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Catheter Angiography Is Still Necessary for the Measurement of Carotid Stenosis

What is the role of noninvasive imaging tests such as MR angiography (MRA), Doppler sonography (DUS), or computed tomographic angiography in the diagnostic evaluation of patients with suspected carotid stenosis? Can they be used instead of conventional angiography to identify candidates for surgery? Should they be used as screening tests to limit conventional angiography to those with a high likelihood of significant stenosis or an uncertain degree of stenosis, as suggested by Hatout et al in this issue of the *AJNR?* Is a combination of noninvasive tests better than one alone? The answers to these questions are not entirely clear and will vary from one practice to another.

For historical and scientific reasons, the measurement of luminal diameter narrowing by conventional angiography remains the single validated method for the identification of candidates for surgical carotid endarterectomy (CEA). All three pivotal multicenter randomized trials of CEA—the North American Symptomatic Carotid Endarterectomy Trial (NASCET [1]), the European Carotid Stenosis Trial (2), and the Asymptomatic Carotid Atherosclerotic Study—used luminal diameter narrowing by conventional angiography as enrollment criteria (3). Furthermore, in NASCET, the degree of stenosis by angiography correlated with increased risk of stroke with medical therapy (1). Cross-sectional area reduction, increased blood velocity, intraplaque hemorrhage, and the presence of plaque ulceration may all be related to stroke risk as well, but the use of these features to select patients for surgery has not been established in a randomized clinical trial.

Consequently, the use of noninvasive modalities in lieu of conventional angiography must be guided by two kinds of data. First, validation studies of the accuracy of these methods for the detection of luminal diameter narrowing as compared with conventional angiography must be performed. It is critical to note that these studies must be done on an individual institutional or machine basis: one cannot assume that published data reflect the performance of any individual Doppler laboratory or MR imager (4). In addition, for any given method, particularly DUS, the accuracy of different threshold values should be tested for different applications. For example, one threshold velocity value may be optimal for screening out patients with $<70\%$ stenosis and another for the detection of patients with $>70\%$ stenosis. Second, because none of these tests will have 100% accuracy, cost-effectiveness studies must be performed (5). These studies examine the trade-off between the reduction in costs and risks of stroke with angiography versus the added costs and risks of surgery in patients who have false-positive noninvasive studies and the costs and risks of stroke in the patients with false-negative studies.

The literature is full of validation and cost-effectiveness studies in this area, yet no clear consensus has been developed. A problem with many validation studies has been bias—including publication bias (only good results are published) and verification bias (only positive studies will be confirmed by angiography). The problem with many cost-effectiveness studies is their critical dependence on the assumptions and data that are fed into their mathematical models—accuracy of the noninvasive methods, risks of angiography and surgery. These data will be locally variable, and therefore the extent to which the data from any published study is applicable to any given institution or practice will be variable.

The decision on what combination of imaging methods should be used for the diagnosis of carotid stenosis must be based on locally generated data, including the risk of stroke with angiography, the accuracy of locally available noninvasive methods, and, to some extent, the risks of surgical or endovascular treatment. Another important factor in this decision is whether the patient is symptomatic. The penalty for a false-negative study in a symptomatic patient is much greater, in terms of stroke risk, than for an asymptomatic patient. For example, the noninvasive diagnosis of occlusion in an asymptomatic patient does not require conventional angiography for confirmation, given the very low risk of stroke with medical therapy even if this was actually a high-grade stenosis. The possibility of a high-grade stenosis in a symptomatic patients, on the other hand, should be pursued with conventional angiography, because the risk of stroke at 2 years with medical therapy may be as high as 30% (1).

In many practices, it may be reasonable to use DUS, MRA, or both to screen patients before angiography, provided that the local accuracy of these tools has been established. For DUS, this will require the identification of the optimal velocity screening thresholds. We adopted the use of DUS for this application at our institution after an extensive validation study (6). In addition, as shown Hatout et al in this issue of the *AJNR,* a well-validated noninvasive method may also allow the accurate diagnosis of severe stenosis. The degree of stenosis by gadolinium-enhanced MRA had a 95% confidence level of $\pm 13.6\%$. Consequently it would appear to be reasonable to proceed with intervention at their institution with a gadolinium-MRA measurement of 80% or greater. At their institution, the accurate diagnosis of carotid stenosis for patients with $>50\%$ but $<80\%$ stenosis by MRA requires conventional angiography.

