Baroreflex Impairment After Subarachnoid Hemorrhage Is Associated With Unfavorable Outcome

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Background and Purpose—Aneurysmal subarachnoid hemorrhage (SAH) is characterized by important changes in the autonomic nervous system with potentially adverse consequences. The baroreflex has a key role in regulating the autonomic nervous system. Its role in SAH outcome is not known. The purpose of this study was to evaluate the association between the baroreflex and the functional 3-month outcome in SAH.

Methods—The study used a prospective database of 101 patients hospitalized for SAH. We excluded patients receiving β-blockers or noradrenaline. Baroreflex sensitivity (BRS) was measured using the cross-correlation method. A good outcome was defined by a Glasgow Outcome Scale score at 4 or 5 at 3 months.

Results—Forty-eight patients were included. Median age was 58 years old (36–76 years); women/men: 34/14. The World Federation of Neurosurgery clinical severity score on admission was 1 or 2 for 73% of patients. In the univariate analysis, BRS (P=0.007), sedation (P=0.001), World Federation of Neurosurgery score (P=0.001), Glasgow score (P=0.002), Fisher score (P=0.022), and heart rate (P=0.037) were associated with outcome. The area under the receiver operating characteristic curve for the model with BRS as a single predictor was estimated at 0.835. For each unit increase in BRS, the odds for a good outcome were predicted to increase by 31%. Area under the receiver operating characteristic curve for heart rate alone was 0.670. In the multivariate analysis, BRS (odds ratio, 1.312; 95% confidence interval, 1.048–1.818; P=0.018) and World Federation of Neurosurgery (odds ratio, 0.382; 95% confidence interval, 0.171–0.706; P=0.001) were significantly associated with outcome. Area under the receiver operating characteristic curve was estimated at 0.900.

Conclusions—In SAH, early BRS was associated with 3-month outcome. This conclusion requires confirmation on a larger number of patients in a multicentre study. **(*Stroke*. 2018;49:1632-1638. DOI: 10.1161/STROKEAHA.118.020729.)**

Key Words: autonomic nervous system ■ baroreflex ■ blood pressure ■ stroke ■ subarachnoid hemorrhage

Aneurysmal subarachnoid hemorrhage (SAH) is associated with a level of mortality varying from 32% to 67% and with incapacitating consequences in 30% of cases.[1]

Patients' outcome relates, on the one hand, to the occurrence of a delayed ischemic deficit and, on the other hand, to the occurrence of systemic, in particular cardiac, complications.[2] Progress has been made in the treatment and prevention of delayed ischemic deficit during the past decade, in particular, through the management of severe vasospasm and assessment of cerebral autoregulation when available. Systemic complications are mainly cardiovascular, particularly the occurrence of arrhythmia, myocardial ischemia, or Takotsubo cardiomyopathy characterized by a modification of cardiac contractility under the effect of activation of the sympathetic system.[3] These complications are difficult to predict and prevent, especially in the case of intubated, sedated patients. Hence, the concern to search for warning signs that may precede aggravation, in particular, in intensive care units.

The arterial baroreflex behaves like a marker of a healthy cardiovascular autonomic nervous system. Its role is to maintain the cardiovascular homeostasis to cope with physiological and pathological changes. The baroreflex is a biofeedback loop, where changes in the heart rate (HR) occur in response to the variations of blood pressure with a decrease in HR when blood pressure increases and vice-versa. Its function is measured as a variation in ms of the RR interval between 2 pulse beats, for each unit of variation in the same direction of systolic arterial blood pressure (ABP) in mm Hg. It is expressed as a slope of interval versus systolic ABP regression line, given in ms/mm Hg, known as baroreflex sensitivity (BRS). The activation of the sympathetic system has been associated with baroreflex impairment.[4–6]

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Baroreflex impairment was associated with a poor outcome after a myocardial infarction.[7] It was also associated with the severity of coronary lesions[8] and also with ischemic stroke.[9] In ischemic and hemorrhagic strokes,[10,11] BRS diminution was associated with an unfavorable outcome. Two other determinants of baroreflex diminution are age[5,12] and carotid atherosclerosis.[6,13–16]

Currently, multicenter trials are being performed to evaluate the therapeutic impact of baroreflex stimulation in resistant hypertension and in heart failure.

