Reply

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Detection and Characterization of Very Small Cerebral Aneurysms by Using 2D and 3D Helical CT Angiography

To the Editor: The article by Villablanca et al (1) in the August 2002 issue of the *AJNR* presents an interesting study, but the results do not support the conclusion that the sensitivity of CT angiography is higher than that of digital subtraction angiography for the detection of cerebral aneurysms ≤5 mm. A significant problem with the study is that the CT angiograms and digital subtraction angiograms were not obtained on the same day. In the two cases of "false-negative" results of digital subtraction angiography, the CT angiograms were obtained 2 and 5 days after the digital subtraction angiograms were obtained. Both of these patients had suffered subarachnoid hemorrhage, and it is possible that these two aneurysms were filled with thrombus at the time of digital subtraction angiography but not at the time of CT angiography. It is well known that subsequent angiograms reveal a source of subarachnoid hemorrhage in 2% to 24% of patients with initially negative angiographic results (2). Repeat digital subtraction angiography performed on the day the CT angiograms were obtained probably would have also revealed the aneurysms. Also, if CT angiography had been the initial study and digital subtraction angiography had been performed later, then the aneurysms would likely have been missed by CT angiography and revealed by digital subtraction angiography.

Even if we accept the sensitivities reported as correct, the patient population used was too small to support the conclusion that CT angiography is more sensitive than digital subtraction angiography. For CT angiography, the sensitivity was 98% (95% confidence interval, 87% to 100%) for reader 1 and was 100% (95% confidence interval, 91% to 100%) for reader 2. For reasons that are unclear, the authors did not report a 95% confidence interval for the digital subtraction angiographic results. For digital subtraction angiography, the sensitivity was 95%, and we calculate the 95% confidence interval to be 84% to 99%. By definition, these confidence intervals tell us that there is a 95% certainty that the true sensitivity is within the interval. Note the tremendous overlap in the 95% confidence intervals, indicating that it is not possible to distinguish a difference in sensitivity. The P values for the difference in sensitivity between CT angiography and digital subtraction angiography based on the data provided are $P = .56$ for reader 1 and $P = .15$ for reader 2. Table 1 of the article by Villablanca et al (1) indicates that patient 22 also had an aneurysm missed by CT angiography, but this missed aneurysm was not included in the data analysis. If Table 1 is correct, then the sensitivity of CT angiography would be even lower.

Maximizing sensitivity for the detection of ruptured cerebral aneurysms is critical for optimal patient care. The missed diagnosis of a ruptured cerebral aneurysm can have devastating consequences. The risk of rebleeding from a ruptured aneurysm without surgery or endovascular treatment is between 20% and 30% for the first month after hemorrhage (3). Patients who rebleed from ruptured aneurysms have an 80% mortality rate (4). The risk of permanent neurologic complication associated with cerebral angiography in patients with subarachnoid hemorrhage, cerebral aneurysm, and arteriovenous malformation is known to be extremely low (0.07%), based on a meta-analysis of recent, prospective studies (5). The neurologic deficits complicating angiography tend to be much less severe than the morbidity and mortality caused by rebleeding of a ruptured aneurysm.

CT angiography is undoubtedly a promising technique for the detection of cerebral aneurysms, and the sensitivity of CT angiography is probably now beginning to approach that of digital subtraction angiography. CT angiography can already serve as a useful adjunct to digital subtraction angiography in cases of angiogram-negative subarachnoid hemorrhage (6). We think that it is premature to consider CT angiography to be a replacement for digital subtraction angiography for the evaluation of patients suspected of harboring cerebral aneurysms. The sensitivity of CT angiography must continue to improve, as the sensitivity of digital subtraction angiography has certainly improved with the development of 3D rotational angiography (7). In addition to the issue of sensitivity, the superior spatial resolution of digital subtraction angiography allows for more definitive treatment planning for patients with cerebral aneurysms. It would be interesting to know whether the authors take the results of their study seriously enough to replace digital subtraction angiography with CT angiography in their practice for patients presenting with subarachnoid hemorrhage.

