Impairment of Cerebral Autoregulation Predicts Delayed Cerebral Ischemia After Subarachnoid Hemorrhage: A Prospective Observational Study

Karol P. Budohoski, MD; Marek Czosnyka, PhD; Peter Smielewski, PhD; Magdalena Kasprowicz, PhD; Adel Helmy, MRCS, PhD; Diederik Bulters, FRCS(SN); John D. Pickard, FRCS, FMedSci; Peter J. Kirkpatrick, FRCS(SN), FMedSci

Background and Purpose—Delayed cerebral ischemia (DCI) is a recognized contributor to unfavorable outcome after subarachnoid hemorrhage (SAH). Recent data challenge the concept of vasospasm as the sole cause of ischemia and suggest a multifactorial process with dysfunctional cerebral autoregulation as a component. We tested the hypothesis that early autoregulatory failure, detected using near-infrared spectroscopy–based index, TOxa and transcranial Doppler–based index, Sxa, can predict DCI.

Methods—In this prospective observational study we enrolled consecutive patients with aneurysmal SAH that occurred <5 days from admission. The primary end point was the occurrence of DCI within 21 days of ictus. The predictive value of autoregulatory disturbances detected in the first 5 days was assessed using univariate proportional hazards model and a multivariate model.

Results—Ninety-eight patients were included. Univariate analysis demonstrated increased odds of developing DCI when early autoregulation failure was detected (odds ratio [OR], 7.46; 95% confidence interval [CI], 3.03–18.40 and OR, 4.52; 95% CI, 1.84–11.07 for Sxa and TOxa, respectively) but not TCD-vasospasm (OR, 1.36; 95% CI, 0.56–3.33). In a multivariate model Sxa and TOxa remained independent predictors of DCI (OR, 12.66; 95% CI, 2.97–54.07 and OR, 5.34; 95% CI, 1.25–22.84 for Sxa and TOxa, respectively).

Conclusions—Disturbed autoregulation in the first 5 days after SAH significantly increases the risk of DCI. Autoregulatory disturbances can be detected using near-infrared spectroscopy and transcranial Doppler technologies. (Stroke. 2012;43:000-000.)

Key Words: brain ischemia • cerebral autoregulation • spectroscopy, near-infrared • subarachnoid hemorrhage • transcranial Doppler

Delayed cerebral ischemia (DCI), commonly attributed to vasospasm, is a major contributor to unfavorable outcome after subarachnoid hemorrhage (SAH). However, recent data challenge the concept of vasospasm as the sole cause of ischemia after SAH.2,3 Studies have demonstrated that disturbed cerebral autoregulation may play a part in the development of DCI and promote poor outcome.4–11 The ability to compensate for the reduced perfusion pressure distal to spastic vessels may be reduced when autoregulatory mechanisms are impaired,4–9 suggesting that accurate detection of dysautoregulation could identify patients at risk of DCI.

Transcranial Doppler (TCD) is an accepted tool used for assessment of cerebral autoregulation.12,13 Near-infrared spectroscopy (NIRS) has shown promise in recent studies as a noninvasive and continuous monitoring modality.14–16 Its usefulness in indirect monitoring of CBF has been convincingly demonstrated during carotid endarterectomy,17 and it has been applied to monitoring autoregulation.15,16

In this prospective observational study we test the hypothesis that TCD and NIRS technologies can be used for noninvasive detection of early disturbances in cerebral autoregulation after SAH and that these disturbances are related to the development of DCI.

Methods

Patients and Management

All patients admitted to the Department of Neurosurgery of this institution between June 2010 and January 2012 with SAH were screened for eligibility. Inclusion criteria were as follows: ≥18 years of age; aneurysmal SAH confirmed with either computed tomography angiography (CTA) or
digital subtraction angiography (DSA); <5 days elapsed from ictus. We have additionally excluded patients with an unclear history of ictus. The study was approved by the local Research Ethics Committee.

Patients were treated according to current guidelines. Initial management included prompt cardiopulmonary support (if required), maintenance of euvolemia, oral nimodipine 60 mg every 4 hours, and treatment of acute hydrocephalus with external ventricular drainage. The decision to treat by surgical clipping or endovascular embolization was performed on the basis of consensus between a team of neurosurgeons and interventional radiologists.

