Impaired Cerebral Autoregulation Is Associated With Vasospasm and Delayed Cerebral Ischemia in Subarachnoid Hemorrhage

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Background and Purpose—Cerebral autoregulation may be impaired in the early days after subarachnoid hemorrhage (SAH). The purpose of this study was to examine the relationship between cerebral autoregulation and angiographic vasospasm (aVSP) and radiographic delayed cerebral ischemia (DCI) in patients with SAH.

Methods—Sixty-eight patients (54±13 years) with a diagnosis of nontraumatic SAH were studied. Dynamic cerebral autoregulation was assessed using transfer function analysis (phase and gain) of the spontaneous blood pressure and blood flow velocity oscillations on days 2 to 4 post-SAH. aVSP was diagnosed using a 4-vessel conventional angiogram. DCI was diagnosed from CT. Decision tree models were used to identify optimal cut-off points for clinical and physiological predictors of aVSP and DCI. Multivariate logistic regression models were used to develop and validate a risk scoring tool for each outcome.

Results—Sixty-two percent of patients developed aVSP, and 19% developed DCI. Patients with aVSP had higher transfer function gain (1.06±0.33 versus 0.89±0.30; P=0.04) and patients with DCI had lower transfer function phase (17.5±39.6 versus 38.3±18.2; P=0.03) compared with those who did not develop either. Multivariable scoring tools using transfer function gain >0.98 and phase <12.5 were strongly predictive of aVSP (92% positive predictive value; 77% negative predictive value; area under the curve, 0.92) and DCI (80% positive predictive value; 91% negative predictive value; area under the curve, 0.94), respectively.

Conclusions—Dynamic cerebral autoregulation is impaired in the early days after SAH. Including autoregulation as part of the initial clinical and radiographic assessment may enhance our ability to identify patients at a high risk for developing secondary complications after SAH. (Stroke. 2014;45:677-682.)

Key Words: cerebrovascular circulation ■ subarachnoid hemorrhage ■ ultrasonography, Doppler

Subarachnoid hemorrhage (SAH) is a devastating condition that affects ≈50 000 Americans yearly.1 Angiographic vasospasm (aVSP) and delayed cerebral ischemia (DCI) are among the leading causes of morbidity and mortality after SAH. Early and accurate prediction of these complications will help develop more effective treatments.

The clinical tools currently used to predict the development of secondary complications after SAH are not satisfactory.2 Although various clinical and radiographic factors have been associated with increased risk of vasospasm and DCI,3,4 multivariable analyses showed that the combination of these factors is poorly predictive of risk.5 This suggests that other risk factors associated with vasospasm and DCI were omitted from these analyses. The effectiveness of cerebral autoregulation (ie, the ability of cerebrovasculature to buffer against changes in pressure) in SAH may be among these factors.

Cerebral autoregulation is increasingly recognized as a factor that requires evaluation in patients with SAH. Several studies have shown that early impairments in autoregulation are associated with vasospasm and DCI after SAH.3–14 Thus, including measures of autoregulation as part of risk scores may allow for more accurate prediction of these conditions.
complications. The aims of this study were to explore the association between autoregulation and the occurrence of aVSP and DCI in SAH and identify cut-off values for measures of autoregulation (transfer function phase and gain) that can aid in prediction of aVSP or DCI. As a secondary aim, we also developed a simple and easy-to-use risk scoring approach that combines clinical, radiographic, and cerebral autoregulatory parameters.

Methods
All patients admitted to the neurointensive care unit at the Brigham and Women’s Hospital with a diagnosis of spontaneous SAH between March 15, 2010, and September 10, 2012, and with transcranial Doppler ultrasound measures within the first 4 days post-SAH were included in our study. Additional inclusion criteria were age >18 years, evidence of SAH on admission CT, and hemodynamic stability. Exclusion criteria were traumatic SAH and other central neurological disorders (tumors, previous stroke, hemorrhage or other vascular malformations). All patients were managed according to recommended guidelines,13,14 and the institutional review board approved the study.

aVSP was diagnosed from digital subtraction cerebral angiography performed between days 6 and 8 post-SAH and compared with the study.

Results
Sixty-eight patients with SAH (31 nonaneurysmal) satisfied our criteria. Sixty-two percent (N=42) of patients developed aVSP, and 19% (N=13) developed DCI. All but 3 of the DCI patients also had aVSP.

Patients with aVSP were slightly younger and more likely to have aneurysmal SAH. They also had higher gain but similar phase on days 2 to 4 compared with those without aVSP (Table 1; Figure 1). Mean flow velocity was also significantly higher in patients who developed aVSP, but the values were significantly <120 cm/s used as cut-off point for clinical transcranial Doppler ultrasound diagnosis of vasospasm. Our findings did not change when we limited our analysis to patients with only middle cerebral artery aneurysms or only middle cerebral artery vasospasm (data not shown).