Despite the lack of strong data validating a com-

pletely noninvasive method to the selection of patients for CEA, many institutions have adopted this approach. There may be other factors driving this development, beyond the intent of reducing the costs and risks associated with angiography. MRA and DUS tend to overestimate stenosis. A complete reliance on these tests will likely increase the volume of CEA performed at a given institution, with a reduction in per-patient costs. This will be profitable to the hospital and vascular surgeon. Furthermore, conventional angiography is time and physician intensive. In many busy practices, it may be more efficient and profitable to keep the radiologist in the reading room interpreting noninvasive studies than tied up in the angiography suite.

In conclusion, the use of noninvasive carotid imaging tools to limit the use of conventional angiography in patients with possible carotid stenosis can be justified in some situations. These applications include both screening out patients with minimal stenoses or complete occlusion from further evaluation and identifying patients with high-grade stenosis as candidates for intervention. The appropriateness of these two applications, however, requires rigorous validation of the local accuracy of the noninvasive approach. In addition, whether the patient is symptomatic must be taken into consideration. The patients in the middle range still require conventional angiography for the accurate measurement of stenosis, to make appropriate treatment decisions. Angiographic complication rates, however, must be within acceptable limits.

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The Promise of High-Field-Strength MR Imaging

The application of MR imaging in medicine and basic research has seen a steady growth in the field strength of the magnets. Subsequent to the installation of the first few high-field-strength (ie, $\geq$ 3T) systems, which were mainly developed for improved MR spectroscopy, functional MR imaging (fMRI) became the dominant driving force behind their proliferation. It was quickly recognized, however, that numerous other MR applications could benefit substantially from the increased field strength, and there are now several 7T systems either running or at some stage of being brought on-line. In addition, an 8T system has been operational for several years, and there are even plans underway for the installation of 9.4T and higher human systems. These high-field-strength systems are at the leading edge of technology development in MR applications, and they are proving to be well worth the effort. This proliferation of high-field-strength magnets has led to improved applications in just about every area of MR, from basic science research laboratories to the clinic. Indeed, it is expected that within the next few years 3T scanners could account for more than a quarter of the clinical MR market.

The reasons for this continued advance in field strength are many. One of the most obvious benefits is improved signal-to-noise ratio (SNR). The intrinsic SNR scales linearly with static magnetic field (1), but in reality the actual SNR achievable is somewhat lower than the intrinsic SNR gain, mainly because of hardware limitations. It is expected that these limitations will be overcome with further research and that the full improvement in SNR obtainable with higher field magnets will eventually be realized.

Many other areas of improved MR applications are evident in relation to increased magnetic field strengths. One of these can be found in the improved applications of contrast reagents, because, as the field strength increases, the detection threshold decreases. This is a strong effect with no real theoretical limit and has significant implications, particularly in the emerging field of molecular imaging.

Another more obvious advantage of high-field-strength MR is the enhanced measurement of susceptibility-induced relaxation, which has led to improvements in fMRI. Not only does the contrast-to-noise ratio improve, but the spatial definition of the signal intensity also improves.

We also expect major advantages in high-field-strength applications to spectroscopy (2). Spectroscopy at high field strengths is enhanced by the increase in SNR, and higher field strengths afford improved spatial resolution in spectroscopy. Finally, increased spectral dispersion will provide more reliable quantification and additional sensitivity gains.

The article by Dasher et al in this issue of the *AJNR* points to yet another area of improved MR applications afforded by high-field-strength magnets, namely, the significant improvement attainable in spatial resolution and contrast. In their report, the

authors present MR images acquired at 8T of the microvasculature of the live human brain as well as the embalmed and unembalmed postmortem human brain. The ability to identify the microvasculature in human brain at a resolution that allows close comparison to histology has significant implications in many fields of CNS disorders and specifically in the treatment of reperfusion injury and in the physiology of solid tumors and angiogenesis. There is every reason to believe that our continued efforts to push the envelope of high-field-strength applications, like the examples presented in Dasher et al's article, will open new vistas in what appears to be a never-ending array of basic science research and clinical applications.

