Pathophysiologic differences in cerebral autoregulation after subarachnoid hemorrhage

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ABSTRACT

Objective: To understand the physiologic basis of impaired cerebral autoregulation in subarachnoid hemorrhage (SAH) and its relationship to neurologic outcomes.

Methods: The cohort included 121 patients with nontraumatic SAH admitted to a neurointensive critical care unit from March 2010 to May 2015. Vasospasm was ascertained from digital subtraction angiography and delayed cerebral ischemia (DCI) was defined as new cerebral infarction on high-resolution CT. Cerebral blood flow and beat-by-beat pressure were recorded daily on days 2–4 after admission. Autoregulatory capacity was quantified from pressure flow relation via projection pursuit regression. The main outcome was early alterations in autoregulatory mechanisms as they relate to vasospasm and DCI.

Results: Forty-three patients developed only vasospasm, 9 only DCI, and 14 both. Autoregulatory capacity correctly predicted DCI in 86% of training cohort patients, generalizing to 80% of the patients who were not included in the original model. Patients who developed DCI had a distinct autoregulatory profile compared to patients who did not develop secondary complications or those who developed only vasospasm. The rate of decrease in flow was significantly steeper in response to transient reductions in pressure. The rate of increase in flow was markedly lower, suggesting a diminished ability to increase flow despite transient increases in pressure.

Conclusions: The extent and nature of impairment in autoregulation accurately predicts neurologic complications on an individual patient level, and suggests potentially differential impairments in underlying physiologic mechanisms. A better understanding of these can lead to targeted interventions to mitigate neurologic morbidity. ***Neurology*® 2016;86:1950–1956**

GLOSSARY

ANCOVA = analysis of covariance; **CI** = confidence interval; **DCI** = delayed cerebral ischemia; **NICU** = neurointensive care unit; **PPR** = projection pursuit regression; **ROC** = receiver operating characteristic; **SAH** = subarachnoid hemorrhage.

While there is a correlation between severity of vasospasm and delayed cerebral ischemia (DCI) after subarachnoid hemorrhage (SAH),[1] the 2 are not always causally linked. Two recent clinical trials showed that treatment with clazosentan, which effectively restores global cerebral blood flow above ischemic thresholds,[2] failed to improve DCI and infarction.[3,4] This is partly because after SAH, vasospastic reaction of the distal vessels may result in small cortical lesions without evidence of macroscopic vasospasm or infarcts,[5] and microcirculatory regulation plays an important role in neurologic and functional outcomes.[6]

Cerebral autoregulation, reflective of blood flow regulation in distal arteries, is frequently disturbed in the early days after SAH without any evidence of changes in flow velocity in major arteries,[7,8] and patients with impaired autoregulation following initial hemorrhage appear to be at higher risk of DCI[7] and poor long-term outcomes.[7,9] This is consistent with the relation between impairments in cerebrovascular function and white matter hyperintensities,[10] and suggests that vascular pathophysiologic mechanisms underlying development of vasospasm and DCI may be distinct.