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Reply

Drs. Cloft and Kallmes mention that a problem with our study is that the CT angiograms and digital subtraction angiograms were not obtained on the same day. They think it is therefore possible that the two aneurysms not detected by digital subtraction angiography were thrombosed at the time of digital subtraction angiography but not at the time of CT angiography. Patient 8, with a 4.9-mm anteriorly projecting anterior communicating artery aneurysm, underwent a single digital subtraction angiography study 48 hours before undergoing CT angiography. Analysis of the digital subtraction angiograms of that patient revealed that the anterior communicating artery, and therefore the aneurysm sac, was not well filled as a consequence of poor cross filling during a cross-compression injection performed to visualize the anterior communicating artery region and probably not from transient thrombosis. Patient 14 had negative results of two digital subtraction angiography studies performed 5 and 2 days before CT angiography. Drs. Cloft and Kallmes note that subsequent angiograms reveal a source of subarachnoid bleeding in 2% to 24% of patients with initially negative angiographic results. Patient 14 had two negative angiograms. Others have noted that performing a third angiographic study in such patients is superfluous (1). It has been our experience that with very small aneurysms, ≤5 mm in maximal diameter, the more frequent cause of negative conventional angiography is projectional obscuration of the lesion when the aneurysm is obscured by the parent artery or nearby branches. Patient 14 had a complex arterial branching pattern that obscured a view of this very small, laterally and posteriorly projecting sac. In the same issue of the *AJNR* with our article is an article by Hochmuth et al (2), which reports that of 56 total aneurysms detected by rotational digital subtraction angiography, seven were not detected by conventional angiography. All seven were <5 mm in maximal diameter, and 43% were located at the middle cerebral artery bifurcation.

Our experimental design was biased in favor of digital subtraction angiography in that if an aneurysm was found by CT angiography but not by digital subtraction angiography and if the lesion was not treated surgically, then the lesion was presumed not to exist and that patient was dropped from the study. This was the case for three study patients with basilar tip aneurysms discovered by CT angiography, each measuring ≤5 mm in maximal diameter. In these cases, the lesion projected directly anterior or posterior to the basilar tip. Because standard anteroposterior and lateral projections are the projections that are routinely obtained, the contrast-opacified basilar tip obscured these small basilar tip lesions. The frequently anteriorly projecting P1 segments of the posterior cerebral artery obscured the basilar tip lesion from the lateral projection. In each of these cases, the aneurysm was an incidental finding in a patient without subarachnoid hemorrhage. Therefore, transient aneurysm thrombosis could not possibly account for nonvisualization on digital subtraction angiograms. Although a Water's projection of the basilar tip might have detected the anteriorly projecting lesions, for aneurysms in other locations, it may not be possible to know which obliquity will render a lesion visible, hence the potential for digital subtraction angiographic false-negative results. Had these three cases been included in the statistical analysis, the sensitivity of digital subtraction angiography would have fallen to 87%. These cases, and those presented in the literature (1, 3, 4), illustrate that it is unrealistic to suppose that projectional obscuration of very small aneurysms is not a real and common limitation of 2D conventional angiography. Extending the logic presented by Cloft and Kallmes, if it is assumed that the spontaneous incidence of thrombosed aneurysms in an average population of ruptured aneurysms is between 1% and 24% at the time of initial digital subtraction angiography, then approximately ≤3.5 aneurysms in this study population could be expected to produce negative results at the time of initial study. Because in 50% of the cases presenting with subarachnoid hemorrhage, CT angiography preceded digital subtraction angiography, one to two cases could be expected to be have negative CT angiographic results based on the same argument. Yet, not a single CT angiographic negative result occurred because of transient aneurysm thrombosis. The only aneurysm missed during CT angiographic review was an oversight on the part of reader 1 (Fig 3), with the aneurysm clearly visible on the 3D images. In our experience, the most common locations for digital subtraction angiographic false-negative results in descending order of frequency include the basilar tip, the middle cerebral artery bifurcation, the anterior communicating artery region, and the internal carotid artery bifurcation.