Table 1. Baseline Demographic, Clinical, and Autoregulatory Characteristics of Patients With and Without Angiographic Vasospasm

<table>
<thead>
<tr>
<th></th>
<th>Vasospasm Present (N=42)</th>
<th>Vasospasm Absent (N=26)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>51.3 (11.3)</td>
<td>57.5 (14.5)</td>
<td>0.06</td>
</tr>
<tr>
<td>Men/women</td>
<td>16/26</td>
<td>12/14</td>
<td>0.61</td>
</tr>
<tr>
<td>Diabetes mellitus, yes/no</td>
<td>5/37</td>
<td>2/24</td>
<td>0.70</td>
</tr>
<tr>
<td>Hypertension, yes/no</td>
<td>20/22</td>
<td>9/17</td>
<td>0.32</td>
</tr>
<tr>
<td>Smoking, yes/no</td>
<td>16/26</td>
<td>4/19</td>
<td>0.12</td>
</tr>
<tr>
<td>Aneurysm, yes/no</td>
<td>31/11</td>
<td>6/20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WFNS score*</td>
<td>2 (1–4)</td>
<td>1.5 (1–2)</td>
<td>0.86</td>
</tr>
<tr>
<td>Hunt and Hess*</td>
<td>2 (2–3)</td>
<td>2 (2–2)</td>
<td>0.61</td>
</tr>
<tr>
<td>Hemoglobin, mg/dL</td>
<td>12.9 (2.0)</td>
<td>12.0 (2.1)</td>
<td>0.11</td>
</tr>
<tr>
<td>Modified Fisher score*</td>
<td>3 (3–4)</td>
<td>3 (2–3)</td>
<td>0.53</td>
</tr>
<tr>
<td>Admission glucose, mg/dL</td>
<td>142.9 (35.0)</td>
<td>142.2 (36.0)</td>
<td>0.94</td>
</tr>
<tr>
<td>Admission magnesium, mg/dL</td>
<td>1.9 (0.3)</td>
<td>1.9 (0.2)</td>
<td>0.51</td>
</tr>
<tr>
<td>Mean flow velocity, cm/s</td>
<td>76.0 (21.6)</td>
<td>64.0 (21.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>82.2 (12.9)</td>
<td>76.6 (12.3)</td>
<td>0.26</td>
</tr>
<tr>
<td>Phase, degrees (low frequency)</td>
<td>35.2 (20.2)</td>
<td>32.9 (31.2)</td>
<td>0.60</td>
</tr>
<tr>
<td>Gain (low frequency)</td>
<td>1.06 (0.33)</td>
<td>0.89 (0.30)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Values represent mean (SD) for all continuous variables and proportions for categorical variables unless otherwise stated. WFNS indicates World Federation of Neurosurgeons.

*Represent median (interquartile range).
Patients who developed DCI were older, more likely to have aneurysmal SAH, had higher Hunt and Hess and World Federation of Neurosurgeons (WFNS) scores, and higher blood glucose on admission (Table 2). DCI patients also had lower phase on days 2 to 4 when compared with patients without DCI (Table 2; Figure 2). Our findings did not change when we adjusted our analysis to account for side and location of DCI (data not shown).

CART Model Building and Model Comparison

Based on our CART analysis; gain >0.98, age ≤60 years, and mean flow velocity on days 2 to 4 >70 cm/s were identified as optimal cut-off points for predicting aVSP, whereas phase <12.5, mean arterial pressure on days 2 to 4 >90 mm Hg, and admission blood glucose >155 mg/dL were identified as optimal cut-off points for predicting DCI. These cut-off points were used for logistic regression models. To better assess the contribution of clinical variables and transfer function parameters to outcome, we used 3 separate logistic regression models: 1 with clinical variables, 1 with transfer function parameters, and 1 with both.

Table 3 summarizes the predictive values of aVSP and DCI models. The addition of gain >0.98 to models containing only clinical predictors (model 1 in Table 3) significantly improved the likelihood (P=0.007) of predicting aVSP, suggesting a better model fit with inclusion of transfer function gain as an independent predictor. Similarly, the addition of phase <12.5 to models containing only clinical predictors (model 4 in Table 3) significantly improved the likelihood of predicting DCI (P=0.03), suggesting a better model fit when phase is included as an independent predictor.

