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The Link between Cerebrovascular Hemodynamics and Rehabilitation Outcomes after Aneurysmal Subarachnoid Hemorrhage

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Abstract

Objective—To assess the relation between cerebrovascular function early after aneurysmal subarachnoid hemorrhage (SAH) onset and functional and rehabilitation outcomes.

Design—Observational cohort study of SAH patients (n=133) admitted to rehabilitation (n=49), discharged home (n=52), or died before discharge (n=10). Hemodynamic markers of cerebral autoregulatory function obtained from blood flow velocities in the middle cerebral artery and arterial pressure waveforms, recorded daily on days 2–4 after symptom onset, and functional independence measure (FIM^{TM}) scores and FIM efficiency for those admitted to acute rehabilitation.

Results—Compared to those discharged home, the range of pressures within which autoregulation is effective was lower in patients admitted to rehabilitation (4.6 ± 0.2 vs 3.9 ± 0.2 mmHg) and those who died (2.7 ± 0.4 ; $p=0.04$). For those admitted to rehabilitation, autoregulatory range and the ability of cerebrovasculature to increase flow were related to discharge FIM score ($R^2=0.33$ and 0.43 ; $p<0.01$) and efficiency ($R^2=0.33$ and 0.47 ; $p<0.01$). The latter marker, along with SAH severity and admission FIM, explained 84% and 69% of the variability in discharge FIM score and efficiency, respectively, even after accounting for age.

Conclusions—Early cerebrovascular function is a major contributor to functional outcomes after SAH, and may represent a modifiable target to develop therapeutic approaches.

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Keywords

Cerebral blood flow; hemorrhagic stroke; functional independence; hemodynamics

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Introduction

Large-vessel vasospasm and delayed cerebral ischemia (DCI) are among the leading causes of morbidity and mortality after aneurysmal subarachnoid hemorrhage (SAH). While their triggers are multifaceted, a derangement in cerebrovascular function is among the culprits. A key component of cerebrovascular function, autoregulation (the ability of the cerebral vasculature to maintain stable cerebral perfusion despite fluctuation in systemic and intracranial pressure), is frequently disturbed in the early days after SAH.¹⁻³ We have recently shown that the extent of this disturbance is a major factor contributing to the development of DCI and consequent ischemic infarcts at an individual level,^{4, 5} suggesting that cerebrovascular function in the acute phase of SAH may be a potential target to mitigate neurologic morbidity and possibly to improve outcomes.

However, short-term neurological outcomes do not always align with longer term functional outcomes. Treatment strategies that are clearly effective in reducing large-vessel vasospasms (and presumably, large infarcts) do not always translate into improved functional outcomes.⁶⁻⁸ This may partly be because impairments in cerebrovascular function are associated with small vessel ischemia,⁹ and lesions that may not be acutely symptomatic or visible on CT scan but are known to have an important effect on the functional outcome after SAH.¹⁰ Thus, it is conceivable that early impairments of cerebrovascular function may play a role in functional outcomes. If so, targeting cerebrovascular function can guide early management in the neurointensive care units to improve functional outcomes after SAH. This is important because while there are several prognostic factors for neurologic or functional outcomes (such as age and SAH severity), these factors are not modifiable. Therefore, early hemodynamic markers of cerebral autoregulation may provide a novel prognostic tool to guide early medical management toward improved functional and rehabilitation outcomes after SAH. Thus, we built upon our prior work, and sought to explore the relation between early hemodynamic markers of cerebral autoregulation and longer term functional and rehabilitation outcomes after aneurysmal subarachnoid hemorrhage.

Methods

We obtained clinical parameters and hemodynamic markers of cerebral autoregulation (described below) of adult patients (n=133) 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, aneurysmal subarachnoid hemorrhage (SAH) on admission computed tomography (CT). Exclusion criteria were traumatic SAH and other neurologic conditions such as tumors, other vascular malformations, and ischemic stroke with hemorrhagic transformation. Patients were treated according to standard protocols.^{11, 12} For each patient, we determined acute-care discharge destinations (home, acute rehabilitation facility, dead, or "other"). We next identified patients who were admitted to Spaulding Rehabilitation

Hospital (SRH) for stroke rehabilitation, and obtained their functional outcomes at the time of rehabilitation discharge (Figure 1). We did not follow up on patients who were admitted to other rehabilitation facilities to avoid possible impact of potential heterogeneities in rehabilitation care across institutions. Subsequently, we assessed the relation of early hemodynamic markers and clinical variables to acute discharge destinations (population-level outcome) and, for those treated at SRH, to functional status on rehabilitation discharge (individual-level outcome).

