early hypoattenuation.[96] Sodium MRI may be able to detect extremely early ischemic changes.[97] Magnetization transfer MRI can also show microstructural damage and possibly selective cellular loss in the salvaged penumbra.[98] Increasing availability of higher Tesla

strength MRI units may also improve tissue characterization, yet comparisons in lesion volume may need to account for field strength.[99]

Functional Imaging

Beyond perfusion, numerous other functional imaging approaches are being developed to study cerebral ischemia. Diaschisis in the contralateral cerebellum has recently been illustrated with MRI of MCA stroke.[100] Functional activation studies are also being explored in the acute phase, although challenges include accounting for hemodynamic effects and practical aspects such as testing paradigms while triaging for revascularization. Deoxygenation of blood flow and penumbral identification based on T2* sensitivity to an oxygen challenge are also being studied.[101] Magnetic resonance spectroscopy may show serial changes in *N*-acetylaspartate and lactate.[102] Recent magnetic resonance spectroscopy investigation has shown that the apparent diffusion coefficient and mean transit time correlate with lactate but not *N*-acetylaspartate, suggesting these two parameters are markers of ischemia but not neuronal loss.[103] MRI methods have recently been developed to measure temperature, pH, and even noise associated with physiological activity.[104–106] Inflammation in the ischemic brain associated with leukocyte activation and macrophage infiltration may be imaged with ultrasmall paramagnetic iron oxide particles.[107–110] Such imaging may be useful in chronicling angiogenesis and neurogenesis upregulated during the subacute phase.[111] Imaging research on inflammation will likely be advanced with novel positron emission tomographic ligands. Innovative imaging approaches in early stages of development include chemical shift imaging, hyperpolarization, and paramagnetic chemical exchange saturation transfer.[112–115]

Monitoring Therapy

These novel imaging strategies for vessel imaging, assessment of perfusion, and parenchyma, and functional aspects may be extremely useful in monitoring therapeutic interventions. Serial imaging at baseline, after revascularization, before discharge, and during repair is already under way at several centers. Future correlation with serology and the use of fusion techniques for conventional angiography with CT or MRI will further enrich knowledge of ischemia in humans. Several groups have already implemented advanced imaging to monitor the effects of hyperoxia, statins, and other medications. The potential benefits of hyperoxia for acute ischemia have been illustrated with magnetic resonance spectroscopy and other MRI techniques.[116–118] MRI has been used to illustrate potential beneficial effects of statin therapy.[119,120] Sildenafil has also been shown on MRI to induce angiogenesis and axonal remodeling after stroke.[121] Cellular trafficking of endogenous responses or therapeutic delivery of stem cells may capitalize on the use of superparamagnetic iron oxide molecules.[122,123] The effects of osmotherapy and hemodynamic interventions can already be assessed with serial MRI.[124] In the future, perfusion image acquisition with varying head position may provide further insight.

Trials and Tribulations

Multicenter Stroke Imaging

Imaging has played a central role in several large multicenter trials of acute stroke therapy. Imaging has been used as selection criteria and detailed in numerous subgroup analyses, yet clinical outcome has always trumped imaging. Most trials have been imaging of therapy and not necessarily trials of imaging. As a result, many stroke imaging techniques remain unvalidated. It remains difficult to simultaneously evaluate novel imaging technologies and stroke therapies in the same clinical trial. Some have attributed the numerous failures of stroke trials to heterogeneity that may be characterized by imaging, yet the costs frequently deter trialists from including intensive imaging approaches. In the future, stroke trials may benefit from using imaging to classify cases from a diagnostic perspective to tailor therapy rather than trialing a single therapy amidst heterogeneity.[125] Unfortunately, the imaging approaches are often quite reductionist, addressing the need to construct a single primary outcome measure. This defies the enormous prowess of information contained in imaging of cerebral ischemia. Negative trial results may consequently lead imaging to be viewed as superfluous and subsequently removed altogether from clinical trials of stroke therapy.

The Diffusion and Perfusion Imaging for Understanding Stroke Evolution (DEFUSE) trial recently demonstrated that specific mismatch patterns may be used to predict outcome with thrombolysis up to 6 hours from symptom onset.[126] Furthermore, a mismatch ratio of 2.6 provided the greatest sensitivity (90%) and specificity (83%) for identifying patients in whom reperfusion was associated with a favorable response.[127] MRA-DWI mismatch was also shown to be a useful predictor of patients likely to benefit from reperfusion.[128] Overall, mismatch was associated with favorable clinical response and smaller infarcts when recanalization was achieved.[129] The Echoplanar Imaging Thrombolysis Evaluation Trial (EPITHET) randomized cases within a 6-hour epoch for thrombolysis, yet generated debate because of the equivocal imaging results.[130–132] In the Desmoteplase in Acute Ischemic Stroke (DIAS-2) trial, imaging results differed between sites that utilized CT versus MRI perfusion imaging, raising more questions about imaging techniques.[133]