Drs. Cloft and Kallmes erroneously state that that we do not report a 95% confidence interval for the digital subtraction angiographic results. Those results, along with the specificity, positive and negative predictive value, and accuracy of digital subtraction angiography *are* provided (p 1193, Table 5). The statement, "By definition, these confidence intervals tell us that there is a 95% certainty that the true sensitivity is within the interval" is also incorrect. A confidence interval does not imply that π (the population sensitivity) is a random variable that assumes a value within the interval 95% of the time nor that 95% of the population values lie between the limits; rather, it means that if we were to select 100 random samples from the population and use these samples to calculate 100 different confidence intervals for π, approximately 95 of the intervals would cover the true population sensitivity and five would not. A two-sided equivalence (5, 6) test to reject nonequivalence yielded a *P* value $< .001$ for sensitivity for both reader 1 (CT angiography versus digital subtraction angiography and surgery) and reader 2 (CT angiography versus digital subtraction angiography and surgery) versus digital subtraction angiography versus CT angiography and surgery. In addition, the confidence intervals are visibly narrower for CT angiography versus digital subtraction angiography, with substantial regions of nonoverlap in the lower sensitivity range, indicating equivalent sensitivity clearly tending toward higher sensitivity for CT angiography versus digital subtraction angiography. We based our conclusions on the value of the absolute sensitivities and on the narrower confidence intervals obtained for CT angiography versus digital subtraction angiography. Regardless of the statistical processes one pursues in drawing conclusions, ultimately, equivalency is all that is necessary to show that CT angiography can serve as a viable alternative to digital subtraction angiography. Table 1 of our article contains a typographical error (aneurysm 38, patient 22), which suggests a second CT angiographic negative case was present but not included in the data analysis.

With respect to neurologic complications related to conventional angiography, although it is true that the risk of *permanent* neurologic complication related to conventional angiography is as low as 0.07% on the basis of a 1998 meta-analysis cited by the commentators (7), the rate of transient neurologic complication in the same meta-analysis cited ranged from 0.5% to 2.3%, with an additional 0.3% to 0.8% rate of serious nonneurologic complications, including groin hematoma requiring surgical or medical intervention, peripheral thromboembolic complications, and hypotension requiring medical therapy. The overall transient *and* permanent complication rate was therefore 0.8% to 3.3%. Although it is true that neurologic deficits complicating angiography tend to be much less severe than the morbidity and mortality resulting from rebleeding of a ruptured aneurysm, the conventional angiography complication rates are substantially higher for digital subtraction angiography compared with CT angiography (8).

The determination of which imaging technique should be used by an institution in the evaluation of patients suspected of harboring cerebral aneurysms should be based on the quality of the imaging modalities available at that institution. This is based in part on the quality of the imaging protocols, the quality of the postprocessing equipment, and the experience and ability of the study interpreters. At our institution, CT angiography studies are performed and interpreted with the same gravity and attention provided to routine catheter angiography. Based on a consistent track record of performance and periodic internal critical reviews, our neurosurgeons and endovascular therapists now routinely require CT angiography for nearly all cases before surgery and are performing treatment based on CT angiography alone in a growing percentage of cases. Others report a similar ability to proceed with surgical treatment by using CT angiography alone (9). As stated in our article, digital subtraction angiography should be performed in all cases in which a small arterial perforator beyond the current spatial resolution of CT angiography is suspected to arise from the aneurysm sac or neck, when hemodynamic flow information within the sac is needed, or when the status of collateral circulation needs to be determined. CT angiography is valuable for evaluating the potential for endovascular therapy and neurosurgical clipping, finding a working projection, and providing accurate aneurysm sac and neck measurements before therapeutic digital subtraction angiography.

The comment that the higher spatial resolution of digital subtraction angiography allows for more definitive treatment planning for patients with cerebral aneurysms is somewhat surprising, because it has been recognized in the literature that an important part of treatment planning is complete lesion characterization, including a detailed analysis of the presence and distribution of intraluminal thrombus and mural calcification. Lesion characterization has less to do with spatial resolution and more to do with the ability to visualize the nonluminal components of an aneurysm. These additional features of aneurysm have been shown to impact the selection of treatment method (10). Although rotational digital subtraction angiography will reduce the incidence of digital subtraction angiographic false-negative results based on projectional obscuration, it will have little impact on the ability to characterize potentially important mural and nonpatent intraluminal features of aneurysms. This will remain a distinct advantage of CT angiography, and, coupled with the low cost, the noninvasive nature of this safe technique will ensure a central role for CT angiography in the evaluation of patients with cerebral aneurysms.

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