Attributing Hypodensities on CT to Angiographic Vasospasm Is Not Sensitive and Unreliable

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Background and Purpose—The presence of low-density areas on CT is used in clinical decision-making regarding treatment of angiographic vasospasm as well as in research as a surrogate marker for severity of angiographic vasospasm. We assess the interobserver variability in attributing hypodensities on CT to angiographic vasospasm-related delayed ischemic neurological deficit.

Methods—Three experienced reviewers, 2 neurosurgeons, and a neuroradiologist independently reviewed CT scans of 413 patients enrolled in the Clazosentan to Overcome Neurological iSChemia and Infarction OccUrring after Subarachnoid hemorrhage (CONSCIOUS-1) trial, who universally underwent catheter angiography to determine severity of angiographic vasospasm. Interobserver variability was calculated using the \( \kappa \) statistic and the \( \chi^2 \) test was used to determine associations between dichotomized outcomes.

Results—There was considerable interobserver variability in attributing CT hypodensities to vasospasm-related delayed ischemic neurological deficit (\( \kappa = 0.51–0.78; 95\% \) CI, 0.35–0.90). Patients with hypodensities attributed to delayed ischemic neurological deficit were significantly more likely to have severe angiographic vasospasm (\( P = 0.001 \)), but a substantial proportion of these patients (19%) also had mild or no spasm. CT hypodensities had a sensitivity and specificity of 41% and 93%, respectively, in identifying patients with severe angiographic vasospasm, even with expert consensus that these represent angiographic vasospasm-related delayed ischemic neurological deficit.

Conclusions—we find considerable interobserver variability in attributing CT hypodensities to angiographic vasospasm and propose that they may not be a robust marker of severity of angiographic vasospasm, even with unanimous expert agreement that they are a result of vasospasm-related delayed ischemic neurological deficit.

Clinical Trial Registration—URL: www.clinicaltrials.gov. Unique identifier: NCT00111085.

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Key Words: computed tomography ■ delayed cerebral infarction ■ interobserver variability ■ subarachnoid hemorrhage ■ vasospasm

Angiographic vasospasm and subsequent delayed cerebral ischemia or delayed ischemic neurological deficit (DIND) are important causes of morbidity and mortality in patients after aneurysmal subarachnoid hemorrhage (SAH).1,2 The treatments of vasospasm with induced hypertension and endovascular angioplasty are however associated with significant morbidity.3-5 The challenge remains to differentiate between patients who may or may not benefit from such treatment.

One finding associated with angiographic vasospasm-related DIND is the presence of hypodensities on CT, which may influence clinicians’ decision to initiate or continue pharmacologically induced hypertension and has also been used in clinical research as a surrogate marker of severity of angiographic vasospasm.6-9 Other factors however may also cause hypodensities on CT scans, including brain retraction during microsurgical clipping10 or thromboembolic events after endovascular coiling,11,12 insertion of ventriculostomy,7 intracerebral hemorrhage associated with aneurysmal rupture,6 and areas of hypodensity adjacent to thick subarachnoid clots.13 It is therefore important to determine whether attributing hypodensities on CT to angiographic vasospasm-induced DIND is subject to interobserver variability.

Considerable interobserver variability has been demonstrated in the interpretation of numerous CT findings that occur after aneurysmal SAH such as hydrocephalus and the amount of cisternal blood.14-16 We perform the first study to investigate interobserver variability in the characterization of CT hypodensities as vasospasm-induced DIND and determine the specificity and sensitivity of hypodensities attributable to DIND in identifying patients with angiographic vasospasm.
Methods

Study Population
We conducted a post hoc analysis of 413 subjects enrolled between January 2005 and March 2006 in Clazosentan to Overcome Neurological iSChemia and Infarction OccUrring after Subarachnoid hemorrhage (CONSCIOUS-1), a randomized, double-blind placebo-controlled Phase 2 dose-finding trial of clazosentan for prevention of angiographic vasospasm after aneurysmal SAH.17 The methods and results are published.17