Editorial, page 1936

Supplemental data at Neurology.org

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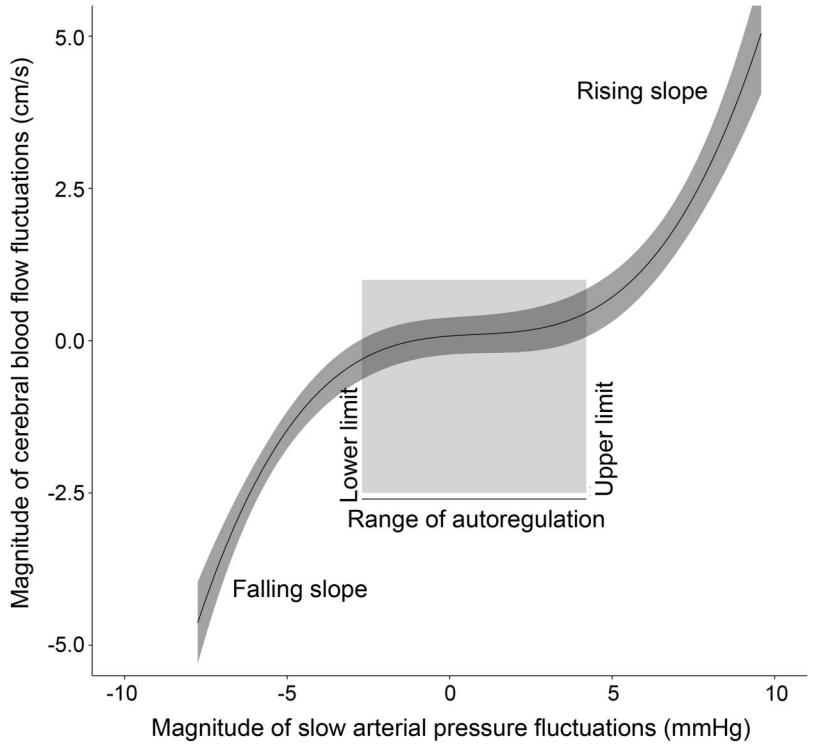
Prior data implicate myogenic dysfunction in development of vasospasm,[11–13] and sympathetic[14,15] and cholinergic[16] dysfunction in neurologic morbidity, but a comprehensive description of the differential vascular pathophysiologies that may contribute to cerebrovascular dysfunction is critical for developing individualized treatment strategies. Thus, we sought to identify early pathophysiologic alterations in cerebral autoregulatory mechanisms after SAH as they relate to development of secondary vascular complications and neurologic morbidity.

METHODS A total of 121 adult patients, admitted to the neurointensive care unit (NICU) at the Brigham and Women's Hospital from March 2010 to May 2015 with a diagnosis of spontaneous, nontraumatic SAH on admission CT, were included in the cohort. Exclusion criteria were traumatic SAH and other neurologic conditions such as tumors and vascular malformations. Patients were treated according to standard protocols.[17,18] Vasoactive drugs received in the NICU were recorded daily. Age, sex, presence of aneurysm, and medical history of hypertension, diabetes, heart disease, and prior stroke were obtained from the medical records.

Figure 1 Five hemodynamic markers of cerebral autoregulatory capacity



Falling slope (rate of blood flow decrease in response to a decrease in pressure), lower and upper limits of autoregulation (within which pressure fluctuations are counter-regulated), autoregulatory effectiveness (slope within autoregulatory range; lower gain indicates more effective autoregulation), and rising slope (rate of increase in flow in response to increases in pressure). Data from reference 22.

Standard protocol approvals, registrations, and patient consents. All protocols were approved by the institutional review board (protocol 2009P00158). Data were collected as part of the patients' routine critical care and analyzed retrospectively. Therefore, written consent was not sought.

Ascertainment of vasospasm and DCI. Vasospasm was diagnosed from digital subtraction cerebral angiography performed between days 6 and 8 and angiographic vasospasm was defined as narrowing of the arterial diameter of >30% compared with angiogram at presentation.[19] For DCI ascertainment, we relied on high-resolution CT scans, instead of clinical deterioration, as the latter is not always a good indicator of ischemia.[20] DCI was diagnosed as a new cerebral infarct on the latest CT scan that was seen <6 weeks after SAH or before discharge or death and not attributable to any other cause, and that was not present on the CT or MRI scan obtained 24–48 hours after any aneurysmal treatment procedures.[19,21] An experienced neuroradiologist blinded to the presence of vasospasm determined the occurrence of new cerebral infarction.