Subarachnoid hemorrhage is a situation that can be seen as a cataclysmic activation of the stress system with deleterious effects, which are well-known by the neurointensivists who manage these patients. In subarachnoid hemorrhage, scarce data are available concerning the association between baroreflex changes and the outcome.[17,18] A previous study (published as an abstract) showed that an early and significantly reduced BRS is observed in SAH patients who develop vasospasm while BRS changes did not correlate to clinical outcome assessed by extended Glasgow Outcome Scale (GOS).[17] Another study in 20 brain-injured patients, including 3 patients with SAH, showed that an altered baroreflex function correlated with unfavorable outcome in these patients.[18]

Investigating the association between BRS and outcome in a population of SAH patients can be particularly useful for the identification of high-risk patients, especially sedated ventilated patients who cannot be clinically monitored.

The main objective of this single-center study was to assess the association between BRS on admission and the 3-month outcome in aneurysmal SAH.

Methods

The article adheres to the American Heart Association journals' implementation of the Transparency and Openness Promotion Guidelines. The data that support the findings of this study are available from the corresponding author on reasonable request

Population

This study is based on the data collected from a prospective series of 101 patients admitted at the teaching hospital Addenbrooke of Cambridge (United Kingdom) in the Neuroscience Department for aneurysmal rupture subarachnoid hemorrhage, between June 2010 and January 2012. This series had been initially studied to predict the occurrence of delayed ischemic deficit in these patients, based on the early changes of cerebral autoregulation.[19]

Inclusion criteria were as follows: ≥18 years of age, aneurysmal SAH confirmed with either computed tomography angiography or digital subtraction angiography, and <5 days elapsed from the occurrence of subarachnoid hemorrhage.

Patients were treated according to current guidelines.[20,21] 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 (if required). 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.[19] When patients were sedated, propofol and at least 1 of the following drugs: fentanyl, remifentanil, and midazolam were used.

The exclusion criteria that we have identified for this study are the treatment with β-blockers or with a sympathomimetic agent, such as noradrenaline, as practiced in intensive care units to increase blood pressure in patients with vasospasm. These patients were excluded because β-blockers or sympathomimetic agents may alter the BRS.

All patients underwent multimodal neuromonitoring, including ABP monitoring for at least 30 minutes per session. Where available, ABP was monitored from the radial artery using a pressure monitoring kit (Baxter Healthcare, CA). Otherwise, ABP was monitored noninvasively with photoplethysmography (Finapress 2300; Ohmeda, the Netherlands).[14]

Data were recorded at a frequency of 200 Hz using ICM+ software (Cambridge Enterprise, United Kingdom; http://www.neurosurg.cam.ac.uk/icmplus).

The collected data for the study included the following variables: age, sex, number of days between the occurrence of the subarachnoid hemorrhage and the date of the recording, the fact whether patients were sedated and mechanically ventilated or not when the recording was made, the World Federation of Neurosurgery (WFNS) score on admission,[22] the Glasgow score on admission, the Fisher grade evaluating the importance of subarachnoid hemorrhage on initial computed tomographic scan, the location of subarachnoid hemorrhage, the treatment applied for ruptured aneurysm, the presence of hydrocephalus and the presence of an external derivation, as well as BRS, the mean ABP, and the HR, and also ABP variability in the low-frequency range (0.04–0.15 Hz) calculated from systolic ABP. All physiological data were calculated from the first recording performed after admission. Subsequently, the occurrence of a documented infection, the occurrence of vasospasm as diagnosed on transcranial Doppler with an increase of mean velocities >120 cm/s and an increase of the Lindegaard index >3, on the middle cerebral artery,[19] the occurrence of a delayed ischemic deficit, and the 3-month GOS score[23] were recorded.

This protocol was approved by the local Research Ethics Committee. All patients were required to sign a written informed consent. In case of lack of capacity, the next-of-kin was approached.

Outcome Measure

All the patients who survived were evaluated at 3 months after discharge at the Addenbrooke's Hospital. The GOS (which classifies patients into 5 categories) was evaluated by the treating neurosurgeon.[23] A good outcome was defined by a GOS equal to 4 or 5.

Calculation of BRS

The time series used to calculate BRS, systolic blood pressure, and the RR intervals were extracted from the recordings made in these patients early after admission. BRS index was calculated in ms/mm Hg using the BRS cross-correlation method, also referred to as x-BRS, which evaluates the baroreflex in the time domain after having adjusted for the variable nature of the delay in variation between the systolic ABP (the input signal) and the RR interval (the output signal).[24] Comparison of this method with other BRS calculation methods using the EUROBAVAR multicenter database has demonstrated that x-BRS results in a lower intraindividual and interindividual variability.[24] x-BRS method has been validated against the gold standard of phenylephrine and nitroprusside bolus injections.[25] Normal values of BRS calculated with the x-BRS method from a data set obtained from 21 patients (4 men and 17 women) aged 20 to 68 years (source: EUROBAVAR database) yielded a mean value for x-BRS of 12.4 ms/mm Hg, as compared with 13.4 ms/mm Hg for BRS calculated locally using the sequence method[26] by the team who set the method for x-BRS calculation and compared with 16.2 ms/mm Hg for BRS calculation from the EUROBAVAR database.[24]