Standard Protocol Approvals, Registrations, and Patient Consents

All protocols were approved by the institutional review boards of Brigham and Women's Hospital (protocol 2009P00158) and SRH (protocol 2015P001839). All data were collected as part of the patients' routine critical care. Therefore, written consent was waived by the IRB and not sought. This study conforms to all STROBE guidelines and reports the required information accordingly (see Supplementary Material).

Hemodynamic Markers of Cerebral Autoregulation

For each patient, blood flow velocities in the middle cerebral arteries and beat-by-beat arterial pressure waveforms were recorded at the NICU daily on days 2–4 after symptom onset (data were not collected on day 1 to avoid interfering with the emergency and hyper-acute medical management). 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. Subsequently, the relation between slow fluctuations in arterial pressure and cerebral blood flow velocities were used to derive hemodynamic markers of cerebral autoregulatory function. To this end, we used the same methodology as the one employed in our previous study.^{5, 13}

Briefly, we assessed cerebral autoregulatory function via projection pursuit regression (PPR) using arterial pressure as the independent variable and middle cerebral artery blood flow velocity as the dependent variable, and derived 5 hemodynamic markers—falling slope, rising slope, lower and upper pressure limits of the autoregulatory region, and autoregulatory slope (i.e., gain)—in a way that permits straightforward interpretation of any alteration in pressure–flow relation (Supplemental Figure S1). Falling and rising slopes reflect the ability of cerebrovasculature to change blood flow in response to decreasing and increasing pressures, respectively, and autoregulatory slope reflects the effectiveness of autoregulation within pressure limits of the active, autoregulatory region (i.e., within the range of autoregulation). The slope within each region provides a measure of the effectiveness of cerebrovascular function 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). We have previously shown that PPR is able to quantify pressure–flow relation accurately and consistently.¹⁴ This approach, its implementation, and its validation were provided in detail elsewhere,^{13, 14} and its application to SAH patients was described in our earlier work.⁵

Clinical Measurements

For all patients, vasoactive drugs received in the NICU were recorded daily. Age, sex, presence of aneurysm, SAH severity (World Federation of Neurological Societies [WFNS], Hunt & Hess, and Fisher scores, and Glasgow Coma Scale [GCS]), discharge destination, and medical history were obtained from the medical records. For those who were admitted to SRH for stroke rehabilitation, we also obtained functional independence measure (FIM™) scores on admission and discharge, and FIM efficiency (aggregate change in FIM score per day spent in rehabilitation) to account for the length of rehabilitation. FIM score is typically assessed on admission to and discharge from a rehabilitation hospital to track changes in the functional status. FIM score evaluates the functional status of patients throughout the rehabilitation process following a stroke, serves as a consistent data collection tool for the comparison of rehabilitation outcomes, and is interpreted to indicate level of independence or level of burden of care.¹⁵ FIM scores were assessed by patients' treating physicians blinded to any measure of cerebrovascular function.

Data Analysis and Statistics

Data were analyzed using Matlab (R2013a) and R-Language (v3.3.1). There were no statistically significant lateral differences between right and left middle cerebral artery (MCA) or any temporal trends (across days 2 – 4 post-ictus) in hemodynamic markers of cerebral autoregulation (repeated-measures ANOVA, $p > 0.1$ for all). Therefore, hemodynamic markers were averaged across sides and days to robustly minimize possible impact of any measurement-related or day-to-day variation in cerebrovascular function and its estimated markers. Conformity of the data to statistical assumptions was verified via standard statistical tests. Differences in clinical variables and hemodynamic markers between groups with different acute discharge destinations (home vs acute rehabilitation vs dead, and SRH vs other facility within the acute rehabilitation group) were tested for statistical significance using 1-way ANOVA, followed by Tukey's HSD test for pairwise comparisons. Test of proportions was used to assess any difference in sex composition between groups. Within the SRH group, simple relations of early hemodynamic markers to discharge FIM and FIM efficiency were assessed via linear regression. To determine relative contributions of SAH severity, age, and early hemodynamic markers to discharge FIM and FIM efficiency, we used a stepwise regression model. Stepwise models constructed via forward addition of variables and those constructed via backward elimination of variables may contain different predictor variables especially if the sample size is small.¹⁶ Therefore, we applied both approaches and used the one with the best criterion. All continuous variables are expressed as mean $\pm$ Standard Error.

