

Radiology *Select*

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Introducing *Radiology Select*: *Stroke*

The prevention, diagnosis, and treatment of acute stroke continue to be a challenge, despite recent advances in screening, risk factor modification, imaging evaluation, and novel thrombolytic and endovascular therapies. Approximately 85% of strokes are ischemic and 15% are hemorrhagic. The majority of the morbidity and mortality of adult ischemic stroke is attributable to emboli to the circle of Willis from cardiac (left atrial appendage thrombus accompanying atrial fibrillation) or large-vessel atheromatous (internal carotid artery [ICA] bifurcation plaque) sources; in children and young adults, dissection and paradoxical embolus through a patent foramen ovale are leading causes of stroke. It has been estimated that most strokes in adults could be prevented simply by means of appropriate control of high blood pressure (1). Indeed, in the recently launched Million Hearts Initiative—aimed at preventing 1 million strokes and heart attacks nationally over the next 5 years—management of the “ABC’S” (aspirin for high-risk patients, blood-pressure control, cholesterol management, and smoking cessation) is paramount (2).

We are delighted to serve as guest editors for this collection of 30 of the most compelling representative articles on stroke that have appeared in the *Radiology* over the past 5–7 years. Selection was no easy task; a simple PubMed search of *Radiology* articles published since July 2004 using the keywords *stroke* or *carotid* identifies over 150 outstanding articles, reflecting, on average, almost two stroke-related articles per issue. Of necessity, we have excluded many noteworthy topics.

Selection criteria were similar to those applied routinely for peer review of original research considered for publication in *Radiology*: specifically, (a) clinical importance, (b) novelty, and (c) potential influence on setting the neuroimaging research agenda. An additional criterion, scientific rigor, was (of course) already present in all of the screened articles. With regard to study design, articles that made the first cut generally fell into one of two categories: early innovative pilot studies of historic importance, or larger, prospective, confirmatory studies with substantial clinical or research importance. When many reports addressed a single limited theme (such as magnetic resonance [MR] arterial spin labeling [ASL] perfusion imaging), preference was typically given to more current, definitive studies—as well as to recent comprehensive reviews—with noteworthy early pioneering studies cited as references for the ambitious reader.

Stroke imaging research published in *Radiology* since late 2004 has primarily centered on two major subject areas: (a) penumbral markers for both prediction of tissue and clinical outcomes and patient selection for advanced treatment options and (b) newer computed tomographic (CT), MR imaging, and ultrasonographic (US) diagnostic markers for assessment of ICA vulnerable plaque and stroke risk. The articles chosen have emphasized trends in physiologic mechanistic imaging (as distinct from anatomic structural imaging), underscoring advances in postprocessing, validation, and standardization of newer radiologic techniques. Although many of the selected reports are too recent to have established themselves as widely cited “enduring classics,” they are nonetheless notable for highlighting priority areas of ongoing stroke research likely to have high clinical impact. Many of the articles serve to address contentious and as yet unsolved issues, as well as to identify gaps in knowledge and new areas of investigation that have arisen in the past 5–7 years (3).



Video

SAM Online Edition and Tablet Edition of *Radiology Select* include a video with David F. Kallmes, MD (moderator), Michael H. Lev, MD, Catherine M. Phan, MD, and Rajiv Gupta, MD, PhD.

Historical Perspective

Before the introduction of CT in 1974, brain imaging required invasive pneumoencephalography or catheter-based arteriography, with the latter typically performed by means of direct carotid puncture. Since the widespread adoption of CT as an essential imaging tool in the late 1970s, numerous frequently cited manuscripts tracking the development of a variety of other CT, US, MR imaging, and catheter-based methods for cerebrovascular evaluation have appeared in *Radiology*.