The x-BRS calculation algorithm was implemented in ICM+ software, and its performance was carefully validated against the original software provided by Dr Berend Westerhof. x-BRS calculations were performed using a moving 10-second window (moved along the time axis in 10 second steps), along with mean values of the other vital signs variables included in the analysis. However, the x-BRS algorithm required systolic ABP and RR time series to be incrementally shifted with respect to each other in search of the highest value of cross-correlation, which meant that the actual total window length used in each x-BRS calculation extended to 17 seconds.[24] All the analyzed physiological data were ultimately averaged for each recording.

ICM+ permitted also to calculate from the same time series the spectral power of ABP in the low-frequency range (0.04–0.15 Hz).

Statistical Analysis

Descriptive analysis included absolute (relative) frequencies for categorical variables and median (minimum–maximum) for continuous variables. Differences in median BRS between groups were investigated by the Mann-Whitney or the Kruskal-Wallis test, accordingly to the number of groups while the null hypothesis of no correlation between BRS and an ordinal type variable was examined by the Spearman correlation test.

Associations between the outcome and each studied variable were evaluated by simple (with a single explanatory variable) logistic regression models. In accordance with the sample size, BRS effect was then adjusted for only 1 more variable. Interaction terms were not allowed. All models of the previous format were considered, and the choice of the best model was based on the likelihood ratio test for nested models and on the Akaike Information Criterion otherwise. To adequately deal with the situation of having a small number of cases in the class of poor outcome, estimation was through maximization of the penalized likelihood as introduced by David.[27]

For the models of interest, the area under the receiver operating characteristic curve (AUC) was computed. This is a measure of the accuracy (discrimination ability) of a model. The threshold value, or cutoff, for BRS was determined by the Youden index, thus maximizing the sum of sensitivity and specificity.

The statistical analyses were performed with the R language and software environment for statistical computation, version 2.3.3.[28] The significance level was set at 0.05.

Table 1. Univariate Analysis Evaluating the Association Between a Good Outcome (GOS 4 or 5) and the Potential Explanatory Variables Considered

Variables	Total (n=48)	GOS 1–3 (n=9)	GOS 4–5 (n=39)	Simple Logistic Regression OR (95% CI)	*P* Value
BRS, ms/mm Hg	11.7 (1.5–38.7)	4.3 (1.5–13.9)	12.6 (3.2–38.7)	1.359 (1.088–1.698)*	0.007*
Age, y	58 (36–76)	60 (47–74)	57 (36–76)	0.977 (0.910–1.049)	0.521
Sex					
Female	34 (70.8)	5 (55.6)	29 (74.4)	1.0	
Male	14 (29.2)	4 (44.4)	10 (25.6)	0.431 (0.096–1.929)	0.271
WFNS	2 (1–5)	4 (1–5)	1 (1–4)	0.332 (0.154–0.599)*	<0.001*
Fisher (2 cat)					
I (1+2+3)	25 (52.1)	1 (11.1)	24 (61.5)	1.0*	
II (4)	23 (47.9)	8 (88.9)	15 (38.5)	0.078 (0.009–0.688)*	0.022*
Sedation					
No	41 (85.4)	4 (44.4)	37 (94.9)	1.0*	
Yes	7 (14.6)	5 (55.6)	2 (5.1)	0.043 (0.006–0.300)*	0.001*
Infection					
No	42 (87.5)	7 (77.8)	35 (89.7)	1.0	
Yes	6 (12.5)	2 (22.2)	4 (10.3)	0.400 (0.061–2.625)	0.340
Days from admission	3 (0–10)	2 (1–7)	3 (0–10)	1.084 (0.766–1.534)	0.648
GCS	15 (3–15)	5 (3–13)	15 (8–15)	2.151 (1.324–3.494)*	0.002*
Mean ABP, mm Hg	128.5 (91.8–183.5)	131.6 (118.6- 183.6)	128.4 (91.8–180.5)	0.979 (0.941–1.018)	0.279
Heart rate, bpm	68.0 (44.3–105.3)	72.5 (53.9–105.3)	65.97 (44.3–85.1)	0.928 (0.866–0.996)*	0.037*
DID					
No	36 (75.0)	5 (55.6)	31 (79.5)	1.0	
Yes	12 (25.0)	4 (44.4)	8 (20.5)	0.323 (0.070–1.486)	0.147
Vasospasm					
No	27 (56.3)	3 (33.3)	24 (61.5)	1.0	
Yes	21 (43.7)	6 (66.7)	15 (38.5)	0.312 (0.068–1.441)	0.136
ABP-LF, mm Hg^2	6.6 (0.4–203.7)	6.9 (1.1–43.8)	2.9 (0.4–203.7)	0.984 (0.960–1.009)	0.215