Results from stroke imaging trials are often based on

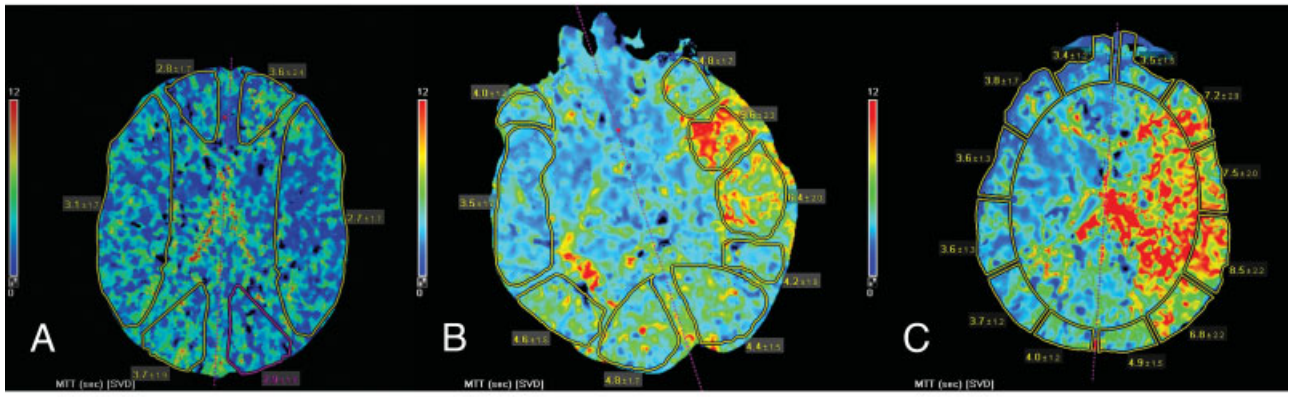

Fig 15. Identical computed tomographic perfusion imaging acquisition in three acute stroke cases shows how relatively subjective approaches may alter quantitative blood flow measurements on mean transit time (MTT) maps. Semiautomated approaches to map standard arterial territories such as the posterior cerebral artery (A) may yield erroneous values. Manually subsegmented portions of the middle cerebral artery territory (B) may show radically different values depending on choice of homologous region used as a control. Cortical regions are inadvertently ignored by measures (B) that attempt to avoid large-vessel influences. Measurements derived from automated region-of-interest sectors around the cortical surface (C) may ignore underlying vascular anatomy and fail to account for entire subcortical regions.

averages or summary statistics, and correlations may be established, yet the subtleties and details of imaging often remain buried. Site differences in technique may confound trial conduct, and current efforts for standardization aim to improve on these limitations.[66,134] Even when detailed lesion volumes are used rather than gross visual estimates, much variability persists.[135] For instance, detailed measures on CT perfusion usually require manual region-of-interest selection based on presumed arterial territories, often avoiding the cortical surface to exclude large vessels (Fig 15). Depending on these factors, the resultant averaged value of each perfusion parameter may vary. Finally, choice of an optimal control for a given patient remains unclear. Contralateral homologous regions may be best to account for age, sex, comorbidities, and other patient-specific factors. Such issues affect MRI as well. Voxel-based predictions may provide incredible power from a statistical perspective, yet such values may be discordant with clinical outcome despite such power. Penumbral selection and predictive models, therefore, may be quite complicated. In fact, many other factors such as demographics, baseline or index stroke features, other imaging patterns, treatment details, subsequent medical care, and complications to day 90 may defy predictive models. Many imaging predictive models have been based on cardioembolic stroke cases in the United States and have limited utility in stroke because of intracranial atherosclerosis among Asian patients. Future imaging trials must therefore account for such differences. Even when predictive values reach 80%, one must question whether this can be used to appropriately exclude patients from therapy in acute stroke. Most often, a decision about revascularization is made after detailed imaging, yet a go/no-go paradigm is unrealistic because the risk/benefit may continue to evolve because of the dynamic nature of stroke pathophysiology. Serial risk/benefit assessments, therefore, may be more appropriate in the management of individual cases.

n of 1 and Tailored Stroke Therapy

Unlike the seemingly controlled framework of a clinical trial, stroke imaging is usually acquired, interpreted, and implemented case by case on a daily basis. This n of 1 approach often considers numerous factors and imaging subtleties unanswered by prior trials. Imaging has become a requisite component of the neurological examination as one simply cannot evaluate and manage a stroke patient in effective fashion without the use of diagnostic neuroimaging capabilities. Such tailored stroke therapy often places tremendous emphasis on imaging findings, typically evaluated by the clinician in real time.