Radiology
All patients underwent CT scans at baseline, after the aneurysm-fixing procedure, 6 weeks from SAH, and additionally as clinically indicated. Reviewers who were blinded to angiographic results centrally reviewed all CT scans and cumulatively classified delayed hypodensities are vasospasm-related DIND or not based on expert opinion. The extent of angiographic vasospasm was determined for all patients through catheter angiography within 48 hours of aneurysm rupture and 7 to 11 days post-SAH. Angiographic vasospasm was defined by the percentage change in arterial lumen diameter between the initial and follow-up angiograms. Angiographic vasospasm was categorized as follows: none/mild (0%–33%), moderate (34%–66%), or severe (67%–100%).

Clinical Characteristics
All patients underwent microsurgical clipping or endovascular coiling as deemed appropriate by the treating physicians. The presence of DIND was defined clinically as a 2-point decrease in the Glasgow Coma Scale and a 2-point increase in the abbreviated National Institutes of Health Stroke Scale in the presence of angiographic vasospasm on catheter angiography of transcranial Doppler.18 Rescue therapy was defined as any intervention aimed at treating what the local investigators considered to be vasospasm, including induced hypertension and endovascular angioplasty.

Statistics
Three experienced reviewers, 2 neurosurgeons, and a neuroradiologist assessed CT images to determine whether or not hypodensities were related to vasospasm. To determine interobserver variability, weighted $\kappa$ values were calculated.19 The $\chi^2$ test was used to compare measured outcomes for binary and dichotomized categorical data. Analysis was performed using SAS 9.1 (Cary, NC).

Results
When classifying CT hypodensities as vasospasm-related or caused by other etiology, there was moderate to substantial agreement between reviewers ($\kappa$, 0.51–0.78; CI, 0.35–0.90; Table 1). All reviewers unanimously agreed that CT hypodensities in 21 patients were due to vasospasm-induced DIND and that hypodensities in 164 others were due to other causes. There was interobserver disagreement in the interpretation of the remaining CT scans.

The cohorts of patients for whom there was consensus among all reviewers that hypodensities represented DIND were compared with patients for whom reviewers unanimously agreed that hypodensities were caused by other etiologies (Table 2). The former had significantly higher rates of severe angiographic vasospasm (43% versus 8%; $P=0.0001$) and the latter had higher rates of little or no angiographic spasm (19% versus 74%; $P=0.0001$). In 19% of patients with hypodensities unanimously attributed to angiographic vasospasm, there was little or no vasospasm on catheter angiography.

CT hypodensities that were unanimously agreed on by all 3 experts to be a result of angiographic vasospasm-induced DIND had a sensitivity of 28% in identifying patients with moderate/severe angiographic vasospasm and 41% in identifying patients with severe spasm. Conversely, hypodensities with reviewer consensus to be a result of other etiologies had higher rates of little or no angiographic spasm (19% versus 74%; $P=0.0001$). In 19% of patients with hypodensities unanimously attributed to angiographic vasospasm, there was little or no vasospasm on catheter angiography.

 Patients with CT hypodensities on the postprocedural scan that were not present at baseline were more likely to have hypodensities unanimously attributed to other causes but those with ventriculostomy insertions were more likely to have hypodensities attributed to angiographic vasospasm-induced DIND ($P=0.07$). The aneurysm-fixing procedure, presence of intracerebral hemorrhage on initial CT scan, DIND, and use of rescue therapy were not associated with the classification of hypodensities as angiographic vasospasm-related or not.

Discussion
The most important finding of this study is that considerable interobserver variability exists in attributing hypodensities on CT scans to angiographic vasospasm-related cerebral infarc-
tion. We also find that CT hypodensities are not a robust marker of angiographic vasospasm severity, even when expert consensus exists that their presence represents angiographic vasospasm-related DIND. It would seem from our results that CT hypodensities are neither a reliable tool on which to base clinical decisions regarding treatment of angiographic vasospasm nor a robust research outcome measure. On the other hand, when looked at another way, there is a strong correlation between severity of angiographic vasospasm and CT hypodensities that cannot be attributed to other obvious causes, but there are outlying cases in which the 2 do not correlate.