The qualitative variables are described by the absolute (relative) frequencies of their categories, and the quantitative variables are expressed as medians (minimum–maximum). Vasospasm refers to mean flow velocity >120 cm/s on transcranial Doppler and a Lindegaard ratio >3.0 on the middle cerebral artery. ABP-LF refers to variability of ABP assessed in the frequency domain and had been calculated as spectral power of ABP in the LF range (0.04–0.15 Hz). ABP indicates arterial blood pressure; BRS, baroreflex sensitivity; CI, confidence interval; DID, delayed ischemic deficiency; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; LF, low-frequency; OR, odds ratio; and WFNS, World Federation of Neurosurgery.

*The variables significantly associated with 3-month outcome.

Results

One hundred and one patients were included in the prospective series. From these patients, 4 were under treatment with β-blockers (exclusion criterion), 47 patients were under treatment with noradrenaline (exclusion criterion), and 2 patients had recordings that could not be used for BRS calculation because of poor quality ABP signal.

Therefore, the total number of patients for analysis was 48. Median age was 58 years old (36–76 years old). The women/men ratio was 34/14. Median of WFNS clinical severity score on admission was 2 (1–5). Seven patients were sedated and mechanically ventilated, 16 patients had hydrocephalus, and 12 patients had external derivation. At the time of BRS measurement, 7 patients were treated with endovascular coiling, 27 patients were treated with clipping, 2 patients were treated with coiling and clipping, and 12 patients were not treated yet for the ruptured aneurysm at the time of BRS measurement (8 patients) or had conservative treatment on the total period of hospitalization (4 patients). Median time for BRS measurement from SAH occurrence was 3 days, and the interquartile range was of 2 days.

In the univariate analysis, BRS (P=0.007), sedation (P=0.001), the WFNS score (P=0.001), the Glasgow score (P=0.002), the Fisher score (P=0.022), and HR (P=0.037) were significantly associated with outcome. Table 1 indicates the results from the univariate analysis evaluating the association between the dichotomized outcome assessed by the GOS, GOS 4 to 5 indicates good outcome and GOS 1 to 3 indicates poor outcome, and the potential explanatory variables considered. Figure 1 plots the distribution of BRS in each class of the dichotomized GOS.

We described in Table 2 the potential impact on BRS of the following variables: age, sex, WFNS, sedation/mechanical ventilation, site of subarachnoid hemorrhage, vasospasm, external derivation, and treatment of the aneurysm.

Area under the receiver operating characteristic curve for the model including only BRS as a predictor was 0.835. The model estimated an odds ratio (95% confidence interval) of 1.313 (1.097–1.674), implying an increase of 31% in the odds for a good outcome for each unit increase in BRS. Area under the receiver operating characteristic curve for the model including only the HR (resp. WFNS) was 0.670 (resp. 0.853), and the predictor was statistically significant.

In a multivariate analysis evaluating the (adjusted) effect of BRS, the best model consisted of BRS (odds ratio, 1.312; 95% confidence interval, 1.048–1.818; P=0.015) and WFNS (odds ratio, 0.382; 95% confidence interval, 0.171–0.706; P=0.001) as explanatory variables and presented an area under the receiver operating characteristic curve of 0.900 (Figure 2). The values of the estimated coefficients and their SD are presented in Table 3.

The model composed of BRS and HR exhibited a worse performance, with a nonsignificant effect of HR on good outcome (BRS, P=0.049; HR, P=0.909).

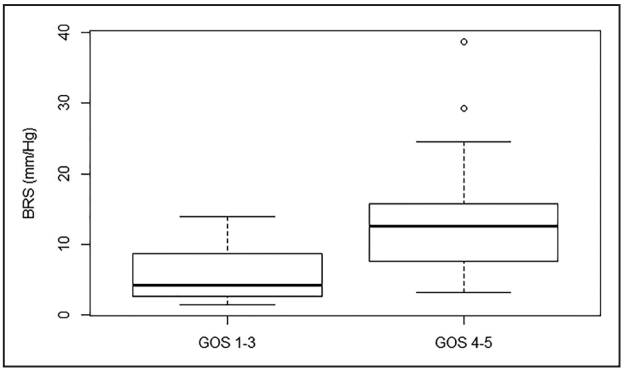

Figure 1. Distribution of baroreflex sensitivity (BRS) early after admission for poor outcome (Glasgow Outcome Scale [GOS] score, 1–3) and good outcome (GOS score, 4–5).