Scoring Tools for aVSP and DCI

We used a logistic regression model containing transfer function parameters and clinical variables to develop simple scoring tools for aVSP (Smoking, Age, Gain, Aneurysmal SAH [SAGA] score) and DCI (WFNS, Hyperglycemia, Arterial Pressure, Phase [WHAP] score). These scores were derived from the β-coefficients of significant predictors of outcome in stepwise multivariate models (models 2 and 4 in Table 3).

The SAGA score (Table 4) ranged from 0 to 11 with median 5 (interquartile range, 4–9) for all participants. A score ≥5 had 90% sensitivity and 69% specificity, whereas a score ≥7 had 62% sensitivity and 96% specificity for aVSP. The SAGA score had excellent discrimination (bootstrapped bias-corrected C-statistic, 0.90±0.03) and achieved good calibration (Hosmer–Lemeshow goodness-of-fit test; P=0.93). Each unit increase in the SAGA score was associated with a 3-fold increased risk of aVSP (Jackknife odds ratio, 2.62; 95% confidence interval, 1.59–4.32; Table 1 in the online-only Data Supplement).

The WHAP score (Table 4) ranged from 0 to 7 (out of a maximum possible 10) with median 1 (interquartile range, 0–3). The WHAP score also had excellent discrimination (bootstrapped bias-corrected C-statistic, 0.94±0.03) and provided a good fit (Hosmer–Lemeshow goodness-of-fit test; P=0.53). The model had a sensitivity of 62%, specificity of 96%, positive predictive value of 80%, and a negative predictive value of 91% in classifying patients with DCI. A score ≥3 had 100% sensitivity and 65.5% specificity, whereas a score ≥6 had 62% sensitivity and 96% specificity. For each unit increase in the WHAP score, the odds of developing DCI increased 3-fold (Jackknife odds ratio, 2.80; 95% confidence interval, 1.6–4.78; Table 1 in the online-only Data Supplement).

Sensitivity Analysis

We compared the forward stepwise model used in our primary analysis for each outcome to that obtained using a backward stepwise selection approach. Both procedures yielded exactly the same models for aVSP. The backward regression approach in models with DCI as the dependent variable was in good agreement with the forward regression procedure on some predictors (WFNS IV to V; mean arterial pressure >90 mm Hg; and phase <12.5), but 2 additional variables (hypertension and aneurysmal SAH) were added to the model. Admission glucose >155 mg/dL was excluded from this model. The performance characteristics of the backward selection model for DCI were slightly higher than that obtained using the forward selection approach (Table II in the online-only Data Supplement), and a score derived using this approach had an area under the receiver operating characteristic curve of 0.96±0.02.

Discussion

We showed that cerebral autoregulation is impaired in the early days after SAH and that this impairment is predictive of...
Table 2. Baseline Demographic, Clinical, and Autoregulatory Characteristics of Patients With and Without Delayed Cerebral Ischemia (DCI)

<table>
<thead>
<tr>
<th></th>
<th>DCI Present (N=13)</th>
<th>DCI Absent (N=55)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>59.9 (12.3)</td>
<td>52.2 (12.6)</td>
<td>0.05</td>
</tr>
<tr>
<td>Men/women</td>
<td>4/9</td>
<td>24/31</td>
<td>0.40</td>
</tr>
<tr>
<td>Diabetes mellitus, yes/no</td>
<td>2/11</td>
<td>5/50</td>
<td>0.61</td>
</tr>
<tr>
<td>Hypertension, yes/no</td>
<td>7/6</td>
<td>22/33</td>
<td>0.36</td>
</tr>
<tr>
<td>Smoking, yes/no</td>
<td>5/8</td>
<td>16/39</td>
<td>0.52</td>
</tr>
<tr>
<td>Aneurysm, yes/no</td>
<td>11/2</td>
<td>26/29</td>
<td>0.02</td>
</tr>
<tr>
<td>Clipping/coiling if</td>
<td>9/2</td>
<td>17/8</td>
<td>0.69</td>
</tr>
<tr>
<td>aneurysmal, yes/no</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WFNS score*</td>
<td>4 (2–4)</td>
<td>1 (1–2)</td>
<td>0.03</td>
</tr>
<tr>
<td>Hunt and Hess*</td>
<td>3 (2–4)</td>
<td>2 (2–3)</td>
<td>0.004</td>
</tr>
<tr>
<td>Modified Fisher score*</td>
<td>3 (3–4)</td>
<td>3 (2–3)</td>
<td>0.23</td>
</tr>
<tr>
<td>Admission glucose, mg/dL</td>
<td>161.3 (35.6)</td>
<td>138.2 (33.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Admission magnesium, mg/dL</td>
<td>1.9 (0.3)</td>
<td>1.9 (0.2)</td>
<td>0.37</td>
</tr>
<tr>
<td>Mean flow velocity, cm/s</td>
<td>71.0 (20.2)</td>
<td>71.5 (22.7)</td>
<td>0.94</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>84.1 (14.9)</td>
<td>80.0 (12.1)</td>
<td>0.3</td>
</tr>
<tr>
<td>Phase, degrees</td>
<td>17.5 (39.6)</td>
<td>38.3 (18.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>(low frequency)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gain (low frequency)</td>
<td>1.0 (0.3)</td>
<td>1.0 (0.3)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

Values represent mean (SD) for all continuous variables and proportions for categorical variables unless otherwise stated. WFNS indicates World Federation of Neurosurgeons.