All patients had TCD performed every 1–2 days by a single investigator (K.P.B.) to screen for cerebral vasospasm. Where clinically indicated, patients received DSA and CT perfusion. Delayed hydrocephalus was treated with external ventricular drainage, lumbar drainage, or serial lumbar punctures (decision was made at the discretion of the treating neurosurgeon) until a decision that permanent cerebrospinal fluid diversion is needed was made. Electroencephalography was performed when seizures were suspected as the cause of neurological deterioration or lack of neurological progress. Phenytoin was used as the first line medication for seizure control.

When DCI was diagnosed, hemodynamic augmentation therapy was instituted. Intravenous crystalloids were administered to maintain a central venous pressure 8–12 mmHg. Blood pressure support was achieved with individually titrated doses of vasopressors (norepinephrine, dobutamine, or arginine vasopressin) to achieve improvements in the neurological status (typically mean arterial pressure of 110–120 mmHg was targeted). Balloon angioplasty and intra-arterial administration of vasodilators were not routinely performed.

Definitions and End Points
The primary end point was DCI within 21 days after SAH. DCI was defined as a new focal neurological deficit or lack of neurological progress (a drop of ≥2 points on the Glasgow Coma Scale [GCS]) lasting >2 hours, after exclusion of intracranial hemorrhage, hydrocephalus, seizures, metabolic derangements, and infection, with or without radiological signs of cerebral vasospasm. In unconscious patients the diagnosis of DCI was made when there was a lack of neurological progress in the absence of confounders (as above and after imaging did not reveal other sources of brain damage) and with evidence of 1 of the following: cerebral vasospasm either on TCD or DSA; perfusion deficit on CT perfusion; cerebral infarction on imaging not attributable to other causes.

The presence of DCI at 21 days was determined on clinical grounds by the responsible neurosurgical team. Patients discharged before completing 21 days of the study were deemed not to have DCI unless readmitted for new neurological symptoms. Patients who died before completing the full 21 days of the study were deemed not to have DCI. Patients who died prior to completion of the study. In three of these patients DSA and CT perfusion; cerebral infarction on imaging not attributable to other causes.

Data Collection and Monitoring
All patients underwent multimodal neuromonitoring of arterial blood pressure (ABP), FV in the middle cerebral artery (MCA) exceeding 120 cm/s with a concomitant Lindegaard Ratio above 3.0 or, when DSA was performed, as narrowing of cerebral arteries on DSA. Routine postoperative CT and DSA were not performed.

Data Collection and Monitoring
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Calculation of Autoregulatory Indices
Calculation of autoregulatory indices was performed with monitoring data anonymized to blind the investigators to the clinical events. The TCD-derived autoregulation index (Sxa) was calculated as a moving linear correlation coefficient between values of systolic FV and ABP from a 300-second window with averaging every 10 seconds. The NIRS-derived autoregulatory index (TOxa) was calculated as a moving linear correlation coefficient between values of TOI and ABP from a 300-second window with averaging every 10 seconds. Both Sxa and TOxa have been previously used to monitor autoregulation in patients with acute cerebral injury, including SAH. ABP was used instead of cerebral perfusion pressure (CPP) because of lack of availability of CPP (previous studies report a good correlation between ABP- and CPP-based indices of autoregulation). The physiological basis for the chosen methodology has been described elsewhere.

The assumption of normal distribution was confirmed using the Shapiro–Wilk test, at the level of significance of 0.05, therefore parametric tests were used. Receiver operator characteristic curve for predicting DCI using continuous recordings of FV, Sxa, and TOxa from day 0 to 5 were constructed. These were used to select thresholds of Sxa and TOxa indicating impaired autoregulation and dichotomized data for further analysis. Empirical regression was used to demonstrate the temporal profile of FV and autoregulatory changes in patients with and without DCI. Kaplan–Meier plots and Cox proportional hazards model (using dichotomized data from days 0–5) were used to assess the difference in the 21-day risk of developing DCI for patients with impaired and intact autoregulation and TCD-vasospasm findings. A binary logistic regression model was used to assess the ability of impaired autoregulation on days 0 to 5 detected using TCD and NIRS to predict the development of DCI. All independent predictors were then used to calculate the positive predictive value (PPV) and negative predictive value (NPV) for DCI.