The impact of stroke imaging on clinical management is of paramount importance. Neurologists or other clinicians must often rely on subtle imaging features guided by key examination findings at the bedside. Despite reverence for blinding in clinical trials, interpretation of imaging in practice should be anything but blinded, based on clinical correlation. Imaging information must be maximally extracted from every image, such as detecting evolving edema from MRA source images when other sequences are unavailable. Guidelines on stroke imaging and suggested parameters typically revolve around timelines for image acquisition, yet many questions about interpretation and subsequent decision making remain unanswered.

Optimal management of the wake-up patient or late time window case continues to baffle clinicians. For both TIA and stroke, time to imaging is key because the information from images is critical.[136] Increasing use of telestroke to organize acute stroke services emphasizes imaging as an essential component, and ongoing research will explore the practice of stroke imaging in this new context.[137]

Conclusions

Imaging of stroke has continued to accelerate our rapidly expanding knowledge of ischemic pathophysiology. Novel modalities provide a fertile ground for discovery of therapeutic targets and the potential to assess effects of promising strategies. The information garnered from imaging of ischemia and the cerebral circulation discussed in this article has also yielded insight on potential future breakthroughs in hemorrhage to be discussed in the second article of this series.

References

1. Le Bihan D, Breton E, Lallemand D, et al. Separation of diffusion and perfusion in intravoxel incoherent motion MR imaging. Radiology 1988;168:497–505.
2. Moseley ME, Mintorovitch J, Cohen Y, et al. Early detection of ischemic injury: comparison of spectroscopy, diffusion-, T2-, and magnetic susceptibility-weighted MRI in cats. Acta Neurochir Suppl (Wien) 1990;51:207–209.
3. Liebeskind DS. Holistic imaging of acute stroke: seeing the big picture. Ann Neurol 2007;61:501–503.
4. Otsuka Y, Waki R, Yamauchi H, et al. Angiographic demarcation of an occlusive lesion may predict recanalization after intra-arterial thrombolysis in patients with acute middle cerebral artery occlusion. J Neuroimaging 2008;18:422–427.
5. Liebeskind DS. Collateral circulation. Stroke 2003;34: 2279–2284.
6. Liebeskind DS. Collaterals in acute stroke: beyond the clot. Neuroimaging Clin N Am 2005;15:553–573, x.
7. Hendrikse J, Klijn CJ, van Huffelen AC, et al. Diagnosing cerebral collateral flow patterns: accuracy of non-invasive testing. Cerebrovasc Dis 2008;25:430–437.
8. Liebeskind DS, Sansing LH. Willisian collateralization. Neurology 2004;63:344.
9. Bondke A, Buschmann IR. Visualization of therapeutic arteriogenesis by MR angiography: functional measurements are superior to surrogate parameters. J Magn Reson Imaging 2007;26:215, author reply 216.
10. Lee SJ, Lee KS, An JY, et al. The lesion patterns and mechanisms of ischemic stroke contralateral to the internal carotid artery occlusive disease. Eur Neurol 2008;60:27–31.
11. Bang OY, Saver JL, Buck BH, et al. Impact of collateral flow on tissue fate in acute ischaemic stroke. J Neurol Neurosurg Psychiatry 2008;79:625–629.
12. Tomita M, Gotoh F, Amano T, et al. "Low perfusion hyperemia" following middle cerebral arterial occlusion in cats of different age groups. Stroke 1980;11:629–636.
13. Pranevicius M, Pranevicius O. Cerebral venous steal: blood flow diversion with increased tissue pressure. Neurosurgery 2002;51:1267–1274.
14. Parsons MW, Pepper EM, Bateman GA, et al. Identification of the penumbra and infarct core on hyperacute noncontrast and perfusion CT. Neurology 2007;68:730–736.
15. Caplan LR, Wong KS, Gao S, Hennerici MG. Is hypoperfusion an important cause of strokes? If so, how? Cerebrovasc Dis 2006;21:145–153.
16. Liebeskind DS. Vasoprotection in ischemic tolerance. In: Schaller BJ, ed. Ischemic tolerance of the brain. Research Signpost, 2009. Kerala, India.
17. Alexandrov AV, Rubiera M. Use of neuroimaging in acute stroke trials. Expert Rev Neurother 2009;9:885–895.
18. Del Zoppo GJ, Saver JL, Jauch EC, Adams HP Jr on behalf of the American Heart Association Stroke Council. Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator. A Science Advisory From the American Heart Association/American Stroke Association. Stroke 2009 May 28.
19. Saver JL, Albers GW, Dunn B, et al. Stroke Therapy Academic Industry Roundtable (STAIR) Recommendations for Extended Window Acute Stroke Therapy Trials. Stroke 2009; 40:2594–2600.
20. Donnan GA, Baron JC, Ma H, Davis SM. Penumbral selection of patients for trials of acute stroke therapy. Lancet Neurol 2009;8:261–269.
21. Wunderlich MT, Goertler M, Postert T, et al. Recanalization after intravenous thrombolysis: does a recanalization time window exist? Neurology 2007;68:1364–1368.
22. Liebeskind DS. Collateral therapeutics for cerebral ischemia. Expert Rev Neurother 2004;4:255–265.
23. Setser RM, Kim JK, Chung YC, et al. Cine delayed-enhancement MR imaging of the heart: initial experience. Radiology 2006;239:856–862.
24. Saba L, Sanfilippo R, Pascalis L, et al. Carotid artery wall thickness and ischemic symptoms: evaluation using multi-detector-row CT angiography. Eur Radiol 2008;18:1962–1971.
25. Yoshida K, Narumi O, Chin M, et al. Characterization of carotid atherosclerosis and detection of soft plaque with use of black-blood MR imaging. AJNR Am J Neuroradiol 2008;29: 868–874.
26. Cappendijk VC, Kessels AG, Heeneman S, et al. Comparison of lipid-rich necrotic core size in symptomatic and asymptomatic carotid atherosclerotic plaque: initial results. J Magn Reson Imaging 2008;27:1356–1361.
27. Yamada N, Higashi M, Otsubo R, et al. Association between signal hyperintensity on T1-weighted MR imaging of carotid plaques and ipsilateral ischemic events. AJNR Am J Neuroradiol 2007;28:287–292.
28. Uwatoko T, Toyoda K, Inoue T, et al. Carotid artery calcification on multislice detector-row computed tomography. Cerebrovasc Dis 2007;24:20–26.
29. Kuker W, Gaertner S, Nagele T, et al. Vessel wall contrast enhancement: a diagnostic sign of cerebral vasculitis. Cerebrovasc Dis 2008;26:23–29.
30. Rouhl RP, van Oostenbrugge RJ, Knottnerus IL, et al. Virchow-Robin spaces relate to cerebral small vessel disease severity. J Neurol 2008;255:692–696.
31. Bash S, Villablanca JP, Jahan R, et al. Intracranial vascular stenosis and occlusive disease: evaluation with CT angiography, MR angiography, and digital subtraction angiography. AJNR Am J Neuroradiol 2005;26:1012–1021.
32. Feldmann E, Wilterdink JL, Kosinski A, et al. The Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis (SONIA) trial. Neurology 2007;68:2099–2106.
33. Ishimaru H, Ochi M, Morikawa M, et al. Accuracy of pre- and postcontrast 3D time-of-flight MR angiography in patients with acute ischemic stroke: correlation with catheter angiography. AJNR Am J Neuroradiol 2007;28:923–926.