Table 2. Statistical Description of the (Univariate) Association Between BRS and Variables of Interest Pertaining to SAH

	BRS	*P* Value
Categorical variables	Median (minimum–maximum)	
Sex		0.867
Female	11.7 (3.2–24.5)	
Male	10.6 (1.5–38.7)	
Location of SAH		0.152
Left	10.4 (2.5–24.5)	
Right	13.6 (2.6–38.7)	
Median	10.9 (1.5–18.4)	
Treatment of ruptured aneurysm at the time of BRS measurement		0.932
Not treated	11.5 (2.6–24.5)	
Coiling	11.3 (1.5–14.6)	
Clipping	10.9 (2.5–38.7)	
Coiling and clipping	12.9 (12.0–13.7)	
Sedation and mechanical ventilation		0.314
No	12.1 (1.5–38.7)	
Yes	8.7 (2.6–13.9)	
Vasospasm on transcranial Doppler		0.885
No	12.0 (3.2–29.3)	
Yes	11.3 (1.5–38.7)	
External derivation		0.408
No	12.0 (2.5–38.7)	
Yes	10.5 (1.5–13.9)	
Continuous variables	Spearman correlation coefficient	
Age	−0.186	0.206
WFNS	−0.371	0.015

The Mann-Whitney or the Kruskal-Wallis test was used to compare medians across categories; the Spearman correlation coefficient and the corresponding test examined the association between BRS and the continuous variables. BRS indicates baroreflex sensitivity; SAH, subarachnoid hemorrhage; and WFNS, World Federation of Neurosurgery.

Discussion

After aneurysmal SAH, we have highlighted a significant association between BRS and the outcome at 3 months. Each

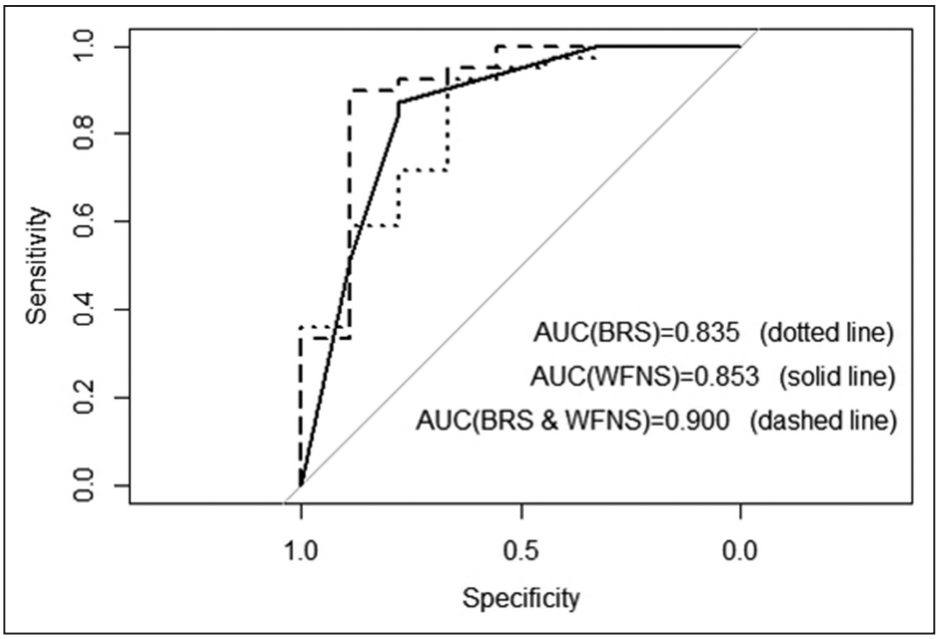

Figure 2. Receiver operating characteristic (ROC) curves for the regression models predicting poor/good outcome from: baroreflex sensitivity (BRS) alone (area under the ROC curve [AUC], 0.835; dotted line), WFNS alone (AUC, 0.853; solid line), and BRS+WFNS (AUC, 0.900; dashed line).

increase of 1 unit on BRS was estimated to raise by 31% the odds for having a good 3-month outcome. This result is novel in a context where known data on the baroreflex in aneurysmal SAH are scarce.

The consequences of changes in the autonomic nervous system with activation of the stress system are, however, known in this pathology. Particularly so for complications related to the activation of the sympathetic system, such as arrhythmia, cardiac ischemia, neurogenic pulmonary edema, and Takotsubo cardiomyopathy.