Statistical Analysis
Statistical analysis was performed using SPPS software (IBM). In patients in whom unilateral vasospasm was diagnosed using TCD, recordings from the ipsilateral side were used for analysis. In patients in whom bilateral vasospasm was not diagnosed, recordings from the side ipsilateral to the aneurysm were used for analysis. In patients with midline aneurysms but without diagnosed vasospasm, an average of both sides was used for analysis. All autoregulatory indices were averaged per session. In patients where ipsilateral recordings were used, the recordings from the contralateral side were disregarded and not used for DCI prognostication.

Results
Ninety-eight patients were included in the study. Six patients died prior to completion of the study. In three of these patients DCI was diagnosed. Fifty two patients had TCD/DSA evidence of cerebral vasospasm, while 32 developed DCI. Table 1 summarizes the basic clinical characteristics of both groups.

Cerebral vasospasm was diagnosed on median day 6 postictus (range 1–13 days) and DCI on day 8 (range 3–12 days).
The averaged values of the monitored parameters from the whole monitoring time and from the first 5 days are presented in Supplemental Table 1. Importantly there were no differences in the level of pCO₂ in the DCI and non-DCI groups for both the whole monitoring period as well as the first 5 days (P=0.998 and P=0.22, respectively), which is known to influence autoregulation. Differences in FV and ABP are seen between groups when averaged values from the whole monitoring are analyzed but not when the first 5 days are used (Supplemental Table 1), suggesting an influence of both macrovascular spasm and hemodynamic augmentation therapy. Figure 1 demonstrates an example of multimodal monitoring performed on day 4 post-SAH in a patient who later developed DCI.

The receiver operator characteristic curve designed to detect the ability of TCD-vasospasm and the two autoregulatory indices (from the first 5 days) to predict development of DCI was used to determine the value of Sxa and TOxa with the optimal sensitivity and specificity for later use in the univariate and multivariate analysis. The obtained thresholds were as follows: Sxa >0.1 and TOxa >0.1 (Supplemental Figure 1).

The temporal characteristic of FV, Sxa, and TOxa divided between DCI and non-DCI groups demonstrated an early
separation between the groups for Sxa and TOxa (Sxa, day 3; TOxa, day 2), but not for FV (day 10; Figure 2). Kaplan–Meier analysis showed that 35.3% of patients with TCD-defined vasospasm in the first 5 days and 30.8% of those with normal TCD recordings developed DCI \((P=0.49)\). On the other hand, 60.5% with impaired autoregulation on TCD developed DCI as opposed to 11.3% of those with intact autoregulation \((P<0.000001)\). Similarly, when autoregulation was impaired on NIRS, 49% of patients developed DCI whereas only 13.3% when NIRS autoregulation was intact \((P=0.0002)\). Cox analysis showed that the cumulative risk of DCI was significantly increased when Sxa and TOxa demonstrated impaired autoregulation in the first 5 days (Odds ratio [OR], 7.46; 95% confidence interval [CI], 3.03–18.40 and OR, 4.52; 95% CI, 1.84–11.07, respectively), but not when TCD-defined vasospasm was detected (OR, 1.36; 95% CI, 0.56–3.33; Figure 3).

When a binary logistic regression model with age, sex, admission World Federation of Neurosurgical Societies scale (WFNS), modified Fisher scale, sepsis, hydrocephalus, external ventricular drain, metabolic derangements, and abnormal TCD readings in the first 5 days post-ictus was used, both Sxa and TOxa (from the first 5 days) remained significant

Figure 1. Example of multimodal neuromonitoring of a patient 4 days after SAH from a ruptured right anterior choroidal artery aneurysm. The hemodynamic parameters including ABP, ICP, and CPP were within normal ranges. TCD examination did not demonstrate cerebral vasospasm. Autoregulatory indices (Sxa and TOxa) demonstrated impaired autoregulation ipsilateral to the side of the aneurysm (values close to 0.5). On day 10 the patient developed left-sided hemiparesis. TCD examination confirmed right MCA vasospasm, and CTP on day 14 demonstrated a subtle prolongation of MTT within the anterior right MCA territory. ABP indicates arterial blood pressure; ICP, intracranial pressure; CPP, cerebral perfusion pressure; TCD, transcranial Doppler; MCA, middle cerebral artery; CTP, computed tomography perfusion; MTT, mean transit time.