*a* Represent median (interquartile range).

aVSP and DCI. In patients with SAH, transfer function gain >0.98 alone was fairly specific for aVSP (73%), and transfer function phase <12.5 alone was highly specific for predicting DCI (98%). The addition of transfer function parameters that reflect the effectiveness of dynamic cerebral autoregulation (ie, phase and gain) to clinical and radiographic measures modestly but significantly improved the specificity and sensitivity of identifying patients at high risk for aVSP and DCI. Thus, although our study was a pilot trial with limited number of subjects, our results highlight the potential importance of cerebrovascular control in the development of aVSP and DCI, as well as the potential advantage of incorporating measures of cerebral autoregulation into predictive models of vasospasm or DCI.

Previous studies that attempted to predict the clinical outcomes of vasospasm or DCI have been limited by how these outcomes were defined and ascertained.10,12 The use of cerebral blood flow velocity alone to diagnose vasospasm is limited,24 and a purely clinical diagnosis of DCI may be confounded by various other medical comorbidities unrelated to ischemic injury. In our study, we relied on imaging criteria alone for DCI, current recommended standard for DCI reporting,16–18 and aVSP was ascertained from conventional 4-vessel angiogram, the accepted gold standard for this diagnosis. The use of continuous variables as predictors has also been a limiting factor,25 making it difficult to apply such models at the

Table 3. Sensitivity, Specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV), and Area Under the Receiver Operating Characteristic Curve (AUROC) for Various Clinical and Autoregulatory Predictors of Angiographic Vasospasm (aVSP) and Delayed Cerebral Ischemia (DCI)

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
<th>AUROC</th>
</tr>
</thead>
<tbody>
<tr>
<td>aVSP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gain &gt;0.98 alone</td>
<td>64.3</td>
<td>73.1</td>
<td>79.4</td>
<td>55.9</td>
<td>0.69</td>
</tr>
<tr>
<td>Model 1*</td>
<td>73.8</td>
<td>84.6</td>
<td>88.6</td>
<td>66.7</td>
<td>0.86</td>
</tr>
<tr>
<td>Model 2*</td>
<td>90.5</td>
<td>69.2</td>
<td>82.6</td>
<td>81.8</td>
<td>0.90</td>
</tr>
<tr>
<td>DCI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase &lt;12.5 alone</td>
<td>46.2</td>
<td>98.2</td>
<td>85.7</td>
<td>88.5</td>
<td>0.72</td>
</tr>
<tr>
<td>Model 3*</td>
<td>53.9</td>
<td>98.2</td>
<td>87.5</td>
<td>90.0</td>
<td>0.92</td>
</tr>
<tr>
<td>Model 4*</td>
<td>61.5</td>
<td>96.4</td>
<td>80</td>
<td>91.3</td>
<td>0.94</td>
</tr>
</tbody>
</table>

Model 1: Stepwise forward selection model containing aneurysmal subarachnoid hemorrhage, smoking, and age ≤60 y as independent variables. Model 2: Model 1 plus transfer function gain >0.98. Model 3: Stepwise forward selection model containing World Federation of Neurosurgeons (WFNS) score IV to V, admission blood glucose >155 mg/dL, and mean arterial pressure >90 mm Hg on days 2 to 4. Model 4: Model 3 plus phase <12.5 degrees.

*P<0.01 comparing model 1 to model 2, and P=0.03 comparing model 3 to model 4.