34. Tan TY, Chen TY. Detection of microembolic signals using power M-mode Doppler sonography in acute stroke patients with intracranial artery stenosis. J Clin Ultrasound 2008;36: 422–426.
35. Zaidat OO, Wolfe T, Hussain SI, et al. Interventional acute ischemic stroke therapy with intracranial self-expanding stent. Stroke 2008;39:2392–2395.
36. Nahab F, Cotsonis G, Lynn M, et al. Prevalence and prognosis of coexistent asymptomatic intracranial stenosis. Stroke 2008;39:1039–1041.
37. Liebeskind DS, Cotsonis GA, Saver JL, et al. Collateral flow greatly impacts the risk of stroke with intracranial atherosclerosis. Stroke 2007;38:477.
38. Tanaka M, Shimosegawa E, Kajimoto K, et al. Chronic middle cerebral artery occlusion: a hemodynamic and metabolic study with positron-emission tomography. AJNR Am J Neuroradiol 2008;29:1841–1846.
39. Surikova I, Meisel S, Siebler M, et al. Significance of the perfusion-diffusion mismatch in chronic cerebral ischemia. J Magn Reson Imaging 2006;24:771–778.
40. Wang X, Lam WW, Fan YH, et al. Topographic patterns of small subcortical infarcts associated with MCA stenosis: a diffusion-weighted MRI study. J Neuroimaging 2006;16: 266–271.
41. Kim JM, Lee SH, Roh JK. Changing ischaemic lesion patterns in adult moyamoya disease. J Neurol Neurosurg Psychiatry 2009;80:36–40.
42. Jefferson AL, Glosser G, Detre JA, et al. Neuropsychological and perfusion MR imaging correlates of revascularization in a case of moyamoya syndrome. AJNR Am J Neuroradiol 2006; 27:98–100.
43. Zubkov AY, Uschmann H, Rabinstein AA. Rate of arterial occlusion in patients with acute ischemic stroke. Neurol Res 2008;30:835–838.
44. Krings T, Noelchen D, Mull M, et al. The hyperdense posterior cerebral artery sign: a computed tomography marker of acute ischemia in the posterior cerebral artery territory. Stroke 2006;37:399–403.
45. Ozdemir O, Leung A, Bussiere M, et al. Hyperdense internal carotid artery sign: a CT sign of acute ischemia. Stroke 2008; 39:2011–2016.
46. Qureshi AI, Ezzeddine MA, Nasar A, et al. Is IV tissue plasminogen activator beneficial in patients with hyperdense artery sign? Neurology 2006;66:1171–1174.
47. Liebeskind DS, Yong WH, Sanossian N, et al. CT and MRI early vessel signs reflect clot composition in acute stroke. Stroke 2008;39:564.
48. Kim YS, Meyer JS, Garami Z, et al. Flow diversion in transcranial Doppler ultrasound is associated with better improvement in patients with acute middle cerebral artery occlusion. Cerebrovasc Dis 2006;21:74–78.
49. Liebeskind DS, Sanossian N, Alger JR, et al. Gradient-echo MRI phase mismapping reveals angiographic correlates in acute ischemic stroke. Stroke 2006;37:637.
50. Sanossian N, Saver JL, Alger JR, et al. Angiography reveals that fluid-attenuated inversion recovery vascular hyperintensities are due to slow flow, not thrombus. AJNR Am J Neuroradiol 2009;30:564–568.
51. Tsivgoulis G, Saqqur M, Sharma VK, et al. Association of pretreatment ASPECTS scores with tPA-induced arterial recanalization in acute middle cerebral artery occlusion. J Neuroimaging 2008;18:56–61.
52. Kimura K, Iguchi Y, Shibazaki K, et al. Large ischemic lesions on diffusion-weighted imaging done before intravenous tissue plasminogen activator thrombolysis predicts a poor outcome in patients with acute stroke. Stroke 2008;39:2388–2391.
53. Liebeskind DS, Szilagyi G, Black SE, Buck BH. Perfusion angiography: a novel technique for characterization of perfusion in cerebral ischemia. Stroke 2008;39:576.
