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Applying Functional MR Imaging to Brain-behavioral Research: Can We Do Better than Simple Clinical Measures?

Ajax E. George and Soonmee Cha

AJNR Am J Neuroradiol 2000, 21 (4) 619-620
<http://www.ajnr.org/content/21/4/619>

This information is current as of June 16, 2024.

Comparisons between Carotid Duplex Sonography and Cerebral Angiography in Assessing the Degree of Carotid Stenosis

In the article *Overestimation of Carotid Stenosis on Angiography: Potential Carotid Doppler Bias* in this issue of the *AJNR* (page 639), Dix and Skrocki compare a number of aspects of carotid stenosis quantification. The angiographic interpretation of percent stenosis on initial assessment performed between 1993 and 1998 was compared with an organized retrospective look at those same studies. The second look was done with the readers blinded to the previous angiographic and sonographic findings. The initial angiography had been performed with knowledge of the sonographic results, which formed part of the clinical information leading to the angiography. Additionally, percent stenosis estimations were assigned from duplex data retrospectively according to the criteria of Bluth (1).

Various comparisons of new and old readings of both angiography and duplex sonography form the body of results. The conclusions are interesting: if the duplex study suggested more trivial stenosis, the angiographic interpretations were reasonably concordant. If the duplex study suggested greater than 60% stenosis, however, the original angiographic interpretation assigned a stenosis degree about 16% ($P < .05$) greater than that assigned during the recent blinded rereading. The authors concluded this was due to some bias prompted by the knowledge of the sonographic interpretation at the time of the original angiography. The final conclusion—radiologists must use strict criteria for measurement of stenosis to avoid inherent bias.

It is difficult to criticize a study that comes to the important conclusion that one should beware and use precise criteria for quantification, especially where carotid stenosis is concerned. Nonetheless, there are possible explanations for these results in addition to those offered by Dix and Skrocki. In the years since the first North American Symptomatic Carotid Endarterectomy Trial (NASCET) publication, the ambiguities and controversies of carotid stenosis measurement have had a great deal of airing in the radiologic, neurologic, and surgical communities and literature. Much of the problem stems from the anatomic aberration of the carotid bulb, the site of so much occlusive disease and almost twice the diameter of its outflow artery, the cervical internal carotid. Prior to these discussions in the literature, the manner of stenosis calculation by various practitioners and groups received little attention. Since then, published discussions have tried to put forth evidence regarding which of numerous ways is best to measure stenosis, and how to translate accurately the results of important studies such as those of NASCET into new ways of assessing carotid disease.

It is likely that the original angiographic interpretations, upon which this study by Dix and Skrocki is partly based, were done with less consideration for the way NASCET assessed stenosis from angiograms. In other words, for the formal retrospective blinded reading, performed specifically for this current investigation, there must have been more awareness of both the specific methods used for NASCET and the debates in the literature than there would have been at the time of the first clinical reading. If this is correct, then a different set of scores closer to those from NASCET would have been expected the second time. This potential bias in the study is not addressed, and is certain to be present to some degree. The flurry about stenosis measurements in the literature, started at the time of the NASCET report in 1991, has grown over the years and continues today. Therefore, have the angiographic scores changed because the angiographers did not have the duplex results to bias them, or have the readers actually changed their own paradigms to try to emulate the measuring techniques of NASCET? Perhaps they have always ignored duplex results when performing angiography, but now the paradigms for stenosis measurement have changed.

It is not surprising that there were differences between the duplex results and the angiographic assessments for these cases. The authors list many reasons for this in their discussion. Perhaps the most important reason for the inconsistent results was the criteria used for the designation of percent stenosis by duplex sonographic parameters, the criteria of Bluth (1). In 1988, Bluth performed an extremely diligent, thorough examination and integration of different aspects of both Doppler and B-scan image parts of duplex sonography. There are multiple ways of deriving percent carotid stenosis; Bluth compared the narrowest part of the stenosis to the diameter of the adjacent bulb wall on transverse sonographic images. This method is very different from that of NASCET, and will produce very different numbers. NASCET compared the diameter of the stenosis to the diameter of the normal internal carotid well beyond the bulb, where the walls are parallel and often half the diameter of the bulb. We cannot expect the final numbers to be the same when the measurements of different structures are used in the calculation.

It is interesting that many sonographic machines have been loaded with software to calculate percent stenosis based on various important, correlative series of the 1980s that helped to establish duplex sonography as an important test for patients with this condition. Whereas there is logic to each of the ways of measuring carotid stenosis, the results of

both NASCET and the Asymptomatic Carotid Atherosclerosis Study (ACAS) are attached to one particular approach to measurement. Therefore, all those dealing with carotid stenosis who wish to use those results must be aware of how their numbers were derived. It is not surprising that the percentages for many duplex carotid studies do not match NASCET or ACAS measurements, especially if the percent stenosis numbers of sonography have been derived from calculations like those in the 1988 study (1), which used completely different ratio calculations for the original derivations.

Near occlusions of the carotid are recognized by Dix and Skrocki as a case when the distal carotid artery should not be measured for stenosis calculation, because the disease has caused a decrease in its size (2). Whereas high-level, modern color duplex studies can recognize near occlusions rather well (3), reliance on Doppler velocity parameters alone can yield misleading results as a stenosis progresses in severity beyond the high peak velocities of severe stenosis. Such worsening degrees of stenosis, through a decrease in pressures and flow that occur simultaneously with the decreasing carotid diameter in near occlusion, will produce decreasing levels of peak Doppler velocity.