Figure 2. Transfer function phase (A), gain (B), and mean flow velocity (C) in patients with and without delayed cerebral ischemia (DCI). Average transfer function phase, gain, and mean flow velocity across days 2 to 4 in the low frequency (LF; 0.03–0.15 Hz) and high frequency (HF; 0.15–0.5 Hz) ranges for patients with and without DCI. *P<0.05.
Cerebral Autoregulation in Subarachnoid Hemorrhage

Table 4. Scoring Tools for Angiographic Vasospasm (aVSP; SAGA Score) and Delayed Cerebral Ischemia (DCI; WHAP Score)

<table>
<thead>
<tr>
<th>Category</th>
<th>(aVSP; SAGA Score)</th>
<th>Delayed Cerebral Ischemia (DCI; WHAP Score)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β-Coefficient*</td>
<td>95% CI for β</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.77</td>
<td>0.15–3.38</td>
</tr>
<tr>
<td>Age ≤60 y</td>
<td>3.43</td>
<td>1.04–5.82</td>
</tr>
<tr>
<td>Gain &gt;0.98</td>
<td>1.92</td>
<td>0.43–3.41</td>
</tr>
<tr>
<td>Aneurysmal SAH</td>
<td>4.02</td>
<td>1.65–6.39</td>
</tr>
<tr>
<td>WHAP score for DCI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WFNS score IV to V</td>
<td>2.80</td>
<td>0.14–5.45</td>
</tr>
<tr>
<td>Hyperglycemia (glucose &gt;155 mg/dL)</td>
<td>1.31</td>
<td>−0.66 to 3.27</td>
</tr>
<tr>
<td>Mean arterial pressure, &gt;90 mm Hg</td>
<td>3.36</td>
<td>0.79–5.92</td>
</tr>
<tr>
<td>Phase &lt;12.5 degrees</td>
<td>3.32</td>
<td>1.90–10.19</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; SAGA, Smoking, Age, Gain, Aneurysmal SAH; SAH, subarachnoid hemorrhage; WFNS, World Federation of Neurosurgeons; and WHAP, WFNS, Hyperglycemia, Arterial Pressure, Phase.

*Obtained from stepwise logistic regression models adjusted for included predictors.

Our modeling approach with statistically derived cut-off points for risk prediction effectively translates these measures into bedside clinical tools. Although we recognize that dichotomizing continuous variables may result in some loss of information, our focus and emphasis in this study was on clinical utility. Consistent with this emphasis, it is also important to note that our measures rely on the use of transcranial Doppler ultrasound, which is a noninvasive tool available at bedside in the majority of neurointensive care units and is already routinely used for clinical monitoring of vasospasm.

The SAGA and WHAP scores developed and proposed in this study incorporate established clinical and autoregulatory measures to enhance our ability to accurately identify SAH patients at high risk for secondary complications in the first few days after their admission. Accurate prediction of aVSP and DCI shortly after initial SAH (within the first 4 days) can facilitate individualized medical or endovascular measures for patients with SAH. Moreover, given their high specificity and sensitivity, the scores developed in this study can also help in the selection or proper risk stratification of patients for future randomized clinical trials. Thus, the SAGA score for vasospasm and WHAP score for DCI, which combine simple clinical and physiological parameters, offer great promise for both clinical and research applications.

The positive association of transfer function gain with aVSP and the negative association of transfer function phase with DCI support the hypothesis that autoregulation may be impaired in the first few days after SAH, and that the degree of this impairment may be related to the development of secondary complications. With intact autoregulation, cerebral vessels effectively buffer against slow arterial fluctuations. Thus, there is delay (high phase) and dampening (low gain) in the transmission of pressure fluctuations to cerebral flow. We showed that in early SAH, autoregulation is impaired as manifested by a low phase (DCI) and a high gain (VSP) between pressure and flow fluctuations. Previous studies support that deterioration in cerebral autoregulation precedes vasospasm without a marked change in blood flow velocity,1,2 and patients with intact cerebral autoregulation after initial hemorrhage seem to have lesser risk of vasospasm and DCI regardless of the absolute cerebral blood flow velocity.7,13,26 The differential association of gain and phase with aVSP and DCI, respectively, may suggest that potentially different mechanisms of dysregulation may contribute to subsequent development of vasospasm and DCI. However, although increased gain and reduced phase both indicate an impairment of cerebral autoregulation, they are insufficient to tease apart physiological mechanisms of autoregulation.27,28

Lastly, we acknowledge that risk scores do best in the population from which they are derived. Therefore, these scores will need to be validated in a larger and independent cohort before they can be fully adopted in clinical settings. Nevertheless, to improve the validity of our findings, we have used in our models only carefully selected predictive factors derived mainly from systematic reviews of DCI risk factors5,6 and established risk factors for vasospasm.4,29,30 Moreover, the likelihood of including superfluous independent predictors was minimized via sensitivity analyses, and generalizability of the models was rigorously tested via well-established internal validation procedures.

In conclusion, our study provides further evidence that cerebral autoregulation is impaired in the early days after SAH, long before there is any other evidence of clinical or radiographic deterioration. The addition of autoregulatory parameters to clinical and radiographic variables can improve our ability to identify patients at a high risk for aVSP and DCI after SAH. Therefore, the SAGA and WHAP scores, which combine simple clinical variables with those related to cerebrovascular regulation, hold promise as clinical tools in neurointensive care units.

