Utility of Screening for Cerebral Vasospasm Using Digital Subtraction Angiography

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Background and Purpose—Cerebral arterial vasospasm (CVS) is a common complication of aneurysmal subarachnoid hemorrhage strongly associated with neurological deterioration and delayed cerebral ischemia (DCI). The utility of screening for CVS as a surrogate for early detection of DCI, especially in patients without clinical signs of DCI, remains uncertain.

Methods—We performed a retrospective analysis of 116 aneurysmal subarachnoid hemorrhage patients who underwent screening digital subtraction angiography to determine the association of significant CVS and subsequent development of DCI. Patients were stratified into 3 groups: (1) no symptoms of DCI before screening, (2) ≥1 episodes of suspected DCI symptoms before screening, and (3) unable to detect symptoms because of poor examination.

Results—Patients asymptomatic before screening had significantly lower rates of CVS (18%) compared with those with transient symptoms of DCI (60%; P<0.0001). None of the 79 asymptomatic patients developed DCI after screening, regardless of digital subtraction angiography findings, compared with 56% of those with symptoms (P<0.0001). Presence of CVS was significantly associated with DCI in those with transient symptoms and in those whose examinations did not permit clear assessment (odds ratio 16.0, 95% confidence interval 2.2–118.3, P=0.003).

Conclusions—Patients asymptomatic before screening have low rates of CVS and seem to be at negligible risk of developing DCI. Routine screening of asymptomatic patients seems to have little utility. Screening may still be considered in patients with possible symptoms of DCI or those with examinations too poor to clinically detect symptoms because finding CVS may be useful for risk stratification and guiding management. (Stroke. 2015;46:3137-3141. DOI: 10.1161/STROKEAHA.115.010081.)

Key Words: cerebral vasospasm ■ delayed cerebral ischemia ■ digital subtraction angiography ■ screening ■ subarachnoid hemorrhage

A neurysmal subarachnoid hemorrhage (aSAH) is a serious cerebrovascular disease, affecting ≈30000 Americans a year and leading to significant neurological disability, with much of this morbidity related to delayed cerebral ischemia (DCI) and cerebral infarction.¹ Cerebral arterial vasospasm (CVS) is a common complication of aSAH, seen in as many as 70% of patients, and has been strongly associated with neurological deterioration and DCI. Most patients developing DCI harbor significant CVS, with both typically occurring 4 to 14 days after hemorrhage (peak 7–10 days). The association between the 2 phenomena, coupled with the more objective quantifiable nature of CVS, has led to the widespread practice of screening for CVS in patients with aSAH as a means of detecting DCI early and intervening before infarction can occur. However, because less than half of those with CVS ultimately develop DCI, definitive prognostic and therapeutic decisions based on CVS screening can be problematic.²

The gold standard for the diagnosis of CVS is digital subtraction angiography (DSA), which allows accurate quantitative assessment of CVS severity in each intracranial artery, as well as therapeutic endovascular interventions, if needed. However, because of limited availability of DSA, many centers use transtemporal Doppler (TCD) ultrasound or computed tomographic angiography (CTA) as alternatives, even though these tests have a lower sensitivity and specificity for CVS detection.³ ⁴ Therefore, most studies evaluating the utility of screening for CVS (as a surrogate or predictor of DCI) have used these suboptimal diagnostic tools and often only in those who are symptomatic or at high risk for DCI.

Our institution has a long history of safely using DSA in the evaluation and management of CVS after aSAH. This led to the evolution of our standard practice to a protocol whereby
all aSAH patients undergo DSA on postbleed day 6 to 9 as a screen for CVS (unless DSA was obtained earlier as evaluation for neurological symptoms suggestive of DCI). The rationale for this screening strategy is that monitoring and medical management to prevent DCI may be adjusted based on DSA results (ie, risk stratification). Given this existing practice, we have a unique opportunity to evaluate the relationship between CVS and DCI in a large relatively unbiased cohort of patients using the gold standard diagnostic test of DSA. The primary objective of this study was to evaluate the utility of screening for CVS (using DSA), specifically by assessing the frequency of significant (moderate–severe) CVS in asymptomatic versus mildly symptomatic or unassessable aSAH patients and whether such unsuspected CVS served as a useful harbinger of higher subsequent DCI risk.

Methods

A prospectively collected database of vascular neurosurgery cases at Washington University/Barnes Jewish Hospital was used to identify aSAH patients presenting from July 2009 (the conception of the database) through December 2013 who had aneurysms treated by surgical or endovascular means. All patient demographics and presenting information (including Hunt and Hess [HH] and modified Fisher scores [MFS]) were obtained from the prospective database. Individual patient charts were then reviewed (by authors EJ Arias and S. Vajapey), including physician and nursing examinations, radiology reports, and all other pertinent hospital course information. We identified all aSAH patients who underwent DSA to evaluate for CVS during their hospital stay.