Besides the occurrence of cardiovascular complications, other mechanisms may explain the association between decreased BRS and poor outcome, in particular, the consequences of increased activity of the sympathetic system, which is known to be associated with lower BRS.[4–6] Indeed, sympathetic activation is associated with increased platelet aggregation, hyperglycemia, inflammation, and an increase of the blood-brain barrier's permeability.[29]

Our results are in line with those of Papaioannou et al,[18] who found in 20 brain-injured patients from multiple causes, including 3 patients with SAH, an association between decreased BRS and a high mortality rate. They are also in line with the results of Schmidt et al[30] who assessed HR variability in the frequency domain in subarachnoid hemorrhage and identified an association between the low-frequency/high-frequency ratio (a ratio between the low-frequency power and the high-frequency power in RR intervals time series), which is an indicator of the sympathetic activity and the occurrence of an infection or of a delayed ischemic deficit. In another study, Schmidt et al[31] highlighted an association between an HR increase >95 per minute lasting >12 hours and the 3-month functional outcome. Their results did not include the baroreceptor sensitivity assessment. Nonetheless, the sympathetic system activation, which includes manifestations, such as the HR increase, is known to be associated with a lower BRS.[4–6] Our results of lower BRS being associated with worse outcome are, therefore, consistent with the pervious results, which indicated an association between sympathetic activation and unfavorable outcome after SAH.

Table 3. Estimates From the Multiple Logistic Regression Model, Estimating the Probability of Having a Good Outcome as a Function of BRS and WFNS Values

Variable	Coefficient (SE)	OR (95% CI)	*P* Value
Intercept	1.498 (1.416)	…	…
BRS, ms/mm Hg	0.272 (0.128)	1.312 (1.048–1.818)	0.015*
WFNS	−0.961 (0.353)	0.382 (0.171–0.706)	0.001

BRS indicates baroreflex sensitivity; CI, confidence interval; OR, odds ratio; and WFNS, World Federation of Neurosurgery.

In our study, the adjustment of the HR effect to BRS annihilated the significance of HR. The baroreflex, which is a biofeedback loop, integrates more global information than HR increase in response to stress. This can be explained by the fact that for good functioning of the baroreflex arc, the following are required[1]: operational afferents that depend on the state of baroreceptors which are known to be altered in atheromatous patients,[2,6,13–16] and an operational integration of the signal related to the brainstem nuclei which are interconnected with other cortical brain areas, especially insular areas. The severity of the acute brain aggression of aneurysmal SAH potentially impairs their functioning by the apoptotic mechanisms that it is believed to trigger[3,32] the efferents that control the contractility and rate of the heart muscle, on the one hand, and the peripheral vasoconstriction, on the other hand. Their action is dependent on the prior cardiovascular condition and the systemic complications of the subarachnoid hemorrhage, which can include impairment of vasomotricity

of the peripheral vascular bed and also impairment of cardiac response. Therefore, lower BRS is likely to integrate the following: prior cardiovascular condition, severity of the subarachnoid hemorrhage, and occurrence of systemic complications during hospitalization.

We did not find a significant association between BRS and vasospasm. As compared with our results, the results by Nellgard et al[17] (published as an abstract) depicted an association between initial decrease of BRS, more specifically on day 1, and the occurrence of vasospasm. In contrast with our study, Nellgard et al[17] studied the kinetics of BRS to assess their impact on vasospasm. Also, they did not find an association between reduced BRS and outcome. However, the number of patients studied was relatively small (n=21), and description of medications that could have influenced BRS was not available because of the abstract form of the report.

Our study included sedated and mechanically ventilated patients in whom the main sedation drug used was propofol. This might have influenced the cardiovascular autonomic nervous system. However, although propofol was found to inhibit the sympathetic nervous activity in reaction to hypotension, it did not modify the responsive reflex HR variation,[33] which is assessed in our study through BRS.

Mechanical ventilation can be another factor that is able to alter BRS. In a study by Van de Louw,[34] mechanical ventilation attenuated respiratory arrhythmia and was associated with altered BRS sensitivity. In our study, we did not find a significant association between mechanical ventilation and BRS, which might be because of the relatively small number of patients.

Our study included 48 patients, of which 9 had a poor outcome. This did not allow for the adjustment of the BRS effect to several potentially confounding factors simultaneously. The relatively small sample is thus the main limitation of our study.