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Neuroethics in a New Era of Neuroimaging

Although investigations about brain, mind, and behavior date back to the ancient philosophers, a new discipline called *neuroethics* has emerged formally only during the past year to embody theoretical and practical issues in the neurologic sciences that have moral and social consequences in the laboratory, in health care, and in the public domain. The first specific references to neuroethics in the literature were made a little more than a decade ago. They described, for example, the role of the neurologist as a neuroethicist faced with patient care and end-of-life decisions (1) and philosophical perspectives on the brain and the self (2). As a discipline, per se, neuroethics was launched in a conference sponsored by the Dana Foundation called "Neuroethics: Mapping the Field" held in San Francisco in May 2002 (3). Bringing together approximately 150 neuroscientists, scholars in biomedical ethics and the humanities, lawyers, public policy makers, and representatives of the media, the conference emphasized four major areas of emphasis: "Brain Science and the Self" (or "Our View of Ourselves") devoted to issues of human freedom and responsibility, the biologic basis of personality and social behavior, choice and decision-making, and consciousness; "Brain Science and Social Policy," including issues of personal and criminal responsibility, true and false memory, education and theories of learning, social pathology, privacy, and the prediction of future brain pathology; "Ethics and the Practice of Brain Science," spanning topics of pharmacotherapy, surgery, stem cells, gene therapy, neuroprosthetics, and parameters for guiding research and treatment; and "Brain Science and Public Discourse," including the development of broad and informed public discourse, mentoring of young trainees, and encouragement of responsible understanding and reporting in the media.

The ethical challenges introduced by advanced capabilities in neuroimaging were recognized as a priority for the new discipline, taking into consideration significant concerns and potentially thorny issues that have surfaced both in research and in the clinical environment. The research imaging issues are the focus of the present editorial; clinical neuroethics issues will be the focus of a forthcoming *AJNR* editorial.

Functional Neuroimaging: Behavior, Reasoning, Thought

In a recent report, Illes et al (4) provided empirical validation of the expanding terrain of brain imaging studies by using measurements of regional blood flow from functional MR imaging. Through an analysis of the more than 3400 peer-reviewed papers examining the application of functional MR imaging, alone or in combination with other neuroimaging modalities in the decade between 1991 (the genesis of functional MR imaging) and 2001, a steady growth in studies with evident ethical and social implications was shown. These included studies of social attitudes, human cooperation and competition, brain differences in violent people, religious experience, genetic influences, and variability in patterns of brain development.

Imagine, for example, a moral reasoning experiment in which you could choose to save the lives of five people on a runaway trolley car by pulling a switch to send it on an adjacent track where one person stands (and who would not survive) (5). Alternatively, you could choose to push one of the people off the trolley and on to the track, thereby blocking the movement of the trolley and saving the remainder of the group. Most people respond that the "switch" option is morally acceptable, while the "push" option is not (6). Functional MR imaging studies of healthy adult participants engaged in resolving such dilemmas (5), making decisions about statements that have moral content (eg, "The judge condemned the innocent man" or "The elderly are useless") versus neutral content ("The painter used his hand as a paintbrush") (7), or making decisions about race and stereotypes (8) have begun to probe such uniquely human processes and have pushed the envelope well beyond the lines of where neuroradiology and cognitive neuroscience have traditionally intersected.

Extending well beyond cortical maps of sensorimo-

tor function, language, and attention, maps that include the medial frontal and orbitofrontal gyri, posterior cingulate gyrus, angular gyrus, amygdala, and fusiform area for moral reasoning, emotion and judgment—arguably among the deepest forms of human thought—have now been described. No doubt, the diagnostic and predictive validity for real-world behaviors, especially those that are potentially value-laden or culturally determined, is still unsolved (8). However, as functional MR imaging and other advanced neuroimaging technologies continue to mature, the issue of validity becomes steadily addressed (10). Therefore, with a growing regard for the novelty and breadth of information that neuroimaging can deliver about the complexity of human behavior, ethical concerns regarding the potential data misuses or abuses have come to the foreground. These range from the creation of a personal sense of stigma to discrimination in health coverage or employment.