Results

Twelve patients were excluded because they were discharged to home with "professional services," a category which includes individuals with very high variability in outcomes (e.g., those with good outcome but special needs as well as those with unfavorable outcome but good social/familial support are included in this group). A further 10 patients were excluded because of missing/insufficient hemodynamic data or unspecified discharge destination ("other" in Figure 1).

Of the 111 patients included in the study, 52 were discharged home, 49 were referred to an acute stroke rehabilitation unit, and 10 were dead before NICU discharge (see Figure 1). As expected, patients who were discharged home were younger, and had a lesser SAH severity (i.e., lower Fisher, Hunt & Hess, WFNS scores, and higher GCS) ($p<0.05$ for all variables; Table 1). Falling and rising slopes (i.e., the ability of cerebrovasculature to change blood flow in response to decreasing and increasing blood pressure, respectively) and autoregulatory slope (i.e., effectiveness of autoregulation) were not different across the three groups ($p>0.2$ for all three). However, the range of autoregulation was significantly smaller in patients who died compared to those who were discharged home or an acute rehabilitation facility ($p<0.05$; Table 1; Figure 2).

Twenty one of the 49 patients (43%) who were discharged to acute rehabilitation care were admitted to SRH for stroke rehabilitation. There were no differences in age or SAH severity between patients discharged to SRH vs other rehabilitation facilities (Table 2). Patients admitted to SRH had an average admission FIM score of 45.9 ± 4.8 , and stayed in rehabilitation care for 31.9 ± 5.2 days. Average discharge FIM was 83.1 ± 6.2 , and the FIM efficiency was 1.65 ± 0.23 . Within the SRH group, rising slope and autoregulatory range were significantly related to discharge FIM and FIM efficiency, individually explaining up to 47% of the variance in rehabilitation outcomes (Figure 3). Falling slope and autoregulatory slope were not significantly related to either discharge FIM or FIM efficiency ($R^2<0.1$ for all).

Combination of Fisher and WFNS scores, admission FIM, autoregulatory range and slope, and rising slope explained a majority of the variation in discharge FIM score (forward/backward stepwise regression, $R^2=0.84$ adjusted for the sample size [$F_{7,10}=13.65$], $p<0.01$), with statistically significant contributions from each of the five variables, even after accounting for patients' ages (Table). Moreover, Hunt & Hess and WFNS scores, admission FIM, and rising slope together explained a majority of the variation in FIM efficiency ($R^2=0.69$, adjusted for the sample size [$F_{4,13}=10.54$], $p<0.01$), with statistically significant contributions from all variables but WFNS score ($p=0.15$) (Table). Normalized effect sizes showed that the biggest contribution to FIM efficiency was from the rising slope (0.26), followed by admission FIM score (0.11), WFNS score (0.07) and Hunt & Hess score (0.05).

As a secondary, clinical validation of the stepwise regression models, we identified individuals who had outcomes much worse than expected from the stepwise regression prediction (i.e., who were "outliers;" described in detail in supplemental material), and explored their clinical history in an attempt to explain the relatively large prediction error. Of the three patients identified this way, one had cancer (the only one in the SRH group) in addition to a history of hypertension and being a current smoker, another one was over 80 years old (the oldest in the SRH group) with a history of kidney disease, and the third one had the lowest GCS at admission to NICU (3) and was a current smoker with a history of hypertension, obesity, and cocaine use.

Discussion

While the rate of mortality after a SAH is improving,¹⁷ SAH is often associated with a high neurological morbidity.¹⁸ Among the known factors associated with neurological morbidity

and functional outcomes are age, aneurysm size and location, SAH severity on admission, neurological grade, myocardial infarction, high blood pressure, and liver disease.¹⁹ Moreover, one study reported a potential relation between SAH severity (assessed using Hunt & Hess score) at admission and discharge FIM scores,²⁰ although other studies failed to find a relation between demographic or clinical characteristics at the SAH onset and functional gains made during rehabilitation.^{21, 22} It is important to note that these prognostic factors for neurologic or functional outcomes are present on admission and are not modifiable.