Another limit is that the data did not encompass information about carotid atherosclerosis as all acute patients were not screened for carotid atherosclerosis. Plaque surface and morphology features, as well as localization of atherosclerotic plaques, are all characteristics that are able to determine different arterial wall damages and nerve destruction with a subsequent alteration of BRS.[14–16]

The strength of our study is that it has been conducted on a homogeneous population in terms of absence of obvious factors known to modify the baroreflex, such as the β-blockers, or factors that may have such an action, as the noradrenaline. In the upcoming studies, it will be useful to integrate these patients who have not been included in the current series to test the association identified between the BRS and the outcome in conditions of usual clinical care, thus accepting the limit of pharmacological factors that may interfere in the assessment of the association between BRS and outcome. A confirmation of these results is needed in a larger multicenter study.

The significant association between BRS measured during hospitalization and the 3-month outcome in our study has been found at an early stage. Should any causality elements be acquired based on larger multicenter studies, this would pave the way for therapeutic opportunities—pharmacological or nonpharmacological—assessing the impact of baroreflex improvement on outcome, in aneurysmal SAH.

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Disclosures

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References

1. Ferro JM, Canhão P, Peralta R. Update on subarachnoid hemorrhage. *J Neurol*. 2008;255:465–479. doi: 10.1007/s00415-008-0606-3.
2. Diringer MN, Bleck TP, Claude Hemphill J 3rd, Menon D, Shutter L, Vespa P, et al; Neurocritical Care Society. Critical care management of patients following aneurysmal subarachnoid hemorrhage: recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference. *Neurocrit Care*. 2011;15:211–240.
3. D'Souza S. Aneurysmal subarachnoid hemorrhage. *J Neurosurg Anesthesiol*. 2015;27:222–240. doi: 10.1097/ANA.0000000000000130.
4. Tafil-Klawe M, Klawe J, Majcherczyk S, Trzebski A. Sympathoinhibitory baroreflex in conscious rabbits: simultaneous recordings of sympathetic and aortic nerve activity. *J Auton Nerv Syst*. 1989;28:227–232.
5. Laitinen T, Hartikainen J, Vanninen E, Niskanen L, Geelen G, Länsimies E. Age and gender dependency of baroreflex sensitivity in healthy subjects. *J Appl Physiol (1985)*. 1998;84:576–583. doi: 10.1152/jappl.1998.84.2.576.
6. Nasr N, Pavy-Le Traon A, Larrue V. Baroreflex sensitivity is impaired in bilateral carotid atherosclerosis. *Stroke*. 2005;36:1891–1895. doi: 10.1161/01.STR.0000177890.30065.cb.
7. La Rovere MT, Specchia G, Mortara A, Schwartz PJ. Baroreflex sensitivity, clinical correlates, and cardiovascular mortality among patients with a first myocardial infarction. A prospective study. *Circulation*. 1988;78:816–824.
8. Katsube Y, Saro H, Naka M, Kim BH, Kinoshita N, Koretsune Y, et al. Decreased baroreflex sensitivity in patients with stable coronary artery disease is correlated with the severity of coronary narrowing. *Am J Cardiol*. 1996;78:1007–1010.
9. Robinson TG, James M, Youde J, Panerai R, Potter J. Cardiac baroreceptor sensitivity is impaired after acute stroke. *Stroke*. 1997;28:1671–1676.
10. Sykora M, Diedler J, Rupp A, Turcani P, Rocco A, Steiner T. Impaired baroreflex sensitivity predicts outcome of acute intracerebral hemorrhage. *Crit Care Med*. 2008;36:3074–3079. doi: 10.1097/CCM.0b013e31818b306d.
11. Sykora M, Steiner T, Rocco A, Turcani P, Hacke W, Diedler J. Baroreflex sensitivity to predict malignant middle cerebral artery infarction. *Stroke*. 2012;43:714–719. doi: 10.1161/STROKEAHA.111.632778.
12. Kardos A, Watterich G, de Menezes R, Csanády M, Casadei B, Rudas L. Determinants of spontaneous baroreflex sensitivity in a healthy working population. *Hypertension*. 2001;37:911–916.
13. Chao AC, Chern CM, Kuo TB, Chou CH, Chuang YM, Wong WJ, et al. Noninvasive assessment of spontaneous baroreflex sensitivity and heart rate variability in patients with carotid stenosis. *Cerebrovasc Dis*. 2003;16:151–157. doi: 10.1159/000070595.
14. Tsekouras NS, Katsargyris A, Skrapari I, Bastounis EE, Georgopoulos S, Klonaris C, et al. The role of carotid plaque echogenicity in baroreflex sensitivity. *J Vasc Surg*. 2011;54:93–99. doi: 10.1016/j.jvs.2010.11.121.
15. Acampa M, Guideri F, Marotta G, Tassi R, D'Andrea P, Giudice GL, et al. Autonomic activity and baroreflex sensitivity in patients submitted to carotid stenting. *Neurosci Lett*. 2011;491:221–226. doi: 10.1016/j.neulet.2011.01.044.
16. Mangin L, Lesèche G, Duprey A, Clerici C. Ventilatory chaos is impaired in carotid atherosclerosis. *PLoS One*. 2011;6:e16297. doi: 10.1371/journal.pone.0016297.
17. Nellgard B, Rydenhag B, Nylén K, Terajima K. Changes in baroreflex sensitivity in correlation to incidence of vasospasm and outcome