The earliest CT investigations, of necessity, focused on subacute and chronic stroke diagnosis, not only because of logistic and scanner speed limitations but also because acute interventions that could alter patient management were not yet available to motivate rapid assessment. Early clinical studies compared the accuracy for stroke detection of first-generation CT scanners with that of existing modalities (including nuclear medicine and angiography) (4–6), but it took another 10 years for the critical acute unenhanced head CT findings of obscuration of the lentiform nucleus and insular ribbon to be reported (7,8). Although as long ago as 1980, authors anticipated the value of coronal and sagittal reconstruction of cranial CT scans for improved lesion conspicuity, the thick axial sections with poor z-axis resolution made clinical implementation impractical at that time (9).

Even more farsighted were early descriptions of CT perfusion imaging (10,11). It was not until the start of the 21st century, however, that both the level of technology and the clinical need made it feasible for acute stroke CT perfusion imaging to become a routine diagnostic test (12–14).

The evolution of MR imaging has also been featured in *Radiology*. Ischemic stroke detection was reported in cats in 1982 (15) and in humans in 1983 (16,17), followed by gadolinium-enhanced stroke evaluation in 1986 (18) and three-dimensional volume MR angiography of the circle of Willis in 1989 (19). More recent technical advances of great potential value in cerebrovascular evaluation include correlative positron

emission tomographic (PET) examinations performed by using dedicated dual PET/MR systems (20), MR microscopy with 7-T very high magnetic field strength units (21), susceptibility-weighted imaging (22), and resting-state functional MR imaging (23).

Discussion of Selected Manuscripts

Unenhanced CT, Dual-Energy Scanning

Food and Drug Administration approval in 1996 of intravenous thrombolytic treatment for acute stroke within 3 hours of onset brought the role of imaging for patient selection to the forefront. To this day, unenhanced head CT to exclude hemorrhage remains the standard of care for intravenous thrombolytic agent administration (24). Indeed, the 1997 *Radiology* article “Acute Stroke: Usefulness of Early CT Findings before Thrombolytic Therapy” has been widely cited (25). Other investigators expanded on this theme in attempts to improve the accuracy of acute stroke detection—for example, by optimizing display settings on picture archiving and communication system monitors (26).

Dual-energy CT, although first proposed soon after the invention of CT in the 1970s (27), has only recently become a clinical reality and, together with multidetector CT angiography and iterative reconstruction techniques, represents one of a few new truly paradigm-shifting advances in CT since Hounsfield’s development of filtered back projection. With dual-energy CT, atomic number can be directly calculated (unlike conventional CT, for which the gray scale reflects only a single parameter, attenuation). Thus, dedicated iodine, calcium, or water images can be created, effectively allowing tissue characterization with CT analogous to that of MR imaging. Clinically, such images could be used for bone subtraction, optimized three-dimensional CT angiography and CT perfusion reformatting, creation of “virtual” unenhanced and monochromatic images from contrast agent-enhanced CT data sets, and reduction of beam-hardening artifacts and to distinguish hemorrhage from calcium

and from contrast enhancement in diagnostically challenging cases.

In the first article selected for this collection, Gupta et al (28) report on the use of dual-energy technology to distinguish hemorrhagic conversion from routine parenchymal contrast blush after endovascular stroke therapy—an essential clinical distinction that cannot routinely be made, even by using advanced MR techniques (29).

CT Angiography

The advent of multidetector CT made possible rapid low-cost CT angiography of the neurovascular system. Head CT angiography had the additional advantage of not only accurately depicting major vascular stenoses and occlusions, but also, by using the same CT angiographic source image data set, providing perfusion-weighted contrast-enhanced whole-brain parenchymal images (12). Indeed, in the next article, Camargo et al (30) show that CT angiographic source images, compared with unenhanced CT scans, are more sensitive for detection of early irreversible ischemia and more accurate for prediction of final infarct volume.

Because much of the morbidity and mortality of acute stroke can be attributed to cardiac embolic sources, there has also been strong recent interest in using cardiac CT angiography to non-invasively detect left atrial thrombus (31) and patent foramen ovale (32, 33), rather than the reference standard, transesophageal echocardiography (TEE). Hur et al (34) reported favorable sensitivity and specificity of CT angiography relative to TEE. More recently, Boussel et al (35) have proposed a combined neurovascular/cardiac CT angiography protocol for rapid, efficient, single-session multidetector CT angiographic workup of acute stroke.