In this study, we have shown that the extent of derangement in cerebral autoregulation early after SAH onset may explain a significant portion of the variability in functional outcome (i.e. discharge FIM) and rate of functional recovery (i.e. FIM efficiency). Specifically, our results show that autoregulatory range (i.e. range of pressure fluctuations within which cerebrovasculature is effective in buffering against pressure fluctuations) and rising slope (the ability of cerebrovasculature to increase blood flow in response to increasing pressure) in the acute stage (days 2 – 4) after SAH onset alone explain over 30% and 40% of the variation in discharge FIM and FIM efficiency, respectively. In fact, these markers of cerebral autoregulation, when combined with measures of SAH severity on admission, explained, respectively, ~85% and ~70% of the variation in functional outcome and rehabilitation efficiency, even after age is accounted for, with statistically significant contributions to predictive power. Thus, there is a clear link between cerebrovascular function in the acute stages of SAH and rehabilitation outcomes.

Remaining variation in the functional outcomes and rehabilitation efficiency cannot be attributed to variation in rehabilitative care. All the patients included in the regression models were treated at the same rehabilitation hospital under standardized protocols, and evaluated using established metrics (FIM score and FIM efficiency). In fact, this is one of the major strengths of the current study. Instead, remaining variation in outcomes is likely to be due to other comorbidities not accounted for in this study. Our secondary analysis of patients whose outcome was worse than what would be predicted from the statistical model supports this inference. The three patients whose functional outcome was inferior to that predicted by the model had multiple comorbidities (combination of cancer, smoking, advanced age, kidney disease, history of hypertension, obesity and cocaine use) known to be associated with unfavorable outcomes and low rehabilitation efficacy. Unfortunately, we were not able to account for these factors in our models due to a relatively small sample size. Nonetheless, this does not undermine the apparent impact of the integrity of early cerebrovascular function on functional and rehabilitation outcomes.

Our results support and extend prior studies both from our group and others. Earlier studies have shown that, at the population level, early impairment in cerebral autoregulation is among the primary factors predisposing to delayed cerebral ischemia and ischemic infarcts^{23, 24} and is associated with poor acute discharge outcomes.²⁵ We have previously shown that impaired cerebral autoregulation, in combination with clinical variables at admission, is predictive of neurologic morbidity with reasonable accuracy at an individual level,⁴ and that the extent and nature of derangement in cerebral autoregulation accurately predicts neurologic complications on an individual patient level even without other clinical

variables that may impact acute outcomes.⁵ Therefore, integrity of early cerebrovascular function relates to radiographic/neurologic outcomes. However, prior studies assessed neurologic outcomes at the time of acute care discharge, and thus, were limited in terms of the time-frame (within 6 weeks) or modality of outcomes (radiographic and/or neurologic outcomes). Therefore, our results extend prior studies and further highlight the importance of early cerebrovascular function in longer term functional and rehabilitation outcomes after SAH.

Involvement of specific aspects of cerebral autoregulation in radiographic/neurological outcomes (our prior study⁵) and functional outcomes (current study) also provides a vascular framework for SAH-related outcomes. In our prior work, we observed that the reduction in cerebral blood flow in response to decreasing pressures (i.e. falling slope) was highly predictive of delayed cerebral ischemia and ischemic infarcts.⁵ In this study, we found that the ability of cerebral vasculature to increase blood flow in response to increases in pressure (i.e. rising slope) is predictive of rehabilitation efficiency and functional outcomes. The former result suggests that, in the early days of SAH, targeting blood pressure to maintain constant blood flow may be critical to avoid ischemic injuries. The latter (i.e., current) result suggests that early perfusion failure could have long-term clinical implications due to small-vessel ischemia and subsequent lesions that may not be acutely symptomatic. At the same time, it is also possible that persistent autoregulatory failure may also interfere with neuroplasticity and rehabilitation potential. The current study does not allow conclusive assessment of these mechanistic links due to its methodological limitations. Nonetheless, this inference highlights the possibility that cerebrovascular function may represent a modifiable prognostic factor for functional and rehabilitation outcomes after SAH, and warrants further mechanistic studies.