Figure 2. Empirical regression demonstrating the temporal changes of FV, TCD-derived autoregulatory index, Sxa, and NIRS-derived autoregulatory index, TOxa, in the DCI (gray line) and non-DCI groups (black line). An early failure of autoregulation is seen in the DCI group as compared with the non-DCI group (B and C). No clear differences in FV are seen in the early phase between the groups (A). Dashed line indicates the average day of DCI diagnosis. FV indicates flow velocity; TCD, transcranial Doppler; DCI, delayed cerebral ischemia; Sxa, systolic flow index; NIRS, near-infrared spectroscopy; TOxa, TOI derived index. *P<0.05.
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predictors of DCI (OR, 12.66; 95% CI, 2.97–54.07 and OR, 5.34; 95% CI, 1.25–22.84, respectively). The only other significant predictor was modified Fisher scale of 3 on admission CT (OR, 6.21; 95% CI, 1.45–26.68; Table 2). When both Sxa and TOxa simultaneously demonstrated impaired autoregulation the odds of DCI increased (OR,: 14.07; 95% CI, 3.86–51.36).

To determine the bias inflicted by the occurrence of DCI before day 5, these patients were excluded (n=8) and the same uni- and multivariate model were applied. Sxa and TOxa remained significant predictors of DCI (Supplemental Table 2 and Supplemental Figure 2).

Sxa demonstrated the highest PPV and NPV for DCI (0.62 and 0.89, respectively). The use of a combination of Sxa, TOxa, and the CT grading scale increased the PPV and NPV to 0.71 and 0.95, respectively (Table 3). However, the modest improvements gained by combining methods suggest a high degree of colinearity between TCD- and NIRS-based autoregulation indices.

### Discussion

We have demonstrated that impaired autoregulation in the first 5 days after SAH is predictive of DCI. These findings support the hypothesis that cerebral autoregulation plays an important role in the development of cerebral ischemia.

It has been previously demonstrated and here we confirmed, that autoregulation can be reliably determined using noninvasive techniques based on TCD, as well as NIRS. Furthermore, the results indicate significant colinearity between TCD- and NIRS-based assessment of cerebral autoregulation.

In the analyzed cohort, autoregulation was preserved on the first day postictus, with no differences demonstrated between DCI and non-DCI groups. Subsequently, in the DCI group, values of both TOxa and Sxa increased, indicating progressing dysautoregulation. Importantly, NIRS demonstrated dysautoregulation on average 1 day earlier than TCD. Significant differences between groups were seen on days 2 and 3 for TOxa and Sxa, respectively, whereas differences in FV were not found until days 10–12 (DCI developed on average on day 6). Analysis of monitoring data from days 0 to 5 post-SAH demonstrated a 7- and 5-fold (for Sxa and TOxa, respectively) increased odds of developing DCI when early dysautoregulation was present, whereas the presence of TCD-defined

### Table 2. Binary Logistic Regression Model for Predicting DCI

<table>
<thead>
<tr>
<th>B (Standard Error)</th>
<th>Wald</th>
<th>P</th>
<th>OR</th>
<th>95% CI for OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age&gt;55 y</td>
<td>−0.68 (0.68)</td>
<td>0.98</td>
<td>0.32</td>
<td>0.51</td>
</tr>
<tr>
<td>Male sex</td>
<td>−0.05 (0.74)</td>
<td>0.004</td>
<td>0.95</td>
<td>0.95</td>
</tr>
<tr>
<td>WFNS</td>
<td>−0.12 (0.27)</td>
<td>0.19</td>
<td>0.66</td>
<td>1.12</td>
</tr>
<tr>
<td>Mod Fisher 3</td>
<td>1.83 (0.74)</td>
<td>6.04</td>
<td>0.014</td>
<td>6.21</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>0.11 (0.85)</td>
<td>0.02</td>
<td>0.9</td>
<td>1.11</td>
</tr>
<tr>
<td>EVD</td>
<td>0.21 (1.05)</td>
<td>0.04</td>
<td>0.84</td>
<td>1.23</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1.49 (0.9)</td>
<td>2.79</td>
<td>0.095</td>
<td>4.42</td>
</tr>
<tr>
<td>Metabolic derangements</td>
<td>−1.13 (1.02)</td>
<td>1.23</td>
<td>0.27</td>
<td>0.32</td>
</tr>
<tr>
<td>FV&gt;120 [cm/s]; LR&gt;3.0</td>
<td>−0.92 (0.79)</td>
<td>1.38</td>
<td>0.24</td>
<td>0.4</td>
</tr>
<tr>
<td>Sxa</td>
<td>2.54 (0.74)</td>
<td>11.75</td>
<td>0.001</td>
<td>12.66</td>
</tr>
<tr>
<td>TOxa</td>
<td>1.68 (0.74)</td>
<td>5.11</td>
<td>0.024</td>
<td>5.34</td>
</tr>
</tbody>
</table>