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**Disclosures**

None.

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SUPPLEMENTAL MATERIAL

Impaired Cerebral Autoregulation is Associated with Vasospasm and Delayed Cerebral Ischemia in Subarachnoid Hemorrhage

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SUPPLEMENTAL METHODS

Clinical Management
All patients with SAH are admitted to the NICU at the BWH. Initial diagnosis is made by admission CT and CTA and confirmed by conventional angiography (angio). They are all treated (clip or coil) within 24 hours of admission. All patients undergo a second angio between days 6-8. TCD studies start on admission. They are all treated with nimodipine and an anticonvulsant. They are all kept euthermic, euvoletic, and euglycemic, and undergo daily TCD monitoring. Patients with abnormal TCD velocities or clinical vasospasm undergo CTA or conventional cerebral angiography. Those with moderate or severe angiographic vasospasm are treated with intraarterial (IA) nicardipine. All patients with clinical, TCD, or angiographic vasospasm are also treated with induced hypertension (systolic blood pressure >160 mm Hg) and hypervolemia (central venous pressure >8 cm H2O) until the resolution of vasospasm.

Outcome Definition and Ascertainment
Angiographic vasospasm (aVSP) was defined as >30% reduction in caliber of any cerebral artery on digital subtraction cerebral angiography performed between days 6-8 post SAH compared to baseline angiogram at SAH presentation1,2 and was assessed by neuroradiologists blinded to TCD measures. Delayed cerebral ischemia (DCI) was defined radiographically as any cerebral infarct on the latest CT scan that was seen within 6 weeks after SAH or before discharge or death, that was not present on admission scan or on the CT scan done within 24 to 48 hours after any aneurysmal treatment procedures1,3,4. All head CT scans were reviewed for DCI ascertainment by two neuroradiologists (A.P and A.Z) blinded to the clinical and TCD data using the standardized protocol recommended by Vergouwen et al4. Procedural infarcts were determined in the following way. All patients had a CT scan within 48 hours after any intracranial procedure. All these post-procedural CT scans were compared to the latest scan done within 6 weeks after SAH or the latest scan made before death or discharge within 6 weeks by the two neuroradiologists. Infarcts seen on the post procedural scans were classified as procedure-related and were not included in our DCI analysis. Only new infarcts not seen on the scans performed within 48 hours of a surgical clip, endovascular procedure, ventricular catheter or intraparenchymal hematoma were considered as cerebral infarction from DCI.

Clinical Data Collection
Data on age, sex, smoking status, history of hypertension, history of diabetes mellitus, blood levels of glucose, magnesium and hemoglobin on admission were available on all patients. Clinical severity of SAH on admission was assessed using both the Hunt and Hess (H&H) scores and World Federation of Neurology Score (WFNS), and radiological severity was assessed using the Fisher grading system. WFNS grades IV-V5 and H&H grades 4-56 were considered as severe clinical conditions and Fisher grades 3-4 were considered as radiographically severe SAH.7

Dynamic Cerebral Autoregulation:
All patients had daily TCD measurements, heart rate, and blood pressure monitoring. Data were analyzed using methods that we have described previously. Briefly, transfer function analysis was used to analyze the relationship between beat-to-beat fluctuations in mean arterial pressure (MAP) and mean flow velocity (MFV) across the low (0.03-0.15 Hz) and high frequency (HF: 0.15-0.5). Since dynamic cerebral autoregulation can take about 2-10 seconds to engage, frequency domain analysis is typically studied at frequency ranges < 0.15 Hz.

The cross spectrum between MAP and MFV signals are used to determine coherence, phase and gain of the transfer function. The transfer function phase shift reflects the temporal difference between cerebral MFV oscillations with respect to MAP oscillations. When the oscillations of MFV and MAP are almost synchronous, the phase shift approaches zero, reflecting impaired dynamic cerebral autoregulation. Transfer function gain, on the other hand, reflects the magnitude of transmission of blood pressure oscillations to cerebral blood flow velocity oscillations. When dynamic cerebral autoregulation is intact, the transmission of low frequency blood pressure oscillations onto cerebral blood flow velocity is dampened. Therefore, lower gain, particularly in the low frequency range, is reflective of more effective dynamic cerebral autoregulation. Coherence reflects the validity of the analysis. It varies between 0 and 1, similar to a correlation coefficient, and expresses the fraction of MFV signal that is linearly associated with MAP. Because effective cerebral autoregulation creates uncertainty in linear estimates of the gain and phase of the system, confidence intervals and precision of estimate for transfer function phases and gains were derived from the level of coherence and transfer function parameters, based on the standard random theory. Subsequently, these precisions were used as weights to obtain the most accurate representation of transfer function estimates in subsequent statistical analysis. Transfer function analyses were performed using custom software written in Matlab (version R2009b, Mathworks, Natick, MA).

