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one that goes beyond the specific topic of delayed injury in brain ischemia—is the important interplay between results in animal models and human findings. Certainly, the tremendous amount of work done in animal models, by groups all around the world, has vastly improved our understanding of acute cerebral ischemia. However, those conducting animal experiments have also learned from the human experience, and perhaps nowhere else are the shortcomings of seemingly good animal models so apparent as in the modeling of acute cerebral ischemia and its treatment. The best illustration may be the fact that more than 100 novel medications have been shown to be highly successful in the treatment of ischemia in animal models, and yet, each has failed to work in humans (2). Certainly, such experience highlights that, while animal models are essential, such models do not preclude careful clinical investigation—something to which we in neuroradiology are in an excellent position to contribute. Indeed, the observation of delayed injury after thrombolysis in humans seems to have sparked renewed interest in this area of study in

animal models; an example is the work of Li et al in this issue.

In short, animal models have a lot to teach us, but our observations in the clinic remain extremely valuable. Such interplay between the clinic and the laboratory should encourage all of us interested in the care of patients with stroke to continue our communications with each other, because we each contribute our own piece of information to solving the mystery of how to treat acute cerebral ischemia.

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Sources of Variability in Measuring Carotid Stenosis on Time-Resolved Contrast-Enhanced MR Angiograms

The assessment of proximal internal carotid stenosis by using magnetic resonance angiography (MRA) has been substantially improved with the addition of time-resolved contrast-enhanced (CE) techniques. In this issue of the *AJNR*, Remonda et al (pages 213–219) report findings from a large clinical series in which two-dimensional (2D) digital subtraction angiography (DSA) was compared with time-resolved three-dimensional (3D) CE MRA for the evaluation of carotid stenosis. A total of 120 patients were enrolled in the study; 240 sets of carotid bifurcation images were available. The image data sets were randomly presented, and two observers measured the stenoses independently. The CE-MRA measurements were then correlated with the DSA measurements. The correlation was excellent, with an overall sensitivity of 98% and specificity of 96% ($P < .001$). The authors performed the investigation over a 2.5-year period, collecting a large amount of imaging data and conducting a retrospective analysis. The study is particularly important because of the large sample size.

A difficult problem for any CE-MRA study is the difference in spatial resolution between DSA and CE MRA. In this study, the in-plane resolution of the DSA images was described as follows: 1024×1024 matrix, 33-cm field of view, and 0.320×0.320 -mm pixel size. By comparison, the time-resolved CE-MRA images were generated with an in-plane resolution of $1.0 \text{ mm} \times 1.5 \text{ mm}$, with a section thickness of 1.8 mm. Thus, the pixel size for the CE-MRA examination was 3–5 times that of the DSA studies.

Four separate CE-MRA image volumes were ob-

tained during the passage of the contrast agent bolus. Each acquisition was approximately 5 seconds in duration. The 3D data sets were converted into 2D maximum intensity projections (MIPs) with orientations similar to those of the DSA images. Depending on the projection, the MIP images showed the vascular anatomy with a resolution varying from 1.0×1.5 mm in the coronal plane to 1.5×1.8 mm in the sagittal plane.

Although this spatial resolution is impressive, I would like to comment on the challenges of measuring proximal internal carotid stenosis from MIPs derived from time-resolved CE-MRA studies. Consider the following situation: DSA and CE MRA are performed in a symptomatic patient. The patient is found to have a 70% stenosis, by using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method. In this example, let us assume that the internal carotid artery distal to the stenosis measures 6 mm, and the residual lumen at the level of the stenosis measures 1.8 mm. By using the imaging parameters described by Remonda et al and by estimating the average resolution of the MIP image as approximately 1.5×1.5 mm, the stenosis could be represented in three ways. If the stenosis is located near the center of one pixel, no partial volume effects would occur, and the stenosis would be correctly delineated. If the stenotic segment extends almost equally into two pixels, the signal intensity would be averaged over the two pixels, and each pixel would appear in the MIP image as part of the lumen. Thus, the lumen would be represented by two pixels instead of one. The resultant stenosis