All 3 neuroradiologists performing DSA at our institution routinely classify angiographic vasospasm following established convention as either none, mild (<25% stenosis), moderate (25%–50% stenosis), or severe (>50% stenosis). For the purposes of this analysis, angiograms with CVS classified as moderate or severe in at least one intracranial vessel were considered to be positive for CVS, whereas those with only mild or no CVS were considered to be negative. All reports of angiograms were also reviewed for complications, including thromboembolic stroke, intracranial hemorrhage, arterial dissection, pseudoaneurysm formation, or groin and retroperitoneal hematoma.

The hospital course for each patient was closely examined for signs of possible DCI. A decline in neurological status on physician examination (including alertness, orientation, cranial nerve palsy, pronator drift, or focal motor deficit) or a decrease in Glasgow Coma Scale of ≥2 on nursing examination, without other identifiable causes present (such as hydrocephalus, hyponatremia, seizure, or fever), was used to define presence of DCI.

Patients were classified into subgroups based on symptomatology at time of screening DSA. Patients who were asymptomatic were allocated to Group 1 (asymptomatic). All other patients were categorized as follows: Those who displayed sustained symptoms of DCI prompting DSA before reaching the screening date (approximately day 7 after aneurysmal bleeding) were excluded from our analysis because their DSA was performed for cause rather than as screening. Patients who manifested at least one episode of symptoms that were not severe or persistent enough to merit urgent DSA, and subsequently underwent screening DSA, were classified as Group II (transiently symptomatic). Patients with too poor an examination to reliably detect symptoms of DCI were classified as Group III (poor examination; Figure).

The same standardized criteria for neurological deterioration were used to determine whether patients had sustained DCI during the remainder of their hospital course (ie, after screening DSA). Although clinical examination in Group III was difficult, presence of DCI was determined by either a further decrease in neurological examination (such as worsened/new motor posturing) or evidence of delayed infarction on cerebral imaging remote from the area of expected postsurgical changes. We reviewed all brain imaging performed in all 3 groups before hospital discharge to evaluate for evidence of cerebral infarction.

Analysis

Patients were divided into 3 groups based on presence of DCI symptoms before undergoing screening DSA (as described earlier, Figure). We compared the incidence of CVS and the incidence of DCI throughout the remainder of the hospital course (primary outcomes) in each of these 3 subgroups using Chi-square testing. The relative risk of CVS in the 3 groups was adjusted for any imbalances in baseline variables using multivariate binomial regression. We then calculated the sensitivity, specificity, and predictive values of CVS on screening DSA for subsequent DCI in the overall cohort and in each subgroup. Groups II and III were also grouped together (transient/uncertain symptoms) and compared with Group I (asymptomatic).

Results

A total of 215 aSAH patients were admitted and underwent aneurysm treatment during the study period. Of these, 116 underwent screening DSA (at a median of 7 days postbleed). Of the other 99 patients, 69 underwent nonscreening DSA because of an acute neurological change before reaching the time point for a screening DSA and 30 did not undergo DSA for evaluation of CVS (13 because their condition was too poor and medical care was either deescalated or withdrawn before reaching the screening date, 11 because their condition was too good and the physician felt that the risk of DSA was not merited, and 6 because of a medical contraindication to DSA, such as impaired renal function or femoral artery dissection on prior DSA; Figure). Those undergoing screening DSA did not differ from the overall aSAH cohort in terms of age, sex, subarachnoid hemorrhage severity, aneurysm treatment modality, or other clinical variables (Table).

Of the 116 patients who underwent screening DSA, 79 were asymptomatic from DCI before undergoing screening DSA (Group I), 25 patients had at least one episode of symptoms concerning for DCI (but did not have earlier DSA because their symptoms were not severe or persistent enough to merit DSA before the planned screening date, Group II), and 12 had too poor an examination to reliably detect symptoms of DCI (Group III). Compared with patients in Group I, patients in Groups II and III were more likely to have higher HH (4–5, Group I, 11%; Groups II, 56%; and Group III, 83%; P < .00001) and MFS (>3, Group I, 72%; Group II and III, 95%, P = .005; Table).