CT Perfusion and Multimodal Imaging

Although diffusion-weighted MR imaging remains the reference standard for emergency determination of infarct core (ischemic tissue likely to be irreversibly infarcted despite early, robust recanalization), CT perfusion, with its relative availability, low cost, and speed, has increasingly been recommended for aid in the diagnosis and characteriza-

tion of acute stroke, transient ischemic attack, carotid occlusive disease, and vasospasm, especially when MR imaging is unavailable (36,37). CT perfusion has also been applied as a biomarker to help predict functional outcome in patients with severe head trauma (38) and to estimate the risk of hemorrhagic transformation in acute stroke (39).

A major concern for both CT perfusion and perfusion-weighted MR imaging has been the validation and standardization of technique across different acquisition and postprocessing platforms from different vendors and with the use of different algorithms. These issues are addressed by Kudo et al (40) in their important study and discussed at length in the accompanying review (41).

Not surprisingly, given the need for rapid assessment and treatment of acute stroke patients ("time is brain"), there has been strong interest in integrating CT, CT angiography, and CT perfusion into a comprehensive stroke imaging protocol that can be accomplished in a single session ("one stop shopping"). This concept is nicely introduced by Kloska et al (42) and is brought up to date by Hopyan et al (43).

MR Imaging Penumbra Markers for Outcome Prediction and Patient Selection

Mismatch between Diffusion-weighted and Perfusion-weighted Imaging

Diffusion-weighted imaging is the reference standard for emergency evaluation of infarct core (44–46). Together with perfusion-weighted MR imaging measurement of the "at-risk" penumbra (critically ischemic but potentially salvageable tissue likely to infarct in the absence of early robust reperfusion), the concept of the diffusion-weighted/perfusion-weighted imaging "mismatch" has been widely applied as a potential selection tool for identifying patients most likely to benefit from (and least likely to be harmed by) advanced stroke treatments administered outside established time windows. An early report by Edelman et al (47) described cerebral blood flow assessment by using dynamic contrast-enhanced T2*-weighted pulse sequences. A 1996

landmark article by Sorensen et al (48) introduced the mismatch concept.

More recently, in a report on a major multicenter study, the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) study, Marks et al (49) suggested that the diffusion-weighted/perfusion-weighted imaging mismatch might help to predict clinical outcome in patients with recanalization treated with intravenous thrombolysis 3–6 hours after symptom onset. Despite this, the use of the mismatch for patient selection has yet to be validated in a large prospective randomized trial, and there remains much controversy not only as to the optimal parameter (and threshold) with which to measure "penumbra", but also—as highlighted by Copen et al (50)—with regard to how long the mismatch (and, hence, penumbral tissue) persists in the setting of a proximal occlusion in the circle of Willis.

Arterial Spin Labeling

Many patients with signs and symptoms of acute stroke at the time of presentation have poor or unknown renal function. Given recent concerns regarding gadolinium-based contrast administration and the risk of nephrogenic systemic fibrosis in this cohort, a rapid reliable technique for determining cerebral perfusion would be a welcome addition to the stroke imaging armamentarium. Arterial spin labeling (ASL) is such a technique (51–53).

Recently, Zaharchuk et al (54) reported that ASL may reveal hemodynamic abnormalities not detectable on perfusion-weighted images. Bokkers et al (55) used ASL to measure cerebrovascular reserve in response to acetazolamide challenge in patients with symptomatic ICA stenosis.

Other Physiologic "Penumbra" Imaging

Many other non-ASL techniques for determining potentially salvageable ischemic tissue at risk, without the use of intravenous gadolinium-based contrast agents, have been proposed. (57–59). A substantial percentage of acute stroke patients have an unknown symptom-onset time, making them ineligible for intravenous thrombolytic therapy which must be administered within 3–4.5 hours of stroke ictus. An

important goal of advanced imaging is to expand eligibility in this cohort. Petkova et al (60) suggested that this might be accomplished by using the signal intensity on fluid-attenuated inversion-recovery MR images as a surrogate marker of stroke age.