Hemodynamic measurements. Transcranial Doppler ultrasound (MultiDop X, DWL) was used to record blood flow velocity bilaterally in the middle cerebral arteries positioned at the M1 segment. Beat-by-beat arterial pressure waveform was recorded via arterial catheter or finger photoplethysmography. End-tidal CO_2 was monitored via a nasal cannula connected to an infrared CO_2 analyzer (VacuMed 17515) in patients without ventilatory support (n = 100). All patients had continuous measurements daily on days 2–4 after symptom onset (data were not collected on day 1 to avoid interfering with the emergency and early management).

Cerebral autoregulatory capacity. To assess cerebral autoregulatory capacity, we used projection pursuit regression (PPR). We have previously shown that PPR is able to quantify pressure–flow relation accurately and consistently[22] and allows quantification of autoregulatory capacity in terms of 5 hemodynamic markers—falling slope, rising slope, lower and upper pressure limits of the active region, and autoregulatory slope (i.e., gain)—in a way that permits straightforward interpretation of any alteration in pressure–flow relation (figure 1). The slope within each region provides a measure of the effectiveness of autoregulation within that region (lower slopes indicating more effective counter-regulation of pressure fluctuations and higher slopes indicating regions where flow more passively follows changes in pressure). This approach and its validation were described previously,[22,23] and further details are provided in the supplemental material on the *Neurology*® Web site at Neurology.org.

Predictive relation between cerebral autoregulatory capacity and neurologic outcome. Assessment of differential changes in cerebral autoregulatory capacity vis-à-vis neurologic outcomes is predicated on the implicit assumption that the alterations in autoregulation are predictive of outcome at the individual patient level. Therefore, we first assessed the predictive relation between the autoregulatory capacity and the outcome via recursive partitioning tree models. These models are analogous to decision trees for multivariable analysis, but with dichotomous dependent variables, and are routinely used in problems similar to ours[24] (see supplemental material). We used the 5 hemodynamic markers of autoregulation averaged across days 2–4 after initial bleed as independent variables, and angiographic vasospasm (days 6–8) and DCI as dependent variables using data from 92 randomly selected patients (training dataset). The

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remaining 29 (i.e., 25%) were used as an independent test to assess generalizability and predictive accuracy. This is a key feature of our approach; while the performance of a predictive model on the training set provides a measure of model accuracy on the existing data, its performance on the test set provides a measure of how well the apparent relationships can generalize over new observations.

Pathophysiologic mechanisms that may underlie impaired autoregulation and neurologic outcomes. Next, we asked whether there is a differential change in any hemodynamic marker of autoregulation across patients who experienced neither vasospasm nor DCI (group 1), who experienced vasospasm (group 2) but not DCI, only DCI (group 3), or both (group 4). A difference in any marker in groups 2–4 compared to group 1 would be reflective of particular contribution of that marker to development of secondary complications.

Using the same approach, we have previously shown the relative contributions of the neurogenic and myogenic controllers to autoregulation in healthy individuals.[23] Briefly, we have previously studied 43 healthy individuals (n = 5 twice) at supine rest and after IV administration of phentolamine, glycopyrrolate, and nicardipine at doses that effectively block, respectively, vascular α-adrenergic receptors, endothelial muscarinic receptors, and smooth muscle calcium channels. Comparisons of the pressure–flow relationship at rest and after blockades allowed us to tease apart the relative contributions of sympathetic, cholinergic, and myogenic mechanisms to autoregulation.[23] Taking advantage of these data, we sought to infer pathophysiologic alterations in autoregulatory mechanisms that may relate to secondary complications.

To this end, we first used analysis of covariance (ANCOVA) decomposition to refine estimates of individual variations in the markers of autoregulation (figure 1) in patients who did not experience any secondary complications (group 1). Consequently, we teased apart the relative contributions of each of the 5 markers of autoregulation to the development of secondary complications by comparing the residuals of the models for all groups to when each group is used alone while adjusting the effects for any differences between other 3 groups that may have existed in patients without complications. Finally, we assessed the relative differences in each hemodynamic marker in 4 groups of SAH patients to those we observed previously in healthy individuals in response to pharmacologic alterations in sympathetic, cholinergic, and myogenic mechanisms of autoregulation.[23] ANCOVA decomposition is routinely used with experimental designs, such as ours, wherein variables of interest (hemodynamic markers of autoregulation) are measured in individuals assigned to different groups (development of secondary complications), and is described in detail in the supplemental material.