54. Yong SW, Bang OY, Lee PH, Li WY. Internal and cortical border-zone infarction: clinical and diffusion-weighted imaging features. Stroke 2006;37:841–846.
55. Coutts SB, Eliasziw M, Hill MD, et al. An improved scoring system for identifying patients at high early risk of stroke and functional impairment after an acute transient ischemic attack or minor stroke. Int J Stroke 2008;3:3–10.
56. Kang DW, Lattimore SU, Latour LL, Warach S. Silent ischemic lesion recurrence on magnetic resonance imaging predicts subsequent clinical vascular events. Arch Neurol 2006;63: 1730–1733.
57. Sylaja PN, Coutts SB, Krol A, et al. When to expect negative diffusion-weighted images in stroke and transient ischemic attack. Stroke 2008;39:1898–1900.
58. Sorimachi T, Ito Y, Morita K, Fujii Y. Thin-section diffusion-weighted imaging of the infratentorium in patients with acute cerebral ischemia without apparent lesion on conventional diffusion-weighted imaging. Neurol Med Chir (Tokyo) 2008; 48:108–113.
59. Tomycz ND, Holm MB, Horowitz MB, et al. Extensive brainstem ischemia on neuroimaging does not preclude meaningful recovery from locked-in syndrome: two cases of endovascularly managed basilar thrombosis. J Neuroimaging 2008; 18:15–17.
60. Shibazaki K, Iguchi Y, Kimura K, et al. New asymptomatic ischemic lesions on diffusion-weighted imaging after cerebral angiography. J Neurol Sci 2008;266:150–155.
61. Alexander AL, Lee JE, Lazar M, Field AS. Diffusion tensor imaging of the brain. Neurotherapeutics 2007;4:316–329.
62. Kane I, Carpenter T, Chappell F, et al. Comparison of 10 different magnetic resonance perfusion imaging processing methods in acute ischemic stroke: effect on lesion size, proportion of patients with diffusion/perfusion mismatch, clinical scores, and radiologic outcomes. Stroke 2007;38:3158–3164.
63. Provenzale JM, Shah K, Patel U, McCrory DC. Systematic review of CT and MR perfusion imaging for assessment of acute cerebrovascular disease. AJNR Am J Neuroradiol 2008; 29:1476–1482.
64. Sparacia G, Iaia A, Assadi B, Lagalla R. Perfusion CT in acute stroke: predictive value of perfusion parameters in assessing tissue viability versus infarction. Radiol Med 2007;112:113–122.
65. Salluzzi M, Frayne R, Smith MR. Is correction necessary when clinically determining quantitative cerebral perfusion parameters from multi-slice dynamic susceptibility contrast MR studies? Phys Med Biol 2006;51:407–424.
66. Wintermark M, Albers GW, Alexandrov AV, et al. Acute stroke imaging research roadmap. Stroke 2008;39:1621–1628.
67. Bang OY, Saver JL, Alger JR, et al. Patterns and predictors of blood-brain barrier permeability derangements in acute ischemic stroke. Stroke 2009;40:454–461.
68. Heiss WD, Sobesky J. Comparison of PET and DW/PW-MRI in acute ischemic stroke. Keio J Med 2008;57:125–131.
69. Liebeskind DS. Of mice and men: essential considerations in the translation of collateral therapeutics. Stroke 2008;39: e187–e188, author reply e189.
70. Shin HK, Nishimura M, Jones PB, et al. Mild induced hypertension improves blood flow and oxygen metabolism in transient focal cerebral ischemia. Stroke 2008;39:1548–1555.
71. Han JH, Leung TW, Lam WW, et al. Preliminary findings of external counterpulsation for ischemic stroke patient with large artery occlusive disease. Stroke 2008;39:1340–1343.
72. Cramer SC. Repairing the human brain after stroke: I. Mechanisms of spontaneous recovery. Ann Neurol 2008;63: 272–287.