Statistical Analysis

All analyses involving TCD and hemodynamic measures were performed using data collected during days 2-4 post-SAH. Data for SAH day 1 were not used because we did not have sufficient TCD data on most patients on day 1, and a significant association between cerebral autoregulation and DCI is not expected on the first day post-SAH. We also did not include the data beyond the fourth day post-SAH in our analysis because vasospasm and/or its treatment may have commenced by day 5. There was no significant difference between transfer function phase and gain in the right and left MCAs or across days 2 – 4. Therefore, transfer function phase and gain were averaged across sides and days for analysis.

Continuous variables were expressed as means (+/- standard deviation) and categorical variables as proportions. After testing for normality of distribution of the data (Shapiro-Wilk test), continuous variables were compared between patient groups (vasospasm vs. no-vasospasm, and DCI vs. no-DCI) using unpaired Student’s t-test (when data is normally distributed) or Wilcoxon Rank-Sum test. Categorical variables were compared using the Fisher’s Exact test. We did not perform comparisons between vasospasm and DCI because all but three of the DCI patients also had angiographic vasospasm.

Optimal Phase and Gain Cut-off Points for aVSP and DCI Prediction
Classification and Regression Tree (CART) models containing clinical variables alone, transfer function parameters alone, or clinical variables and transfer function parameters together as independent variables were used to derive optimal cut-off points for significant predictors of vasospasm or DCI. Separate models with aVSP or DCI as dependent variables were constructed. Each CART-derived cut-off point for continuous predictors were examined for clinical plausibility and only cut-off points that made clinical sense were used in subsequent analysis. The theory and application of CART models for similar risk stratification models is described extensively elsewhere.14-16 Briefly, CART models utilize a binary recursive-partitioning algorithm to determine the optimal criteria for splitting independent variables into groups so that misclassification rate of a categorical dependent variable is minimized.

After deriving cut-off points for continuous variables, we used a forward step-wise logistic regression (entry criterion of p<0.10) to derive parsimonious multivariable models for prediction of each outcome (vasospasm and DCI). To better assess the contribution of clinical variables and transfer function parameters to these prediction models, we utilized three separate logistic models for each dependent variable: one with clinical variables alone as independent variables, one with transfer function parameters alone, and one with both clinical variables and transfer function parameters. Subsequently, we assessed the discriminative performance of each of these models using the area under the receiver-operator characteristic (ROC) curve, and compared their statistical fit via likelihood ratio test. In addition to the results of these tests, we also report positive predictive value (the ratio of true positives to the sum of true and false positives – TP / (TP + FP)) and negative predictive value (TN / (TN + FN)) as well as the sensitivity (TP / (TP + FN)) and specificity (TN / (TN + FP)) to facilitate interpretation of the predictive power of these models.

Derivation and Validation of a Scoring Tool

Point estimates of the beta coefficients of significant predictors in the final stepwise models were rounded to the nearest whole number and these numbers were used as covariate-weighted scores to predict outcome as has been described previously.17-19 For example, a variable with a beta-coefficient of 3.1 received 3 points when present and 0 when absent, while another with a beta-coefficient of 1.9 received 2 points when present. An individual’s overall risk score was calculated as the sum total of his covariate-weighted scores for all independent variables. The discriminative performance of the scoring tool for each outcome was again assessed via ROC curves, and model calibrations were assessed using the Hosmer-Lemeshow goodness-of-fit test.

Ideally, an independent data set would be needed to externally validate each scoring tool. However, we relied on two separate procedures for internal validation: (1) bootstrapping, because it produces stable and unbiased estimates of predictive accuracy20 and (2) Jack-knife (leave-one-out) resampling procedure, because of our relatively small sample size. Average bias-corrected C-statistic obtained from 1000 bootstrap models (each equal in size to our original dataset and allowing for multiple sampling of the same individual) was used to more accurately estimate the model performance of each scoring tool and its potential for generalization to other populations while Jack-knife estimates provided a further measure of model bias and variance.

Sensitivity Analysis
In forward step-wise models, independent variables are added to the model in random order until the overall predictive power cannot be further improved. One might use a backward-elimination approach instead, wherein all independent variables are initially included in the model, and subsequently, those that do not reach statistically significant predictive power are eliminated. Regression models constructed via both approaches may contain different predictor variables, especially if the sample size is small. As a sensitivity analysis, we constructed backward stepwise models for each dependent variable and evaluated the agreement between this model selection procedure and the forward stepwise approach used in primary analysis, in terms of the selection of final independent variables.