95% CI indicates 95% confidence interval; EVD, external ventricular drain; FV, flow velocity; LR, Lindegaard Ratio; OR, odds ratio; Sxa, systolic flow index; TOxa, TOI derived index; WFNS, World Federation of Neurosurgical Societies scale.

Model Summary: $\chi^2 = 43.53, P=0.000009, R^2=0.556$ (Nagelkerke).

Bold text indicated significant P value.
vasospasm during the first 5 days did not result in increased risk of DCI. These results indicate that assessment of autoregulation using TCD or NIRS can be used to gauge the risk of DCI.

The role of disturbed autoregulation in the pathophysiology of DCI has been previously demonstrated. However, the small numbers, inclusion of only poor grade SAH patients, use of invasive monitoring techniques, and univariate analysis did not allow for wide generalization. Nevertheless, it has been shown that early dysautoregulation is predictive of poor outcome. The present study confirms these findings in a large cohort, constituting all clinical grades of SAH patients, using noninvasive NIRS and TCD methodology. However, the temporal characteristics of autoregulatory disturbances presented here differ from previous results. In our cohort autoregulation was intact in the first 48 to 72 hours post-SAHI with subsequent deterioration seen in the DCI group. Jaeger et al. demonstrated impaired autoregulation in the acute phase in the majority of patients with improvements seen in the noninfarction groups. The inclusion of all WFNS grades in the present study, in contrast to poor grade patients only in the study by Jaeger et al., provides a possible explanation for these differences.

In a multivariate model which included age, sex, WFNS grade, hydrocephalus and external ventricular drainage, sepsis, metabolic derangements, and early vasospasm on TCD, only modified Fisher grade 3 and disturbed autoregulation during the first five days were independent predictors of DCI. Disturbed autoregulation on TCD was the strongest predictor, with a 13 fold increased risk of DCI, while a fivefold increase was seen when NIRS autoregulation was impaired. Furthermore, NIRS-based autoregulation disturbances occurred one day before TCD-based impairments, providing an earlier indication of clinical worsening. The moderate improvement in PPV and NPV for DCI when both modalities were used jointly suggests high co-linearity. The relative advantages of NIRS, such as the feasibility of continuous monitoring or the vascular territories covered (the location of NIRS optodes coincides with MCA and ACA watershed area) make it a desirable technique.

Despite the good discriminatory value of both Sxa and TOxas shown using Kaplan–Meier analysis, 11% and 13% of patients with intact autoregulation in the first 5 days post-SAH developed DCI, respectively. Experimental data suggest that DCI is a multifactorial process, with a number of contributors likely to play a role. Furthermore, highly focal disturbances of cerebral blood flow and autoregulation may not be identified with the used methodology because of limited spatial resolution.

In the present study we have used DCI as the primary outcome measure. We acknowledge that cerebral infarction on imaging have been suggested as a more objective method, the gold standard for outcome reporting. However, in our institution routine follow-up imaging is not performed, precluding their use as a universal outcome measure. Clinical outcome after SAH, although related to the incidence of cerebral infarctions, is influenced by a number of factors including medical complications not connected with DCI, such as sepsis or cardiopulmonary complications. Therefore, the use of clinical outcome as an end point would likely result in diluting the relationship between autoregulation and cerebral blood flow instability. The diagnosis of DCI is difficult, and care needs to be taken to reliably exclude confounders. Furthermore, the diagnosis is difficult in patients who are unconscious, where neurological assessment cannot be readily performed. In the present study DCI was diagnosed by the neurosurgical team in charge of the patient only when all predefined criteria were met.