73. Pan J, Konstas AA, Bateman B, et al. Reperfusion injury following cerebral ischemia: pathophysiology, MR imaging, and potential therapies. Neuroradiology 2007;49:93–102.
74. Zhou C, Shimazu T, Durduran T, et al. Acute functional recovery of cerebral blood flow after forebrain ischemia in rat. J Cereb Blood Flow Metab 2008;28:1275–1284.
75. Kruyt ND, Nys GM, van der Worp HB, et al. Hyperglycemia and cognitive outcome after ischemic stroke. J Neurol Sci 2008;270:141–147.
76. Ribo M, Molina CA, Delgado P, et al. Hyperglycemia during ischemia rapidly accelerates brain damage in stroke patients treated with tPA. J Cereb Blood Flow Metab 2007;27: 1616–1622.
77. Pignataro G, Meller R, Inoue K, et al. In vivo and in vitro characterization of a novel neuroprotective strategy for stroke: ischemic postconditioning. J Cereb Blood Flow Metab 2008; 28:232–241.
78. Singer OC, Humpich MC, Fiehler J, et al. Risk for symptomatic intracerebral hemorrhage after thrombolysis assessed by diffusion-weighted magnetic resonance imaging. Ann Neurol 2008;63:52–60.
79. Bang OY, Buck BH, Saver JL, et al. Prediction of hemorrhagic transformation after recanalization therapy using T2*-permeability magnetic resonance imaging. Ann Neurol 2007; 62:170–176.
80. Rosell A, Foerch C, Murata Y, Lo EH. Mechanisms and markers for hemorrhagic transformation after stroke. Acta Neurochir Suppl 2008;105:173–178.
81. Ay H, Arsava EM, Rosand J, et al. Severity of leukoaraiosis and susceptibility to infarct growth in acute stroke. Stroke 2008;39:1409–1413.
82. Mandell DM, Han JS, Poublanc J, et al. Selective reduction of blood flow to white matter during hypercapnia corresponds with leukoaraiosis. Stroke 2008;39:1993–1998.
83. Barber PA, Foniok T, Kirk D, et al. MR molecular imaging of early endothelial activation in focal ischemia. Ann Neurol 2004;56:116–120.
84. Conway SA, Bowling SM, Geyer JD, et al. Quantitative magnetic resonance angiography of the cerebrovasculature in physiologic and pathologic states. J Neuroimaging 2008;18:34–37.
85. Murayama K, Katada K, Nakane M, et al. Whole-brain perfusion CT performed with a prototype 256-detector row CT system: initial experience. Radiology 2009;250:202–211.
86. Youn SW, Kim JH, Weon YC, et al. Perfusion CT of the brain using 40-mm-wide detector and toggling table technique for initial imaging of acute stroke. AJR Am J Roentgenol 2008;191:W120–W126.
87. Kamena A, Streitparth F, Grieser C, et al. Dynamic perfusion CT: optimizing the temporal resolution for the calculation of perfusion CT parameters in stroke patients. Eur J Radiol 2007;64:111–118.
88. Langner S, Stumpe S, Kirsch M, et al. No increased risk for contrast-induced nephropathy after multiple CT perfusion studies of the brain with a nonionic, dimeric, iso-osmolal contrast medium. AJNR Am J Neuroradiol 2008;29:1525–1529.
89. Wiesmann M, Berg S, Bohner G, et al. Dose reduction in dynamic perfusion CT of the brain: effects of the scan frequency on measurements of cerebral blood flow, cerebral blood volume, and mean transit time. Eur Radiol 2008;18: 2967–2974.
90. Serafin Z, Kotarski M, Karolkiewicz M, et al. Reproducibility of dynamic computed tomography brain perfusion measurements in patients with significant carotid artery stenosis. Acta Radiol 2009;50:226–232.