Statistics. Data were analyzed using Matlab (v7.10) and R-Language (v3.1.3). Conformity of the data to statistical assumptions that underlie recursive partitioning trees and ANCOVA was verified via standard statistical tests, and data were transformed via Box-Cox transform if necessary. All continuous variables are expressed as mean ± SE. Our sample was somewhat biased against DCI (overall only 20% of the patients developed DCI), leading to a training set consisting of different numbers of representatives from different outcomes (DCI or no DCI). This may result in a model that is biased towards the majority class (no DCI), and, when applied to a test set that is similarly imbalanced, it can yield an optimistic accuracy estimate. To avoid this, we restored balance on the training set by oversampling the small class via a smoothed-bootstrap simulation.[25] Predictive performances of recursive partitioning trees for both training and independent test sets were assessed via the area under receiver operating characteristic (ROC) curve.

RESULTS Characteristics of the study population are shown in table 1. As expected, cerebral autoregulatory capacity was impaired during days 2–4. The rates of change of cerebral blood flow (i.e., falling and rising slopes) were lower, the range of autoregulation was reduced, and autoregulation within this range was less effective (i.e., had a higher gain) (table 2). There was no temporal trend in falling slope, rising slope, lower limit of autoregulation, and effectiveness of autoregulation (repeated-measures analysis of variance, $p > 0.1$ for all), but the upper limit of autoregulation tended to increase (on population level, from 1.8 ± 0.2 [SE] mm Hg on day 2 to 2.1 ± 0.2 on day 3 and 2.2 ± 0.2 on day 4, $p = 0.06$).

At the population level, patients who developed both vasospasm and DCI had significantly lower autoregulatory gain compared to other groups (figure 2 and table 2). Patients who developed DCI had a distinct autoregulatory profile compared to the others. Most notably, falling slope was significantly steeper, consistent with a substantial reduction in flow (and subsequent ischemia) in response to transient

Table 1 Study population (n = 121)

	Values
Age, y, mean ± SE	57 ± 13
M/F	50/71
Hunt & Hess scale, mean ± SE	2.44 ± 0.09
WFNS, mean ± SE	2.17 ± 0.13
Fisher score, mean ± SE	3.06 ± 0.07
No. (%) intubated	21 (17)
No. (%) of vasospasm only	43 (36)
No. (%) of DCI only	9 (8)
No. (%) of both vasospasm and DCI	14 (12)
No. (%) with history of hypertension	57 (47)
No. (%) with history of hyperlipidemia	33 (27)
No. (%) current/past smoker	41 (3)/51 (42)
No. (%) moderate to severe alcohol consumption	25 (21)
Medications during NICU stay, n (%)	
Calcium channel blocker	116 (96)
Magnesium	38 (31)
β-blocker	30 (25)
Hydralazine	15 (12)

Abbreviations: DCI = delayed cerebral ischemia; NICU = neurointensive care unit; WFNS = World Federation of Neurosurgical Societies.

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Table 2 Hemodynamic markers of autoregulation at the population level