Topics concerning how best to determine appropriate candidates for stroke prevention treatments

are extremely important and timely. This study by Dix and Skrocki addresses some of the ways to calculate percent stenosis, in order to relate to the results of clinical trials. This article adds another dimension to this topic, maintains interest in the problem of consistency of carotid stenosis measurements, and sets the scene for the continuing interest that carotid angioplasty and stenting add to reducing the risks of stroke disease.

ALLAN J FOX, M.D.

*London Health Sciences Centre
London, Ontario*

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Applying Functional MR Imaging to Brain-behavioral Research: Can We Do Better than Simple Clinical Measures?

In the impressive brain-behavior multidisciplinary study in this issue of the *AJNR* (page 621), Capizzano et al evaluated four study groups: demented patients with subcortical ischemic vascular disease (SIVD)(n = 11), demented patients with probable Alzheimer's disease (n = 18), a mildly cognitively impaired group with white matter disease (n = 14), and a healthy control group (n = 20).

The investigators derived imaging measures of brain structure including segmentation of brain into volumes of gray and white matter, CSF and white matter abnormalities, functional measures using ¹HMRSI, including derivation of *N*-acetylaspartate (NAA) and NAA/Creatine (Cr) ratios corrected for atrophy and tissue composition, and behavioral measures including the Clinical Dementia Rating and Mini Mental Status Exam.

Statistical methods confirmed several hypotheses. In the SIVD group, NAA and NAA/Cr in the cerebral cortex and white matter, but not in the hippocampus, were reduced independent of atrophy and tissue composition when compared with the control group, suggesting neuron loss or metabolic impairment in these regions. The presumed Alzheimer's group, but not the vascular group, showed decreased NAA/Cr in the hippocampus. Cortical NAA measures were inversely correlated with the

number of lacunes and with the volume of white matter disease.

This study underscores how very far radiologic research has come but also how very far it needs to go. Consider the following points:

1) The significant results in this article consisted of reductions in brain metabolites in the 10.25% to 12.64% ranges for the subcortical vascular dementia group. Similarly, the presumed Alzheimer's group showed 10.33% reduction in NAA/Cr when compared with the control group, and a similar reduction when compared with the subcortical vascular dementia group. Only NAA/Cr was significantly reduced in the Alzheimer's group, not NAA. Thus, the order of magnitude of the functional differences in this article, and in similar studies in the literature, is quite small.

2) Despite state-of-the-art measuring techniques, there were no significant correlations found between MMSE scores and either structural or metabolic changes for any of the groups studied. This is evidence of the low sensitivity of our measures.

3) Reduced NAA or NAA/Cr has also been reported in the frontal lobes of schizophrenic patients, the white matter of multiple sclerosis, St. Louis encephalitis, and traumatic brain injury patients, and the hippocampi of schizophrenic and epileptic patients. This is evidence of the low specificity of our measures.

4) Clinical measures alone, such as the widely used DSM-III-R criteria, have shown only 51% sensitivity, 66% accuracy, and high (97%) specificity in autopsy studies (1). In other words, clinical criteria apply to healthy subjects with great reliability, but for the diagnosis of demented patients can have the sensitivity of a coin toss. Thus, the typical radiologic experiment that attempts only to predict group membership (ie, is the scan that of a patient or a control subject) is further confounded by insensitive and inaccurate clinical measures.

Despite the above reservations, Capizzano et al have shown quite remarkable results that support, but do not prove, the hypothesis that in subcortical vascular dementia, the white matter lesions, notably lacunes, disconnect the cortex from the subcortical white matter. This accounts for the metabolite cortical deficits in the SIVD group, and not in the presumed Alzheimer's group. Nevertheless, the presence of coexisting Alzheimer's disease remains an issue the investigators acknowledge. We would like to propose the following study to address this question.

The presumed etiology of subcortical vascular dementia is small vessel occlusive disease. Functional radioisotope studies such as positron emission tomography and single-photon emission CT (SPECT), and functional MR imaging reports such as the current study, have shown decreases in cerebral blood flow, oxygen consumption, NAA, and NAA/Cr in subcortical vascular dementia. It would be very interesting to evaluate cortical function by using a cerebrovascular vasodilatory agent such as acetazolamide (Diamox) or CO₂ as a provocative test to evaluate cortical vascular reserve. In patients with SIVD, these vasoreactive agents may unmask the underlying hemodynamic reserve by showing decreased perfusion parameters when compared

with a normal brain. In normal subjects and in patients with Alzheimer's disease, there is increased blood flow after acetazolamide or CO₂ challenge. The effect of acetazolamide on regional cerebral blood flow was shown by Bonte et al (2), who demonstrated improved temporoparietal perfusion in presumed Alzheimer's disease patients following acetazolamide-challenged SPECT imaging; those with SIVD showed no change or decreased cerebral blood flow. This study could be performed using contrast-enhanced or unenhanced perfusion-weighted MR sequences such as dynamic susceptibility contrast imaging or arterial spin labeling techniques.

Potentially, functional MR imaging may prove to be useful because improved perfusion results in improved metabolite activity and NAA or NAA/Cr measures. Regardless of the method of measurement, acetazolamide-challenged MR imaging may provide valuable insights into the study of subcortical diseases such as SIVD and cortical diseases such as Alzheimer's disease.

AJAX E. GEORGE, M.D.
SOONMEE CHA, M.D.

*NYU Medical Center
New York, NY*

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