The overall incidence of moderate–severe CVS was 35/116 (30%) and was associated with higher HH grade (49% for HH 4–5 versus 23% for HH 1–3, P = 0.007) and higher MFS (36% in MFS 3–4 versus 8% for MFS 0–2, P = 0.01). DSA was positive for CVS in 18% (14 of 79) of Group I patients (all moderate severity) compared with 60% (15 of 25) of Group II patients and 50% (6 of 12) of Group III patients (P < .0001). Even after adjusting for the higher HH grade and MFS in these groups, the risk of CVS remained higher in Group II (adjusted odds ratio 5.5, 95% CI [confidence interval] 1.8–16.4, P = 0.002) and Group III (aOR 3.8, 95% CI...
0.83–17.1, \( P=0.08 \) compared with Group I (overall aOR for Groups II and III versus Group I was 5.0, 95% CI 1.8–14.2, \( P=0.002 \)). For comparison, of the 69 patients who underwent nonscreening DSA because of an acute neurological change before reaching the 7 day screening date, 30 (43.5%) had moderate–severe CVS. None of the 79 patients who were asymptomatic at time of DSA (Group I) went on to develop DCI during the remainder of their hospital course, including those 14 with CVS on screening DSA. The therapies implemented in response to finding CVS in these 14 patients included intra-arterial verapamil (in 2 patients), vasopressors for management of

### Table. Patient Demographics

<table>
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<th></th>
<th>All Patients (n=215)</th>
<th>All Screened Patients (n=116)</th>
<th>Asymptomatic (n=79)</th>
<th>Transiently Symptomatic (n=25)</th>
<th>Poor Exam (n=12)</th>
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<td>48 (41%)</td>
<td>42 (53%)</td>
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<td>28 (24%)</td>
<td>21 (27%)</td>
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<td>36 (17%)</td>
<td>21 (18%)</td>
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<td>24 (11%)</td>
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<td>7 (58%)</td>
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<td>46 (40%)</td>
<td>28 (35%)</td>
<td>10 (40%)</td>
<td>8 (67%)</td>
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<td>Coronary artery disease</td>
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<td>5 (4%)</td>
<td>1 (1%)</td>
<td>3 (12%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14 (7%)</td>
<td>7 (6%)</td>
<td>7 (9%)</td>
<td>0 (0%)</td>
<td>1 (8%)</td>
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</table>
headache (1 patient), solely continuing high rates of IV fluids for maintenance of euvolemia (7 of 14), whereas the remaining 4 patients had their medical management deescalated with weaning of their IV fluids. None went on to develop symptoms of DCI or cerebral infarction.

Fourteen of the 25 patients in Group II went on to develop definitive DCI, including 12 of 15 who were positive for CVS versus 2 of 10 who were negative for CVS. Therefore, not only was having at least one episode of symptoms concerning for DCI before screening DSA a risk factor for DCI (compared with the asymptomatic group, $P<0.001$), but presence of CVS was a strong marker of increased risk in this group (odds ratio 16.0, 95% CI 2.16–118.27, $P=0.003$). This occurred despite much more aggressive management being instituted in this group, including 10 of the 15 patients with CVS being placed on vasopressor therapy after DSA and 10 of 15 patients receiving intra-arterial verapamil during DSA. Four of the 25 Group II patients developed infarcts on imaging remote from the initial hemorrhage or surgical site.

Of the 12 patients with poor neurological examination at time of DSA (Group III), 4 of 6 patients where CVS was found on screening DSA versus 2 of 6 patients where CVS was not found on screening DSA went on to develop DCI. Three of these patients developed infarcts on imaging remote from the initial hemorrhage or surgical site.

Overall, taking Groups II and III together (those who were transiently symptomatic or had poor neurological exams), the sensitivity and specificity of finding CVS on screening DSA for the subsequent development of DCI was 80% (95% CI 63%–92%) and 71% (51%–85%), respectively. Overall, odds ratio for development of definitive DCI in patients with CVS on screening DSA was 9.6 (95% CI 1.7–60.8). Positive predictive value of finding CVS on screening DSA for subsequent DCI was 76% (60%–87%), whereas negative predictive value (absence of CVS on screening DSA) was 75% (54%–90%) for not developing DCI.

One of 116 screening angiograms (0.9%) resulted in a complication: an asymptomatic patient sustained a thromboembolic left middle cerebral artery stroke causing aphasia and left facial weakness.

**Discussion**

Many practitioners screen aSAH patients for CVS as a means of risk stratifying and promptly intervening to prevent the morbidity associated with DCI. A recent survey of active members of the joint American Association of Neurological Surgeons/Congress of Neurological Surgeons Cerebrovascular Section found that most use a spectrum of screening practices, including TCD (70.1%), DSA (24.9%), or CTA (23.7%), between days 5 and 10. The clinical utility of such screening is predicated on a robust association of CVS and DCI and the ability of the screening method to reliably detect meaningful DCI. Here we report on the predictive value of screening for CVS, as evaluated using the gold standard method (DSA) in a large cohort of aSAH patients who either were asymptomatic, were transiently symptomatic, or had poor neurological examinations in detecting subsequent development of definitive DCI.