in patients with subarachnoid hemorrhage. *Acta Anaesthesiologica Scandinavica*. 2007;51(suppl 118):31–32. Abstract.
18. Papaioannou V, Giannakou M, Maglaveras N, Sofianos E, Giala M. Heart rate and blood pressure variability and baroreflex sensitivity in patients with acute brain injury. *J Crit Care*. 2005;20:394.
19. Budohoski KP, Czosnyka M, Smielewski P, Kasprowicz M, Helmy A, Bulters D, et al. Impairment of cerebral autoregulation predicts delayed cerebral ischemia after subarachnoid hemorrhage: a prospective observational study. *Stroke*. 2012;43:3230–3237. doi: 10.1161/STROKEAHA.112.669788.
20. Bederson JB, Connolly ES Jr, Batjer HH, Dacey RG, Dion JE, Diringer MN, et al; American Heart Association. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke*. 2009;40:994–1025. doi: 10.1161/STROKEAHA.108.191395.
21. Connolly ES Jr, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, et al; American Heart Association Stroke Council; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; Council on Cardiovascular Surgery and Anesthesia; Council on Clinical Cardiology. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2012;43:1711–1737. doi: 10.1161/STR.0b013e3182587839.
22. Teasdale GM, Drake CG, Hunt W, Kassell N, Sano K, Pertuiset B, et al. A universal subarachnoid hemorrhage scale: report of a committee of the World Federation of Neurosurgical Societies. *J Neurol Neurosurg Psychiatry*. 1988;51:1457.
23. Jennett B, Bond M. Assessment of outcome after severe brain damage. *Lancet*. 1975;1:480–484.
24. Westerhof BE, Gisolf J, Stok WJ, Wesseling KH, Karemaker JM. Time-domain cross-correlation baroreflex sensitivity: performance on the EUROBAVAR data set. *J Hypertens*. 2004;22:1371–1380.
25. Wesseling KH, Karemaker JM, Castiglioni P, Toader E, Cividjian A, Settels JJ, et al. Validity and variability of xBRS: instantaneous cardiac baroreflex sensitivity. *Physiol Rep*. 2017;5:e13509. doi: 10.14814/phy2.13509.
26. Di Rienzo M, Bertinieri G, Mancia G, Pedotti A. A new method for evaluating the baroreflex role by a joint pattern analysis of pulse interval and systolic blood pressure series. *Med Biol Eng Comput*. 1985;23(suppl 1):313–314.
27. David F, Bias reduction of maximum likelihood estimates. *Biometrika*. 1993;80:27–38.
28. R, Development, Core and Team. *R: A Language and Environment for Statistical Computing*. Vienna, Australia: R. Foundation for Statistical Computing. 2012.
29. Sykora M, Diedler J, Turcani P, Hacke W, Steiner T. Baroreflex: a new therapeutic target in human stroke? *Stroke*. 2009;40:e678–e682. doi: 10.1161/STROKEAHA.109.565838.
30. Schmidt JM, Sow D, Crimmins M, Albers D, Agarwal S, Claassen J, et al. Heart rate variability for preclinical detection of secondary complications after subarachnoid hemorrhage. *Neurocrit Care*. 2014;20:382–389. doi: 10.1007/s12028-014-9966-y.
31. Schmidt JM, Crimmins M, Lantigua H, Fernandez A, Zammit C, Falo C, et al. Prolonged elevated heart rate is a risk factor for adverse cardiac events and poor outcome after subarachnoid hemorrhage. *Neurocrit Care*. 2014;20:390–398. doi: 10.1007/s12028-013-9909-z.
32. Cahill J, Cahill WJ, Calvert JW, Calvert JH, Zhang JH. Mechanisms of early brain injury after subarachnoid hemorrhage. *J Cereb Blood Flow Metab*. 2006;26:1341–1353. doi: 10.1038/sj.jcbfm.9600283.
33. Ebert TJ. Sympathetic and hemodynamic effects of moderate and deep sedation with propofol in humans. *Anesthesiology*. 2005;103:20–24.
34. Van de Louw A. Breathing cardiovascular variability and baroreflex in mechanically ventilated patients *Am J Physiol Regul Integr Comp Physiol*. 2008;295:R1934–R1940.

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