	Healthy[a] (n = 48)	SAH without complications (n = 55)	VSP only (n = 43)	DCI only (n = 9)	VSP and DCI (n = 14)
Falling slope, cm·s^{-1}·mm Hg^{-1}	0.88 ± 0.08	0.70 ± 0.05	0.74 ± 0.08	1.00 ± 0.19[b,c]	0.92 ± 0.12[b]
Lower limit of autoregulation, mm Hg	−2.80 ± 0.23	−2.19 ± 0.34	−1.68 ± 0.29	−1.97 ± 0.50	−1.80 ± 0.58
Autoregulatory gain, cm·s^{-1}·mm Hg^{-1}	−0.02 ± 0.05	0.37 ± 0.04	0.37 ± 0.07	0.47 ± 0.16	0.15 ± 0.14[b,c,d]
Upper limit of autoregulation, mm Hg	4.88 ± 0.43	1.81 ± 0.29	2.00 ± 0.26	1.96 ± 0.38	2.06 ± 0.49
Range of autoregulation, mm Hg	7.70 ± 0.50	4.00 ± 0.33	3.69 ± 0.27	3.93 ± 0.75	3.87 ± 0.48
Rising slope, cm·s^{-1}·mm Hg^{-1}	0.97 ± 0.07	0.74 ± 0.05	0.70 ± 0.07	0.57 ± 0.19	0.85 ± 0.10

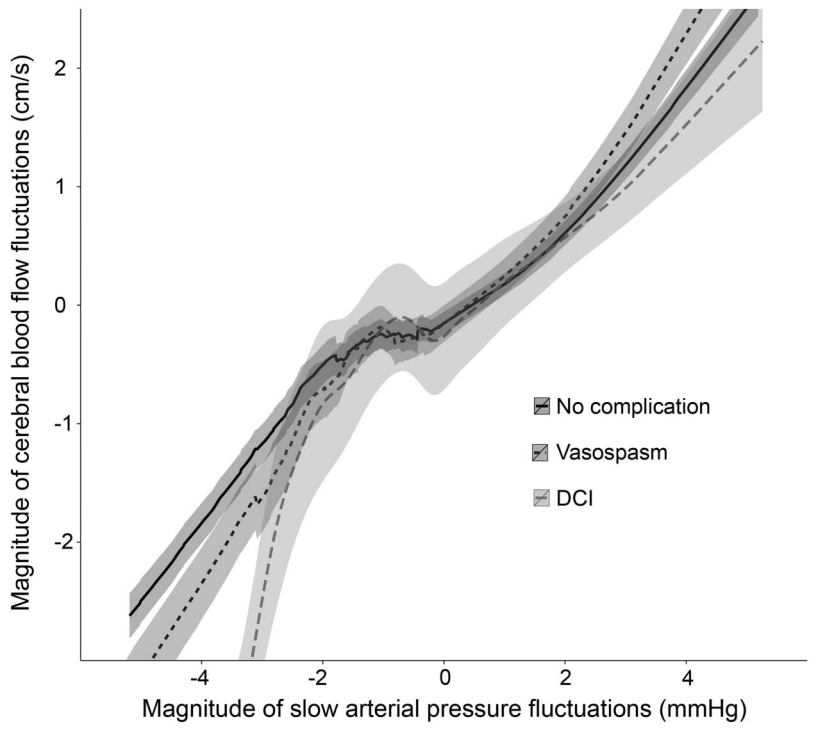
Abbreviations: DCI = delayed cerebral ischemia; SAH = subarachnoid hemorrhage; VSP = vasospasm.
[a] Data taken from reference 22 to provide reference values.
[b] Pairwise comparison $p < 0.05$ vs SAH without complications.
[c] Pairwise comparison $p < 0.05$ vs VSP only.
[d] Pairwise comparison $p < 0.05$ vs DCI only.

reductions in pressure. Moreover, in patients who experienced DCI, the autoregulatory gain was significantly smaller, and the rising slope was markedly (though not statistically significantly, $p = 0.1$) lower (figure 2 and table 2), suggesting a diminished ability to increase flow despite transient increases in pressure.