91. Matsushima S, Kubota T, Yamada K, et al. Effect of vascular stenosis on perfusion-weighted imaging; differences between calculation algorithms. J Magn Reson Imaging 2008;27: 1103–1108.
92. Hendrikse J, van Osch MJ, Rutgers DR, et al. Internal carotid artery occlusion assessed at pulsed arterial spin-labeling perfusion MR imaging at multiple delay times. Radiology 2004; 233:899–904.
93. Murphy BD, Fox AJ, Lee DH, et al. White matter thresholds for ischemic penumbra and infarct core in patients with acute stroke: CT perfusion study. Radiology 2008;247:818–825.
94. Arakawa S, Wright PM, Koga M, et al. Ischemic thresholds for gray and white matter: a diffusion and perfusion magnetic resonance study. Stroke 2006;37:1211–1216.
95. Nowinski WL, Qian G, Kirgaval Nagaraja BP, et al. Analysis of ischemic stroke MR images by means of brain atlases of anatomy and blood supply territories. Acad Radiol 2006;13: 1025–1034.
96. Takahashi N, Lee Y, Tsai DY, et al. Improvement of detection of hypoattenuation in acute ischemic stroke in unenhanced computed tomography using an adaptive smoothing filter. Acta Radiol 2008;49:816–826.
97. Jones SC, Kharlamov A, Yanovski B, et al. Stroke onset time using sodium MRI in rat focal cerebral ischemia. Stroke 2006; 37:883–888.
98. Tourdias T, Dousset V, Sibon I, et al. Magnetization transfer imaging shows tissue abnormalities in the reversible penumbra. Stroke 2007;38:3165–3171.
99. Kosior RK, Wright CJ, Kosior JC, et al. 3-Tesla versus 1.5-Tesla magnetic resonance diffusion and perfusion imaging in hyperacute ischemic stroke. Cerebrovasc Dis 2007;24: 361–368.
100. Liu Y, Karonen JO, Nuutinen J, et al. Crossed cerebellar diaschisis in acute ischemic stroke: a study with serial SPECT and MRI. J Cereb Blood Flow Metab 2007;27: 1724–1732.
101. Santosh C, Brennan D, McCabe C, et al. Potential use of oxygen as a metabolic biosensor in combination with T2*-weighted MRI to define the ischemic penumbra. J Cereb Blood Flow Metab 2008;28:1742–1753.
102. Munoz Maniega S, Cvoro V, Chappell FM, et al. Changes in NAA and lactate following ischemic stroke: a serial MR spectroscopic imaging study. Neurology 2008;71:1993–1999.
103. Cvoro V, Wardlaw JM, Marshall I, et al. Associations between diffusion and perfusion parameters, N-acetyl aspartate, and lactate in acute ischemic stroke. Stroke 2009;40: 767–772.
104. Marshall I, Karaszewski B, Wardlaw JM, et al. Measurement of regional brain temperature using proton spectroscopic imaging: validation and application to acute ischemic stroke. Magn Reson Imaging 2006;24:699–706.
105. Sun PZ, Zhou J, Sun W, et al. Detection of the ischemic penumbra using pH-weighted MRI. J Cereb Blood Flow Metab 2007;27:1129–1136.
106. Wang HH, Menezes NM, Zhu MW, et al. Physiological noise in MR images: an indicator of the tissue response to ischemia? J Magn Reson Imaging 2008;27:866–871.
107. Buck BH, Liebeskind DS, Saver JL, et al. Early neutrophilia is associated with volume of ischemic tissue in acute stroke. Stroke 2008;39:355–360.
108. Nighoghossian N, Wiart M, Cakmak S, et al. Inflammatory response after ischemic stroke: a USPIO-enhanced MRI study in patients. Stroke 2007;38:303–307.