The results of this study are important, because treatment of angiographic vasospasm can be associated with morbidity, particularly in patients with cardiovascular disease who may not tolerate hemodynamic therapy. Although the decision to treat vasospasm is based on numerous clinical variables, including the patient’s neurological status, the presence of CT hypodensities suspected to be the result of angiographic vasospasm may be a factor in the decision to continue or prolong aggressive therapy. The implication of our results is that a subset of patients (4 patients, 19% in this series) diagnosed with DIND have little or mild angiographic vasospasm. This “false-positive” group is at risk of overtreatment with pharmacologically induced hypertension and hypervolemia, assuming these measures are not effective for DIND not associated with angiographic vasospasm, which is not known.

Interestingly, patients with hypodensities unanimously attributed to angiographic vasospasm-delayed DIND or other causes did not show significant differences in the manifestation of DIND or use of rescue therapy (P=nonsignificant). Because DIND is a clinical manifestation of severe angiographic vasospasm, this may demonstrate once again that the classification of CT hypodensities as angiographic vasospasm-related DIND is unreliable. Furthermore, it seems that the initiation of rescue therapy is sometimes based on other factors.

Previous studies have used CT hypodensities as a surrogate marker of severity of angiographic vasospasm as a primary research outcome measure. Gruber et al analyzed CT hypodensities and showed that endovascular treatment of aneurysms was associated with more “vasospasm-related ischemic infarctions” when compared with microsurgical clipping. The considerable interobserver variability and suboptimal predictive value of this outcome measure may explain discrepancies between their findings and other studies showing less angiographic vasospasm and DIND as well as better outcomes in coiled patients.

Dehdashti et al attributed CT hypodensities to angiographic vasospasm-induced DIND if they were delayed in onset, not present on postoperative CT scan, not caused by surgical manipulation of vessels, and not due to a direct treatment complication. Other authors have classified hypodensities as angiographic vasospasm-induced DIND if they appeared in a delayed manner regardless of whether they were associated with neurological deficits as long as they were “not attributable to other pathologies.” We show however that although the 3 current reviewers were in consensus that the presence of hypodensities that were absent on postoperative CT scan represents DIND (P=0.07), the outcome remained subject to considerable variability. Furthermore, reviewers were more likely to unanimously attribute hypodensities to vasospasm when a ventriculostomy was inserted (P=0.07), which is an important finding because ventriculostomy insertion may be independently associated with more cerebral infarcts after SAH. It would appear that differentiating between hypodensities related to treatment complications and angiographic vasospasm is indeed difficult.

The discrepancies between angiographic vasospasm and CT hypodensities may have several causes. CT is not as sensitive as MRI at detecting ischemia and infarction. Angiography may not have been done in some cases when vasospasm was actually present. Finally, other processes have been suggested to cause hypodensities on CT after SAH such as cortical spreading ischemia and microthromboembolism.

The main limitation of this study is the use of only 3 reviewers. Strengths of our study include the large patient sample, systematic and consistent documentation of CT findings, and the acquisition of catheter angiograms on all patients both at baseline and during the period of risk of angiographic vasospasm.

Conclusions

Angiographic vasospasm results in DIND and infarction, but several other variables may also cause hypodensities on CT scans. Considerable interobserver variability exists in the characterization of CT hypodensities as angiographic vasospasm-related infarctions. Furthermore, the predictive value of low-density areas in identifying patients with severe angiographic vasospasm is suboptimal, even when experienced reviewers unanimously believe that they are a consequence of angiographic vasospasm. Clinicians and researchers must therefore use caution in basing clinical decisions and research study results on this radiographic finding.

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Disclosures

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References

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