The arbitrary chosen timeframe for testing autoregulation of days 0 to 5 post-SAH was based on previous publications where the onset of cerebral vasospasm was shown to peak after day 6 to 10. We aimed to choose a period before the onset of cerebral vasospasm for two reasons: (1) to minimize findings of dysautoregulation resultant from distal vasodilatation, a compensatory mechanism during large artery narrowing; and (2) for pragmatic reasons, to determine the potential for early stratification of risk and allocation of in-hospital resources such as Intensive Care Unit stay or early discharge. It needs to be acknowledged that this method places TCD FV/ Lindegaard Ratio prediction of DCI at a disadvantage, as TCD monitoring commonly becomes abnormal shortly before the onset of clinical symptoms. However, we believe that the chosen timeframe augments the clinical usefulness of the present study, potentially strengthening the argument for early discharge of good-grade low-modified Fisher scale patients with functioning autoregulation, as well as allowing for early initiation of close observation in the intensive care setting for patients at high risk of DCI.

We have used a MCA FV >120 cm/s with a Lindegaard Ratio >3.0 to define vasospasm. TCD is an accepted method for evaluating the presence of vasospasms. Although higher thresholds have been used, 120 cm/s is accepted for monitoring patients after SAH and has been shown to correlate with ischemic symptoms. Furthermore, even with the low threshold, 30% of patients with normal FV developed DCI suggesting that the use of higher cut off values would likely further reduce the sensitivity of this method.

In the present study we have not used CPP for calculation of autoregulatory indices. Although better discriminatory value of invasive indices has been demonstrated in head injury, patients with SAH do not routinely receive intracranial monitoring.

The implemented methodology of assessing cerebral autoregulation has intrinsic limitations. It relies on the presence...
of slow blood pressure oscillations as triggers of autoregulatory responses, and it has a relatively low signal-to-noise ratio, requiring averaging. We used a minimum of 30 minutes recording for calculation of autoregulation indices. Although previous studies have reported longer periods,5,25 performing continuous TCD measurements for longer than 30 to 60 minutes was deemed unsuitable for SAH patients.

The results of the conducted observational study require further validation implementing the proposed thresholds for dysautoregulation to determine their real usefulness as screening tools. Furthermore, it remains to be established whether increased risk of DCI in patients with early impairments in the state of autoregulation can be influenced with pharmacological means as well as prophylactic measures, such as early hemodynamic augmentation.

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Disclosures
ICM+ Software is licensed by Cambridge Enterprise, Cambridge, UK; http://www.neurosurg.cam.ac.uk/icmplus/. Drs Czosnyka and Smielewski have a financial interest in a fraction of the licensing fee.

References


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### SUPPLEMENTAL MATERIAL

**Table 1** ABP, FV, Sxa and TOxa averaged from the full 21 days of monitoring (total duration of monitoring) and from the first five days

<table>
<thead>
<tr>
<th>Variable</th>
<th>DCI group (n=32)</th>
<th>Non-DCI group (n=66)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total duration of monitoring</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pCO2 [kPa]</td>
<td>4.78±0.66</td>
<td>4.78±0.65</td>
<td>0.998</td>
</tr>
<tr>
<td>ABP [mmHg]</td>
<td>102±18</td>
<td>95±18</td>
<td><strong>0.0004</strong></td>
</tr>
<tr>
<td>FV [cm/s]</td>
<td>122±53</td>
<td>94±78</td>
<td><strong>0.000001</strong></td>
</tr>
<tr>
<td>Sxa [au]</td>
<td>0.08±0.18</td>
<td>-0.03±0.18</td>
<td><strong>0.000001</strong></td>
</tr>
<tr>
<td>TOxa [au]</td>
<td>0.23±0.20</td>
<td>0.05±0.17</td>
<td>&lt;<strong>0.000001</strong></td>
</tr>
<tr>
<td><strong>Day 0-5 post SAH</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pCO2 [kPa]</td>
<td>4.97±0.82</td>
<td>4.75±0.57</td>
<td>0.22</td>
</tr>
<tr>
<td>ABP [mmHg]</td>
<td>94±17</td>
<td>91±15</td>
<td>0.4</td>
</tr>
<tr>
<td>FV [cm/s]</td>
<td>96±40</td>
<td>81±37</td>
<td>0.09</td>
</tr>
<tr>
<td>Sxa [au]</td>
<td>0.09±0.16</td>
<td>0.00±0.14</td>
<td><strong>0.006</strong></td>
</tr>
<tr>
<td>TOxa [au]</td>
<td>0.16±0.17</td>
<td>0.04±0.17</td>
<td><strong>0.02</strong></td>
</tr>
</tbody>
</table>