At the individual level, markers of autoregulation were able to predict vasospasm with relatively high specificity and sensitivity (area under ROC 0.77, 95% confidence interval [CI] 0.67–0.85) on the training data, but were less accurate on the independent test data (ROC 0.57, 95% CI 0.37–0.75). Hemodynamic markers alone were able to predict development of DCI with remarkable specificity and sensitivity. The area under the ROC for the training and independent test datasets was 0.86 (0.80–0.91) and 0.80 (0.66–0.90). That is, the 5 hemodynamic markers were able to correctly predict the occurrence of DCI in 86% of the patients, and this predictive power generalized to 80% of the patients who were not included in the original model. Subsequent ANCOVA decomposition at the individual level indicated a primary contribution of (1) lower and upper limits of autoregulation in patients who developed only vasospasm; (2) falling slope, and effectiveness (i.e., gain) of autoregulation in those who developed only DCI; and (3) upper limit of autoregulation and rising slope in patients who developed both vasospasm and DCI (see figure 3A).

None of our results was associated with other clinical factors that may impair cerebrovascular function or worsen outcomes (e.g., age, hyperlipidemia, diabetes, vasoactive drugs during NICU stay). One exception was the history of hypertension, which was independently associated with lower and upper limits of autoregulation (overall pressure–flow relation was shifted to the right) and outcomes.

Figure 2 Pressure-flow relation in patients with subarachnoid hemorrhage



DCI = delayed cerebral ischemia.

DISCUSSION Previous research has shown that cerebral autoregulatory capacity is impaired in the early days of SAH, and our results show that the extent and nature of this impairment accurately predicts neurologic complications on an individual patient level. Our analytical model utilizing 5 hemodynamic markers of autoregulatory function was particularly predictive of the development of cerebral infarction, the major contributor to morbidity and mortality after SAH. Furthermore, this predictive power was not only limited to the study sample, but it was generalizable to other patients (80% accuracy on

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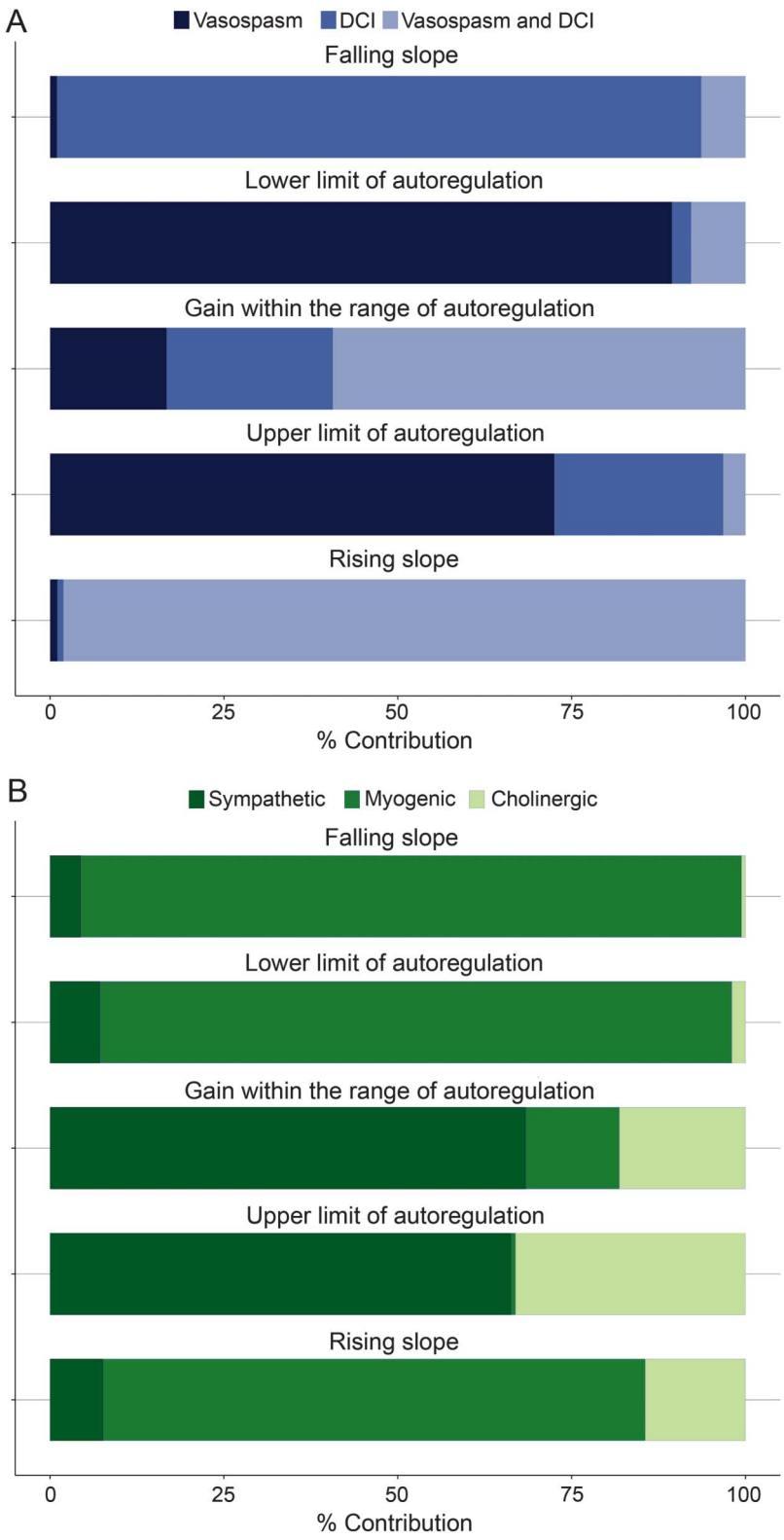
Figure 3 Secondary complications, markers of cerebral autoregulatory capacity, and associated physiologic mechanisms