The prima facie question for advanced neuroimaging, in fact, is moral and social acceptability of research topics and study design. We must ask, for example, whether all studies of normative neurobehavioral phenomena are ethically acceptable. How might social or racial biases affect applications of the technology, the conditions under which imaging is performed, or the way interpretations are made? What does a statistically normal activation pattern of *moral behavior* really mean, and, by extension, what would the implication of an *abnormal* brain activation pattern be in a healthy person normally (ie, within predicted behavioral or physiological norms) performing a task that involves moral judgment, deception, or even sexual responsiveness (11)? Dilemmas posed by incidental findings of structural anomalies in medical research have been raised in the past and have surfaced recently for research MR images specifically (12, 13). However, incidental findings of *functional* anomalies may give rise to an entirely new kind of challenge related to both the interpretation and appropriate use of data. Ensuing questions relate to what protocols may need to be put in place for the discovery of such findings and how (or if) they should be communicated to a participant (14, 15). It is imperative to consider the clinical significance of a finding, what a participant would want to know, and the risks of inadvertent disclosure or exploitive use of such information. Although one may debate whether these risks are significant, in this century marked by technological innovation and a society quick to embrace high technology, it would be imprudent to think that they do not exist at all. Just as the regulations of the new 2003 Health Insurance Portability and Accountability Act extend The Belmont Report principles and guidelines for the protection of human participants in research, what will protect the quantitation of human thought in 2010?

In 1932, Aldous Huxley wrote in *Brave New World* (16), "The ethical issues raised by. . . feats of human engineering are qualitatively no different from those we shall have to face in the future. The difference will be quantitative: in scale and rate. Even so, the individual steps may still go on being so small that none of them singly will bring those issues forcibly to light: but the sum total is likely to be tremendous. That is why we have to look for those issues now. . . "

We have, in fact, entered an era in which issues surrounding the *ethics of neuroimaging* and the *neuroimaging of ethics* (ie, ethical reasoning and behavior) are now both at hand (17). Neuroradiologists have a vital role to play in identifying the issues as the new discipline of neuroethics continues to evolve and in ensuring that the enthusiasm for and benefits of neuroimaging information outweigh associated risks in any of the areas in which neuroimaging may be used practically. Knowledge harnessed from lessons of the past in genomics and other areas of biomedical research, and from the multidisciplinary perspectives of all stake holders, can provide essential information for delineating priorities for neuroimaging and ethics in research and education for the short term and for the allocation of sustainable resources and infrastructure over the long term.

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The Need for a West Nile Virus MRI Registry

West Nile virus (WNV) infection was first recorded in North America in 1999 in the vicinity of New York City. By December 2002, the infection had been reported in most U.S. states and several Canadian provinces. Each year, from 1999 through 2001, there were fewer than 70 hospitalized cases in the United States, with the mortality rate varying from approximately 9% to 16%. In 2002, however, a large outbreak of WNV infection occurred in the United States, with more than 4,000 serologically confirmed cases and 277 deaths. Substantial numbers of patients with severe neurologic disease were reported in outbreaks of WNV infection in previously known endemic areas (Romania, 1996; Russia, 1999; Israel, 2000).

Sporadic reports of small numbers of WNV cases have noted a variety of MR imaging findings. One early report noted periventricular white matter T2 focal areas of hyperintensity and meningeal contrast enhancement (1). In a recent single-case report, Rosas and Wippold noted bilateral T2 hyperintensities within the basal ganglia and thalami. No hemorrhage was noted within these lesions, and no meningeal abnormality was reported (2).