109. Saleh A, Schroeter M, Ringelstein A, et al. Iron oxide particle-enhanced MRI suggests variability of brain inflammation at early stages after ischemic stroke. Stroke 2007;38:2733–2737.
110. Kim J, Kim DI, Lee SK, et al. Imaging of the inflammatory response in reperfusion injury after transient cerebral ischemia in rats: correlation of superparamagnetic iron oxide-enhanced magnetic resonance imaging with histopathology. Acta Radiol 2008;49:580–588.
111. Ding G, Jiang Q, Li L, et al. Angiogenesis detected after embolic stroke in rat brain using magnetic resonance T2*WI. Stroke 2008;39:1563–1568.
112. Takasawa M, Moustafa RR, Baron JC. Applications of nitroimidazole in vivo hypoxia imaging in ischemic stroke. Stroke 2008;39:1629–1637.
113. Heckl S. Future contrast agents for molecular imaging in stroke. Curr Med Chem 2007;14:1713–1728.
114. Wu Y, Zhou Y, Ouari O, et al. Polymeric PARACEST agents for enhancing MRI contrast sensitivity. J Am Chem Soc 2008; 130:13854–13855.
115. McCarney ER, Armstrong BD, Lingwood MD, Han S. Hyperpolarized water as an authentic magnetic resonance imaging contrast agent. Proc Natl Acad Sci U S A 2007;104: 1754–1759.
116. Singhal AB, Ratai E, Benner T, et al. Magnetic resonance spectroscopy study of oxygen therapy in ischemic stroke. Stroke 2007;38:2851–2854.
117. Shin HK, Dunn AK, Jones PB, et al. Normobaric hyperoxia improves cerebral blood flow and oxygenation, and inhibits peri-infarct depolarizations in experimental focal ischaemia. Brain 2007;130:1631–1642.
118. Henninger N, Bouley J, Nelligan JM, et al. Normobaric hyperoxia delays perfusion/diffusion mismatch evolution, reduces infarct volume, and differentially affects neuronal cell death pathways after suture middle cerebral artery occlusion in rats. J Cereb Blood Flow Metab 2007;27:1632–1642.
119. Nicholas JS, Swearingen CJ, Thomas JC, et al. The effect of statin pretreatment on infarct volume in ischemic stroke. Neuroepidemiology 2008;31:48–56.
120. Ding G, Jiang Q, Li L, et al. MRI of combination treatment of embolic stroke in rat with rtPA and atorvastatin. J Neurol Sci 2006;246:139–147.
121. Ding G, Jiang Q, Li L, et al. Magnetic resonance imaging investigation of axonal remodeling and angiogenesis after embolic stroke in sildenafil-treated rats. J Cereb Blood Flow Metab 2008;28:1440–1448.
122. Walczak P, Zhang J, Gilad AA, et al. Dual-modality monitoring of targeted intraarterial delivery of mesenchymal stem cells after transient ischemia. Stroke 2008;39:1569–1574.
123. Sykova E, Jendelova P. Migration, fate and in vivo imaging of adult stem cells in the CNS. Cell Death Differ 2007;14: 1336–1342.
124. Chen CH, Xue R, Zhang J, et al. Effect of osmotherapy with hypertonic saline on regional cerebral edema following experimental stroke: a study utilizing magnetic resonance imaging. Neurocrit Care 2007;7:92–100.
125. Moustafa RR, Baron JC. Pathophysiology of ischaemic stroke: insights from imaging, and implications for therapy and drug discovery. Br J Pharmacol 2008;153(suppl 1):S44–S54.
126. Albers GW, Thijs VN, Wechsler L, et al. Magnetic resonance imaging profiles predict clinical response to early reperfusion: the diffusion and perfusion imaging evaluation for understanding stroke evolution (DEFUSE) study. Ann Neurol 2006;60:508–517.
127. Kakuda W, Lansberg MG, Thijs VN, et al. Optimal definition for PWI/DWI mismatch in acute ischemic stroke patients. J Cereb Blood Flow Metab 2008;28:887–891.
128. Lansberg MG, Thijs VN, Bammer R, et al. The MRA-DWI mismatch identifies patients with stroke who are likely to benefit from reperfusion. Stroke 2008;39:2491–2496.
129. Olivot JM, Mlynash M, Thijs VN, et al. Relationships between infarct growth, clinical outcome, and early recanalization in diffusion and perfusion imaging for understanding stroke evolution (DEFUSE). Stroke 2008;39:2257–2263.
130. Davis SM, Donnan GA, Parsons MW, et al. Effects of alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET): a placebo-controlled randomised trial. Lancet Neurol 2008;7:299–309.
131. Sandercock P, Wardlaw J, Dennis M, et al. EPITHET—where next? Lancet Neurol 2008;7:570–573.
132. Schellinger PD. EPITHET: failed chance or new hope? Lancet Neurol 2008;7:286–287.
133. Hacke W, Furlan AJ, Al-Rawi Y, et al. Intravenous desmoteplase in patients with acute ischaemic stroke selected by MRI perfusion-diffusion weighted imaging or perfusion CT (DIAS-2): a prospective, randomised, double-blind, placebo-controlled study. Lancet Neurol 2009;8:141–150.
134. Provenzale JM, Wintermark M. Optimization of perfusion imaging for acute cerebral ischemia: review of recent clinical trials and recommendations for future studies. AJR Am J Roentgenol 2008;191:1263–1270.
135. Rivers CS, Wardlaw JM, Armitage PA, et al. Acute ischemic stroke lesion measurement on diffusion-weighted imaging—important considerations in designing acute stroke trials with magnetic resonance imaging. J Stroke Cerebrovasc Dis 2007; 16:64–70.
136. Lavallee PC, Meseguer E, Abboud H, et al. A transient ischaemic attack clinic with round-the-clock access (SOS-TIA): feasibility and effects. Lancet Neurol 2007;6: 953–960.
137. Wardlaw JM, Farrall AJ, Perry D, et al. Factors influencing the detection of early CT signs of cerebral ischemia: an internet-based, international multiobserver study. Stroke 2007; 38:1250–1256.