would measure 3.0 mm, which is a stenosis of 50% according to the NASCET method. The simple inclusion of one additional pixel in the measurement may result in medical rather than surgical management. This distinction requires an unusually high level of accuracy in the measurement technique. The equally possible scenario in which the stenotic segment extends into three or four pixels further complicates measurement. In this case, the lumen diameter may be overestimated by volume averaging over multiple pixels (underestimation of the stenosis), or, conversely, the signal intensity within the pixels may simply be below the MIP threshold and be completely excluded from the image, resulting in a complete loss of the signal (overestimation of the stenosis). Thus, partial volume effects lead to a high degree of variability in the representation and measurement of the stenotic segment. The observer frequently faces the problem of which pixels to include in the measurement and where the edge of the vessel is actually located. The problem is particularly difficult when the diameter of the stenosis approximates the pixel size. This systematic variability should be detectable in the reported data as error bars in the measurements and marked interobserver variability. The authors report that interobserver variability was good ($\kappa > 0.70-0.89$), but they provide few details about how this was achieved.

The authors remark that the source images and MIPs are equivalent. Most investigators report slight improvements in specificity when the source images are included in the evaluation. I would recommend continued review of the source images whenever a need to quantify the stenosis exists. This is best accomplished with a workstation or picture archiving and communication system (PACS) with which the physician can easily magnify the region of interest, cross-reference the image, and make the measurements electronically.

The authors appropriately presented the DSA and CE-MRA images in a random manner. However, that the two observers made some of their measurements at different locations and from different projections of the stenosis is very likely. The use of a slightly different projection can lead to a large discrepancy in the measurement of the lumen because, frequently, the lumen of the stenosis is not perfectly round. Often, the residual lumen is oval or crescent shaped; in these instances, variations in the view that the observer selected for measurement add considerable variability. Although the observers would be searching for the image with the most severe stenosis, more than one image may qualify for the purpose of measurement.

I support the authors in their selection of a time-resolved approach to image acquisition. Time resolution has considerable advantages compared with single-image CE-MRA methods. For instance, coordination of the exact arrival time of the bolus into the region of interest is less critical, because image acquisition begins before the arrival of the contrast agent bolus and continues throughout the arterial and venous phases.

An important feature of time resolution is its ability to help in the identification of differential rates of opacification in nearly occluded vessels. Many CE-MRA techniques provide a single image during the peak of the contrast bolus. Severely diseased vessels with slow flow may become opacified late, and they may not be optimally visualized. Another condition that benefits from time resolution is left subclavian steal, in which the series of images captures the initial passage of the bolus through the carotid artery and, in later frames, into the left vertebral artery.

Time resolution can also be used to generate a precontrast mask that can be subtracted from subsequent time frames to improve vessel conspicuity. This procedure effectively eliminates background signal and allows the administration of multiple injections of contrast agent in the same session. Some authors use elliptical-centric or variable-rate k-space sampling techniques to accelerate image acquisition with time-resolved sequences.

Remonda et al confirm the value of CE MRA in providing a definitive assessment of carotid occlusion. This observation is indeed useful; it enables the initiation of medical care in patients with this condition or allows consideration of a revascularization procedure. Nonenhanced 2D time-of-flight (TOF) MRA has generally performed well in the identification of occluded carotid arteries. However, because this technique relies on in-flow enhancement, the possibility that a nearly occluded vessel with extremely slow flow could be misinterpreted as a completely occluded vessel always causes lingering doubt. Fortunately, CE MRA appears to eliminate this doubt, and it may be equivalent to DSA in helping to establish the diagnosis of carotid occlusion.

I believe that Remonda et al have shown that time-resolved CE MRA is equivalent to DSA in the quantification of carotid artery stenosis. This milestone for CE-MRA will have a positive effect on patient care by improving the diagnostic accuracy and minimizing the need for confirmatory tests to establish the severity of the stenosis.

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