Classification and Regression Tree analysis was done using SPSS 21 (IBM Corp. Armonk, NY). All other analyses were done using STATA 11 (StataCorp. 2009, College Station, TX). A p-value of <0.05 was assumed for statistical significance.
SUPPLEMENTAL TABLES

Table I. Model Performance Characteristics of the SAGA Score for aVSP and WHAP score for DCI

<table>
<thead>
<tr>
<th></th>
<th>SAGA</th>
<th>WHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>90.4</td>
<td>61.5</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>69.2</td>
<td>96.4</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>82.6</td>
<td>80.0</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>81.8</td>
<td>91.4</td>
</tr>
<tr>
<td>Area under the ROC</td>
<td>0.90 (0.82, 0.97)</td>
<td>0.93 (0.87, 0.99)</td>
</tr>
<tr>
<td>Bootstrapped Area under the ROC</td>
<td>0.90 (0.78-0.99)</td>
<td>0.94 (0.82, 1.00)</td>
</tr>
<tr>
<td>Hosmer-Lemeshow test (p-value)</td>
<td>0.95</td>
<td>0.53</td>
</tr>
<tr>
<td>Odds Ratio (CI)</td>
<td>2.62 (1.62-4.24)</td>
<td>2.80 (1.66-4.74)</td>
</tr>
<tr>
<td>Bootstrap estimate (CI)</td>
<td>2.62 (1.47-4.67)</td>
<td>2.80 (1.47-5.31)</td>
</tr>
<tr>
<td>Jack-Knife estimates (CI)</td>
<td>2.62 (1.59-4.32)</td>
<td>2.80 (1.64-4.78)</td>
</tr>
<tr>
<td></td>
<td>Backward Model</td>
<td>Forward Model</td>
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<tr>
<td>----------------------</td>
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<td>--------------</td>
</tr>
<tr>
<td></td>
<td>β (95% CI for β)</td>
<td>β (95% CI for β)</td>
</tr>
<tr>
<td><strong>aVSP</strong></td>
<td></td>
<td></td>
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<tr>
<td>Smoking</td>
<td>1.77(0.15, 3.38)</td>
<td>1.77(0.15, 3.38)</td>
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<tr>
<td>Age &lt;=60</td>
<td>3.43(1.04, 5.82)</td>
<td>3.43(1.04, 5.82)</td>
</tr>
<tr>
<td>Gain &gt;0.98</td>
<td>1.92(0.43, 3.41)</td>
<td>1.92(0.43, 3.41)</td>
</tr>
<tr>
<td>Aneurysmal SAH</td>
<td>4.02(1.65, 6.39)</td>
<td>4.02(1.65, 6.39)</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>90.4</td>
<td>90.4</td>
</tr>
<tr>
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<td>Area under the ROC</td>
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<td>0.90</td>
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<tr>
<td><strong>DCI</strong></td>
<td></td>
<td></td>
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<tr>
<td>Phase &lt;12.5</td>
<td>6.1 (1.9-10.2)</td>
<td>3.3 (0.1-6.6)</td>
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<tr>
<td>WFNS IV-V</td>
<td>2.6 (-0.4-5.5)</td>
<td>2.8 (0.1-5.4)</td>
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<tr>
<td>Aneurysmal SAH</td>
<td>2.4 (-0.3-5.0)</td>
<td>Not included</td>
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<tr>
<td>MAP &gt;90mmHg</td>
<td>4.8 (1.3-8.3)</td>
<td>3.4 (0.8-5.9)</td>
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<tr>
<td>Background hypertension</td>
<td>2.3 (-0.4-4.9)</td>
<td>Not included</td>
</tr>
<tr>
<td>Admission glucose &gt;155mg/dl</td>
<td>Not included</td>
<td>1.3(-0.7-3.3)</td>
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<tr>
<td>Sensitivity (%)</td>
<td>76.9</td>
<td>61.5</td>
</tr>
<tr>
<td>Specificity (%)</td>
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<td>96.4</td>
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<tr>
<td>PPV (%)</td>
<td>71.4</td>
<td>80.0</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>94.4</td>
<td>91.4</td>
</tr>
<tr>
<td>Area under the ROC</td>
<td>0.95</td>
<td>0.94</td>
</tr>
<tr>
<td>Hosmer-Lemeshow p-value</td>
<td>0.97</td>
<td>0.72</td>
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</table>
SUPPLEMENTAL REFERENCES