Contributions of cerebral autoregulatory capacity to secondary complications (A) and contribution of neurogenic and myogenic mechanisms to each marker (B, data from reference 23). DCI = delayed cerebral ischemia.

independent test sample), even without other clinical variables that may impair cerebrovascular function or worsen outcomes (we deliberately did not include clinical variables that are known to be related to outcomes, to explore the role of cerebrovascular function in outcomes explicitly). Thus, these data may allow individualized treatment strategies and open the door for testing of autoregulation-based SAH management and personalized therapies. Importantly, our results also delineate potential pathophysiologic alterations in cerebrovascular function that may underlie poor outcomes, and provide a critical step towards development of novel preventative and therapeutic strategies to avoid or ameliorate irreversible and sometimes deadly complications after SAH.

Earlier studies have shown that impaired autoregulation is associated with unfavorable outcomes. Autoregulatory index is reported to be low in individuals with low discharge modified Rankin Scale and NIH Stroke Scale scores,[26] autoregulatory dysfunction appears to be among the primary factors predisposing to DCI,[27] and the combination of large artery vasospasm and worsening of autoregulation within the first week postbleed correlates to subsequent DCI.[28] However, these studies did not go beyond correlations at the population level and attempt to predict individual patients' neurologic outcome. In fact, the relation of cerebrovascular function to individual outcomes was not immediately apparent from our results at the population level (table 2). More recently, we have shown that transfer function estimates of autoregulation, in combination with clinical variables at admission, are able to predict vasospasm and DCI with reasonable accuracy at an individual level,[29] but our reliance on traditional measures precluded identification of aspects of pressure–flow relation as they relate to outcomes.

An important aspect of our study is our ability to delineate the individual components of the pressure–flow relationship and their predictive ability for the development of cerebral infarction. There is growing evidence that DCI is not always secondary to vasospasm,[30–32] and may develop in the absence of vasospasm if distal cerebral vessels cannot compensate sufficiently in response to changes in pressure. In patients who develop DCI secondary to vasospasm, the infarcts are more likely to parallel vascular distribution of the vasospasm, whereas in those who develop DCI without vasospasm, watershed territory infarcts are more common.[1] This is consistent with our result that patients who develop DCI have distinct autoregulatory profiles, and lends strong support to the notion that assessment of cerebral autoregulatory capacity may be critical for identification of patients at high risk and for targeting treatment strategies most effectively to reduce neurologic morbidity.