The WNV is a flavivirus closely related to the viruses causing central nervous system infection in St. Louis, Japanese, Kunjin, and Murray Valley encephalitis. Among these encephalitides, only Japanese encephalitis has been reviewed for imaging findings in case reports with moderately large numbers of patients (3, 4). Hemorrhagic lesions of the cerebral basal ganglia and thalami were frequent MR imaging findings in Japanese encephalitis. St. Louis encephalitis is a recurrent seasonal infection in the southern United States, but MR imaging findings of substantia nigra signal intensity abnormality are noted in only one case report (5). Descriptions of MR imaging findings in some other varieties of encephalitis with seasonal occurrence in the United States are scarce to nonexistent. Einsiedel et al recently reported the imaging findings in a single case of Murray Valley encephalitis with severe neurologic disease involving the brain and spinal cord. High signal intensity lesions on T2 sequences were noted in the thalami, substantia nigra, red nuclei, reticular formation, and the cervical spinal cord. No hemorrhage was reported, but the authors considered the distribution of the lesions to be similar to that of Japanese encephalitis (6).

Many of the patients with WNV encephalitis in the 2002 epidemic in Louisiana were treated at rural or small urban hospitals. CT scanning was sometimes the only available diagnostic imaging study. Magnets of a variety of field strengths were used, when locally available, frequently for only one brain scan early in the course of the disease. Almost all of the CT scans and many of the MR imaging brain scans were considered normal. Nine patients with MR imaging scan abnormalities each had distinctly different findings. A fatal case presented with diffuse high T2 signal intensity in the vermis and cerebellar white matter, putamina, and adjacent white matter but no evident involvement of the thalami. Another patient presented with focal cerebral white matter lesions, some with restricted diffusion, closely resembling multiple sclerosis. Clinical detection of Parkinsonian tremor and sometimes flaccid paresis occurred in some patients with coincident apparently normal CT scans and MR images of the brain and cervical spine. Subsequent follow-up MR imaging in some but not all patients with Parkinsonian features showed T2 high signal intensity abnormalities in the cerebral basal ganglia and thalami. Imaging experience in WNV infection has confirmed what was already known in the study of patients with a variety of encephalitides. CT lacks the sensitivity for detection of some pathologic findings. In a case report at RSNA 2002, Butman noted progressive MR imaging findings in the basal ganglia, thalami, pons, and dentate nuclei in serial MR imaging scans over a period of 5 weeks. The first MR imaging scan obtained soon after the onset of the illness was considered normal (7).

Some observations on the imaging of WNV meningoencephalomyelitis are possible. Fluid-attenuated inversion recovery MR imaging, diffusion-weighted, and T1 post–intravenous contrast sequences are most useful in the detection of disease. A gradient echo sequence may assist in the detection of hemorrhage in lesions. Serial MR imaging scans over an interval of several days to weeks may be necessary to show any abnormality and can document developing and changing scan findings. Hypertension or diabetes in elderly, debilitated WNV patients may be causes of focal cerebral white matter microvascular ischemic changes (leukoaraiosis), which could be similar to WNV white matter disease. A previous MR imaging brain scan could be essential for comparison in correctly assessing scans obtained in such patients with WNV infection. Positron-emission tomography and molecular imaging are potentially useful future diagnostic tools that may extend further the margins of disease detection and possibly provide earlier diagnostic findings in the study of encephalitis.

A WNV MR imaging registry has been established

by the Centers for Disease Control and Prevention, in Atlanta, and the Louisiana State University Health Sciences Center, in New Orleans. It is hoped that the registry data will provide comprehensive information on the imaging characteristics of WNV infection. Parallel studies of other varieties of encephalitis may be possible. All scans sent to the registry are rendered anonymous. The original scan annotated data are deleted, and a scan is identifiable only by a randomized number. The scan images are reviewed independently by three experienced neuroradiologists on a fully secure universal picture archiving communication system system. All scan findings are systematically tabulated for statistical analysis. The submission of scans to the WNV registry does not affect the use of such cases by contributors in scientific case reports and publications. The contributors to the registry will be acknowledged in any future publications resulting from the registry data.

Physicians who are aware of patients with laboratory-confirmed WNV infection who have had MR imaging scans are asked to contact the WNV MR imaging registry at westnile@unipacs.com.

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