The results of our observational study indicate that moderate–severe CVS is relatively uncommon in asymptomatic patients (18%), and that none of these patients subsequently developed definitive symptoms of DCI or cerebral infarction throughout the remainder of their hospital stay, regardless of whether CVS was found on DSA. Given these results, one can question the utility of screening this relatively large subgroup of asymptomatic aSAH patients (representing over one third of the total number managed at our institution). The main justification for this practice would be to identify patients with unsuspected angiographic CVS and allow for treatment of this condition before onset of symptoms of DCI; however, only 14 out of 79 patients were identified to fall into this group as a result of screening. Furthermore, given the relatively weak nature of the medical interventions instituted in this group, it is difficult to conclude that these interventions were responsible for the complete lack of DCI seen in this group. Rather, it is much more likely that these asymptomatic patients would have continued along their benign course for the remainder of their hospital course, despite harboring moderate CVS.

In contrast to these findings, of the 25 Group II patients who had exhibited some transient/mild symptoms before screening, 15 were positive for moderate–severe CVS—12 of whom went on to develop definite DCI during the remainder of their hospital course. This occurred despite much more aggressive management of this group, including frequent use of vasopressors and intra-arterial vasoforminals. In this group, the finding of CVS was highly predictive of subsequent DCI, and so screening for CVS in those with possible but unclear symptoms may reliably detect a high-risk population who require aggressive interventions to prevent DCI and infarction.

Similarly, in patients with too poor an examination to reliably detect symptoms of DCI (Group III), the finding of moderate–severe CVS on screening DSA predicted a greater risk of subsequently developing DCI (often cerebral infarction). Given the difficulty in detecting neurological symptoms of DCI in this group and the high rate of CVS and DCI, screening this population seems useful. Overall, our data suggest screening patients with possible or uncertain DCI symptoms (Groups II and III) for CVS seems to have moderately high sensitivity and specificity for subsequent development of DCI. Although some patients without moderate–severe CVS on screening DSA still developed DCI, the finding of moderate–severe CVS conferred a higher risk designation that could be useful in managing such patients.

In addition to sensitivity and specificity, the net benefit of a screening test is determined by any associated risks. In our series, there was a 0.9% (1 out of 116) complication rate in patients undergoing screening DSA, specifically an asymptomatic patient sustaining a clinically significant thromboembolic stroke. Given this complication rate along with the low incidence of significant CVS in asymptomatic patients, the lack of DCI development in asymptomatic patients, and the low amount of evidence that our interventions in these patients prevented DCI development, it is difficult to justify angiographic screening of asymptomatic patients for CVS.

Although there is disagreement about the sensitivity, specificity, and interobserver reliability of TCD, it is the most common screening method used among the responders, likely because of its noninvasive nature and ease of use in ICU.
patients. Furthermore, TCD does not have the risks associated with radiation and contrast used during CTA and DSA. CTA has also gained popularity in recent years, with various publications demonstrating an acceptable level of detection of vasospasm and a relative cost savings when compared with TCD, but this technique is limited by metal artifacts from coils and clips, and its diagnostic accuracy remains inferior to the gold standard of DSA. DSA is still viewed as the gold standard for detection of CVS, but is being used less frequently, likely because of its invasive nature, potential for complications, and relative higher use of resources when compared with TCD and CTA. However, DSA is the definitive tool for diagnosis of CVS because it can give temporal information related to flow dynamics in addition to providing optimal evaluation of blood vessel caliber.

Our study is limited because of its retrospective nature and population size. Our patient cohort does encompass a 4 and a half year span at a major academic institution, but still included only few in the high-risk (transient symptomatic/poor examination) groups that underwent screening DSA. Nonetheless, the conclusions drawn from this article have been striking enough to influence practice at our institution (ie, reduction in screening asymptomatic aSAH patients). Future prospective studies on this topic may be warranted, and further analysis could include either a cohort study comparing a 4-year span of asymptomatic patients who do not undergo screening DSA with those included in this article or a trial randomizing asymptomatic patients to DSA screening, CTA screening, or no screening for vasospasm.

Conclusions

Angiographic screening for CVS may not be beneficial in asymptomatic aSAH patients in whom the rate of significant findings are low and the clinical implications of these findings seem modest (no/low risk of DCI even with CVS). On the contrary, angiographic screening for CVS seems useful in patients with transient symptoms or neurological examinations that are so poor that symptoms of DCI cannot reliably be detected because DSA findings are often positive for significant CVS, and this result can inform risk of DCI and influence management.

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Disclosures

Dr Derdeyn receives modest consulting fees from MicroVention, Silk Road, Penumbra, Inc and is on the scientific advisory board with stock options from Pulse. Dr Dorward consults with DePuy Spine, receives honoraria with Stryker Spine, and receives travel/food from Medtronic, DePuy, Stryker, and Nuvasive. The other authors report no conflicts.

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