Finally, cerebral hyperperfusion syndrome is a feared complication of carotid endarterectomy in patients with longstanding severe ICA stenosis. Murakami et al (61) suggest that brain temperature measured with MR spectroscopy may help identify patients at highest risk.

Novel Imaging Markers for Carotid Artery Vulnerable Plaque and Stroke Risk

US and MR Imaging of Vulnerable ICA Plaque

The degree of ICA origin stenosis is a well-established biomarker for stroke risk: A greater-than-70% stenosis is considered an indication for endarterectomy or stent implantation rather than continued maximal medical therapy. The mechanism of carotid artery strokes is embolic. The endothelial surface of a denuded or ulcerated atheromatous plaque releases tissue factors that, in an area of sluggish turbulent blood flow adjacent to a severe stenosis, serves as a nidus for platelet-fibrin-red cell clumping, causing formation of emboli that can subsequently propagate through a patent ICA to lodge in a proximal branch of the circle of Willis (typically the middle cerebral artery), causing a stroke (62).

Although the percentage of ICA stenosis remains the most important clinical determinant of embolic ICA stroke risk, there is increasing evidence that this risk can be further stratified on the basis of the histologic characteristics of the plaque, the so-called plaque vulnerability (63). Pertinent findings include inflammatory changes associated with contrast enhancement and neovascularity of the overlying vasa vasorum, intraplaque hemorrhage, and fibrous cap thinning or ulceration (64).

On US studies, hypoechoic plaque and late-phase contrast enhancement are signs of plaque vulnerability (65–69).

Analogous findings can be demonstrated with MR imaging and can be used to accurately monitor serial changes such as response to lipid lowering therapies (70,71). Astor et al (72) studied over 2000 patients to determine that ICA luminal narrowing occurs when carotid wall thickness exceeds 1.5 mm, suggesting “that the carotid arteries are able to compensate for a greater degree of thickening than are the coronary arteries.”

That intraplaque hemorrhage is associated with emboli is suggested by correlation with white matter lesions (73, 74). Importantly, highly vulnerable plaque with intraplaque hemorrhage can occur in symptomatic patients with even mild ICA stenosis (<50%) (75).

Conventional Arteriography: Neurointerventional

Although CT angiography has largely replaced conventional arteriography for routine diagnostic screening of cerebrovascular disease, digital subtraction arteriography (DSA) remains the reference standard for definitive characterization of aneurysms, arteriovenous malformations, and vasculitis, as well as a prerequisite for neurointerventional procedures. The qualifications required to perform cerebral arteriography are nicely outlined by Connors et al (76).

The potential complications of DSA must always be weighed against the anticipated diagnostic and therapeutic benefits (77, 78). That microemboli sufficiently large to cause lesions seen on diffusion-weighted MR images are common—even in “routine” interventional cardiac procedures—was nicely demonstrated by Busing et al (79), who showed that “asymptomatic cerebral infarction following cardiac catheterization occurred in 15% of patients in whom duration of the procedure was significantly longer than in those without infarction”.

Carotid artery stent implantation has been another frequent topic in the pages of *Radiology* (80). Early reports, such as that from Groschel et al (81), helped to establish procedural guidelines—including the potential benefits of statin administration—that could assist in the design of prospective clinical trials.

Societal and Cost-effectiveness Analyses

Given the current interest in utilization review and appropriateness criteria, *Radiology* has served as a valuable forum for cost-effectiveness and outcome studies in general (82,83), and for comparisons among various screening imaging modalities for the evaluation of carotid artery stenosis and stroke risk in particular (84–88).

Pediatric Stroke

Two important themes of the pediatric stroke studies published in *Radiology* over the past decade are sickle cell disease and perinatal ischemic and traumatic hemorrhagic injury (89–93), and these areas are highlighted in this issue of *Radiology Select*.

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