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Using the same approach as the current study, we have previously shown how pharmacologic blockade of sympathetic, cholinergic, and myogenic mechanisms alters autoregulation in healthy individuals[23] (figure 3B). We reported that α-adrenergic blockade significantly reduces autoregulatory effectiveness,[23] cholinergic blockade significantly increases the rising slope,[23] and myogenic blockade results in a larger change in flow in response to a given change in pressure.[23,33] Taking advantage of this previous research, we were able to infer pathophysiologic mechanisms that may be associated with development of vasospasm or DCI: when interpreted in light of our earlier data, differences in markers of autoregulation appear to suggest that (1) a primarily myogenic dysfunction may underlie vasospasm; (2) a primary sympathetic overactivation (lower autoregulatory gain compared to those who did not develop DCI) and cholinergic dysfunction (perhaps as a result of sympathetic overactivity; blunted rate of change in response to rising pressure) may contribute to development of DCI; and (3) patients with myogenic, sympathetic, and cholinergic dysfunction may experience both vasospasm and DCI. This is consistent with the earlier data from in vitro models, animals, and humans: a disruption in vascular myogenic mechanisms appears to be among the driving factors of vasospasm[11,12]; development of DCI may be related to overactivation of sympathetic system[14] and reversed by cervical sympathetic blockade[15]; and cholinergic dysfunction in the pial arteries is reported to play a role in development of both vasospasm[13] and cognitive impairments[16] after SAH.

This conclusion is clearly limited by being restricted to mechanisms already shown to underlie autoregulatory function; pathophysiologic alterations can be different from those induced by pharmacologic blockades in healthy individuals. Indeed, there is a myriad of other mechanisms that may underlie development of secondary complications after SAH.[34] Nonetheless, our results strongly suggest extending these mechanisms to include pathophysiologic alterations in mechanisms underlying autoregulation. It should be noted, however, that this is the first application of this approach to an acutely ill population. Thus, the results should be interpreted cautiously and considered as preliminary. Interventions that specifically target these mechanisms may lead to novel therapies for the prevention of vasospasm and DCI after SAH, and warrant further investigation. Second, to ascertain DCI, we relied on high-resolution CT scans. It is possible that CT can miss subtle ischemic events that can be detected by MRI,[35] potentially reducing the sensitivity of detecting minor ischemic lesions that may be clinically relevant. In fact, this may underlie part of our ~20% error in identification of patients who experienced DCI. Third, we did not include any clinical or epidemiologic factors in our predictive model. This was a deliberate choice to explore the role of autoregulatory dysfunction on neurologic outcomes explicitly, rather than that of clinical or epidemiologic factors demonstrated before. In fact, accounting for other factors that may impair the cerebrovascular function or outcomes after SAH did not change our conclusions. It is important to acknowledge that we found an association between history of hypertension, autoregulation, and neurologic outcomes. This is consistent with prior studies showing that history of hypertension impairs autoregulation, especially its lower and upper limits,[36] and that history of hypertension may be related to development of DCI.[37] Thus, chronic hypertension might represent an independent predisposing factor for autoregulatory dysfunction and outcomes after SAH. However, we cannot comment on whether the apparent relation of history of hypertension and impaired cerebral autoregulatory capacity to outcomes is causative or simply represents parallel phenomena. This observation warrants further study.

AUTHOR CONTRIBUTIONS

Gabriela A. Santos collected and analyzed the data and drafted the manuscript. Nils Petersen collected and analyzed the data. Amir A. Zamani analyzed the data. Rose Du collected the data. Sarah LaRose collected and analyzed the data. Andrew Monk collected and analyzed the data. Farzaneh A. Sorond conceived the study and collected the data. Can Ozan Tan conceived the study, analyzed the data, including statistical analysis, and drafted the manuscript. All authors contributed to the revision of the manuscript.

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DISCLOSURE

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