This conclusion is also supported by animal studies. For example, in rats, targeting smooth muscle signaling network after SAH is reported to restore vascular myogenic function (which is among the primary controllers of falling and rising slopes¹³), to ameliorate neural degeneration, and to improve clinical and behavioral outcomes.²⁶ Similarly, mitogen-activated protein kinase 1/2 inhibition is reported to alleviate dysfunction in cerebrovascular receptor signaling and to improve functional outcomes,²⁷ potentially via its action on myogenic function. Lastly, an antagonistic effect of losartan (an angiotensin-1 receptor antagonist) on endothelial function has been reported to restore cerebral autoregulation and improve outcomes after SAH.²⁸ While inferential, these studies, together with the current results, strongly suggest that targeting cerebrovascular dysfunction after SAH may provide new and promising avenues to optimize functional outcomes after SAH and to minimize its burden on patients and healthcare resources. This highlights the importance of future avenues to develop therapeutic approaches that can target cerebrovascular function after SAH.

Summary and Conclusions

These results show that the ability of cerebrovasculature to buffer against pressure fluctuations and to increase blood flow in response to increasing pressure, in the acute stage (days 2 – 4) after SAH onset, together with measures of SAH severity on admission,

explains up to 80% of the variation in longer term functional outcome and rehabilitation efficiency, even after age is accounted for. When considered along with prior animal studies, this suggests that cerebrovascular function may represent a modifiable prognostic factor for functional and rehabilitation outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Study population

Gray-shaded boxes denote patients excluded, and the box "SRH" denotes the patients included in the final analysis of the relation between hemodynamic markers and rehabilitation outcomes

Figure 2. The difference in early hemodynamic markers of cerebral autoregulation between individuals who were discharged home, discharged to acute rehabilitation, or were dead before acute care discharge

Hemodynamic markers were derived from the relationship between arterial pressure as the independent variable and middle cerebral artery blood flow velocity fluctuations as described in the Methods (see also Supplemental Figure S1).

Figure 3. Linear relations between early hemodynamic markers of cerebral autoregulation and rehabilitation outcomes

y-axes show the discharge FIM^{TM} score (upper panels) and FIM efficiency (aggregate change in FIM score per day spent in rehabilitation; lower panels), and x-axes show the rising slope (the ability of cerebrovasculature to change blood flow in response to increasing pressure; left panels) and autoregulatory range (the range of blood pressure fluctuations within which autoregulation is effective; right panels).

Table 1

Patient demographics and admission scores at the time of NICU admission.

	Home (n = 52)	Acute Rehabilitation (n = 49)	Dead (n = 10)
Age	47.8 ± 1.4	63.4 ± 1.7 [*]	57.9 ± 3.8 [*]
Sex (M/F)	24/28	16/33	5/5
Fisher score	2.8 ± 0.1	3.3 ± 0.1 [*]	3.4 ± 0.2 [*]
H&H score	1.9 ± 0.1	3.0 ± 0.2 [*]	3.7 ± 0.3 ^{*†}
WFNS score	1.3 ± 0.1	2.9 ± 0.2 [*]	3.9 ± 0.4 [*]
GCS	14.7 ± 0.1	11.5 ± 0.6 [*]	8.1 ± 1.5 ^{*†}

One-way ANOVA:

^{*}
 $p < 0.05$ vs Home,

[†]
 $p < 0.05$ vs Acute Rehabilitation.

WFNS Score Dead vs. Acute Rehabilitation $p = 0.07$.

Table 2

Stepwise regression models showing the relative contributions of SAH severity, age, and early hemodynamic markers to discharge FIM and FIM efficiency

	<i>Dependent variable:</i>	
	FIM	FIM Efficiency
Rising Slope	42.091 (24.720)	2.192 *** (0.573)
Autoregulatory Range	2.945 (4.786)	
Rising Slope $\times$ Autoregulatory Slope	-166.207 ** (61.710)	
Autoregulatory Range $\times$ Autoregulatory Slope	28.341 ** (12.397)	
Admission FIM	0.407 ** (0.167)	0.015 * (0.007)
Hunt and Hess Score		0.547 * (0.283)
WFNS Score	-8.012 * (3.974)	-0.312 (0.201)
Fisher Score	21.300 *** (5.691)	
Constant	-20.107 (16.970)	-1.178 (0.741)
Observations	18	18
R ²	0.905	0.764
Adjusted R ²	0.839	0.692
Residual Std. Error	11.796 (df = 10)	0.607 (df = 13)
F Statistic	13.646 *** (df = 7; 10)	10.542 *** (df = 4; 13)

Note:

*
p<0.1;

**
p<0.05;

***
p<0.01