ABP-arterial blood pressure; DCI-delayed cerebral ischemia; FV-flow velocity in the middle cerebral artery; Sxa-systolic flow index; TOxa-TOI derived index

* Two tailed t-test. Significance level at < 0.05
Table 2 Binary logistic regression model for predicting DCI after exclusion of all patients who developed DCI prior to day 5 (n=90)

<table>
<thead>
<tr>
<th>Variable</th>
<th>B (SE)</th>
<th>Wald</th>
<th>p</th>
<th>OR</th>
<th>95% CI for OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age&gt;55 y</td>
<td>-0.96 (0.74)</td>
<td>1.70</td>
<td>0.19</td>
<td>0.38</td>
<td>0.90-1.62</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.13 (0.79)</td>
<td>0.03</td>
<td>0.88</td>
<td>1.14</td>
<td>0.24-5.35</td>
</tr>
<tr>
<td>WFNS</td>
<td>0.20 (0.29)</td>
<td>0.45</td>
<td>0.51</td>
<td>1.22</td>
<td>0.68-2.19</td>
</tr>
<tr>
<td>Mod Fisher 3</td>
<td>1.56 (0.80)</td>
<td>3.82</td>
<td>0.051</td>
<td>4.77</td>
<td>0.996-22.82</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>0.17 (0.91)</td>
<td>0.03</td>
<td>0.85</td>
<td>1.18</td>
<td>0.20-7.11</td>
</tr>
<tr>
<td>EVD</td>
<td>-0.65 (1.25)</td>
<td>0.27</td>
<td>0.60</td>
<td>0.52</td>
<td>0.05-6.06</td>
</tr>
<tr>
<td>Sepsis</td>
<td>2.29 (1.08)</td>
<td>4.49</td>
<td><strong>0.034</strong></td>
<td><strong>9.84</strong></td>
<td>1.19-81.56</td>
</tr>
<tr>
<td>Metabolic derangements</td>
<td>-1.24 (1.13)</td>
<td>1.21</td>
<td>0.27</td>
<td>0.29</td>
<td>0.03-2.64</td>
</tr>
<tr>
<td>FV &gt; 120 [cm/s]; LR &gt; 3.0</td>
<td>-0.12 (1.0)</td>
<td>0.015</td>
<td>0.90</td>
<td>0.88</td>
<td>0.12-6.34</td>
</tr>
<tr>
<td>Sxa</td>
<td>2.51 (0.76)</td>
<td>11.02</td>
<td><strong>0.001</strong></td>
<td><strong>12.32</strong></td>
<td>2.78-54.27</td>
</tr>
<tr>
<td>TOxa</td>
<td>1.67 (0.79)</td>
<td>5.58</td>
<td><strong>0.018</strong></td>
<td><strong>6.51</strong></td>
<td>1.38-30.85</td>
</tr>
</tbody>
</table>

95% CI: 95% confidence interval; EVD-external ventricular drain; FV-flow velocity; LR-Lindegaard Ratio; OR-odds ratio; SE – standard error; Sxa-systolic flow index; TOxa-TOI derived index; WFNS-World Federation of Neurosurgical Societies scale

Model Summary: Chi sq. 42.30, p=0.000014, R²=0.536 (Nagelkerke)
Figure 1 ROC curve analysis of the ability of early findings using FV (gray line), TCD-derived autoregulatory index, Sxa (black line), and NIRS-derived autoregulatory index, TOxa (dashed black line) to predict the occurrence of DCI.
Figure 2 Kaplan-Meier plots of cumulative incidence of DCI within 21 days post SAH for the categorized FV and autoregulatory indices (Sxa and TOxa) from days 0-5 after excluding all patients who developed DCI prior to day 5.