TITLE:

Baroreflex impairment after subarachnoid haemorrhage is associated with unfavourable outcome

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NASR. BRS impairment is associated with unfavourable outcome in SAH

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Abstract

Background and Purpose

Aneurysmal subarachnoid haemorrhage (SAH) is characterized by important changes in the autonomic nervous system (ANS) with potential adverse consequences. The baroreflex has a key role in regulating ANS. 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 beta-blockers or noradrenaline. Baroreflex sensitivity (BRS) was measured using the cross-correlation method. A good outcome was defined by a Glasgow Outcome Score (GOS) at 4 or 5 at 3 months.

Results

Fourty-eight patients were included. Median age was 58 years old (36 to 76); F/M: 34/14. The WFNS clinical severity score upon admission was 1 or 2 for 73% of patients.

In the univariate analysis, BRS (P=0.007), sedation (P=0.001), WFNS 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 curve (AUC) for the model with BRS as 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%. AUC for heart rate alone was 0.670.

In the multivariate analysis, BRS (OR: 1.312[1.048-1.818]; P=0.018) and WFNS (OR: 0.382[0.171-0.706]; P=0.001) were significantly associated with outcome. AUC 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.

Introduction

Aneurysmal subarachnoid haemorrhage 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 (DID) over the last 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 Tako Tsubo 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 in order to cope with physiological and pathological changes. The baroreflex is a biofeedback loop where changes in the heart rate occur in response to the variations of blood pressure with a decrease in heart rate when blood pressure increases and vice-versa.

Its function is measured as a variation in milliseconds (ms) of the R-R interval between two pulse beats, for each unit of variation in the same direction of systolic blood pressure (sABP) in mmHg. It is expressed as a slope of interval versus sABP regression line, given in msec/mmHg, known as baroreflex sensitivity (BRS).

The activation of the sympathetic system has been associated with baroreflex impairment (4 , 5, 6).

Baroreflex impairement 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 haemorrhagic stroke (10, 11), BRS diminution was associated with an unfavourable outcome.

Two other determinants of baroreflex diminution are age (5, 12), and carotid atherosclerosis (13, 6, 14-16).

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

Subarachnoid haemorrhage 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 haemorrhage, scarce data is available ~~we do not have any data~~ 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 that develop vasospasm, while BRS changes did not correlate to clinical outcome assessed by extended Glasgow Outcome Scale (17). Another study in 20 brain-injured patients, including 3 patients with SAH, showed that an altered baroreflex function correlated with unfavourable 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 baroreflex sensitivity on admission and the 3 month outcome in aneurysmal subarachnoid haemorrhage.

Methods

The manuscript adheres to the AHA Journals' implementation of the Transparency and Openness Promotion (TOP) Guidelines. The data that support the findings of this study are available from the corresponding author upon 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 (UK) in the

Neuroscience Department for aneurysmal rupture subarachnoid haemorrhage, 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 subarachnoid haemorrhage confirmed with either computed tomography angiography (CTA) or digital subtraction angiography (DSA); <5 days elapsed from the occurrence of subarachnoid haemorrhage.

Patients were treated according to current guidelines (20,21). Initial management included prompt cardiopulmonary support (if required), maintenance of euvolemia, oral nimodipine 60mg 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 one of the following drugs: fentanyl, remifentanyl and midazolam, were used.

The exclusion criteria which we have identified for this study are the treatment with beta-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 beta-blockers or sympathomimetic agents may alter the baroreflex sensitivity (BRS).

All patients underwent multimodal neuromonitoring including arterial blood pressure (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, UK, http://www.neurosurg.cam.ac.uk/icmplus).

The collected data for the study included the following variables: age, gender, number of days between the occurrence of the subarachnoid haemorrhage and the date of the recording, the fact whether patients were sedated and mechanically ventilated or not when the recording was made, the WFNS score upon admission (22), the Glasgow score upon admission, the Fisher grade evaluating the importance of subarachnoid haemorrhage on initial CT scan, the location of subarachnoid haemorrhage, the treatment applied for ruptured aneurysm, the presence of hydrocephalus and the presence of an external derivation as well as BRS, the mean arterial blood pressure (MAP), and the heart rate (HR) and also ABP variability in the low frequency range (LF:0.04-0.15Hz) calculated from systolic ABP. All physiological data were calculated from the first recording carried out after admission. Subsequently, the occurrence of a documented infection, the occurrence of vasospasm as diagnosed on Transcranial Doppler with an increase of mean velocities

above 120cm/sec and an increase of the Lindegaard index above 3, on the middle cerebral artery (19), the occurrence of a delayed ischemic deficit (DID), and the 3 month-Glasgow Outcome Scale 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 baroreflex sensitivity (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. Baroreflex sensitivity index was calculated in msec/mmHg 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 (sABP) (the input signal) and the RR interval (the output

signal) (24). Comparison of this method with other BRS calculation methods using the EUROBAVAR multi-centre database has demonstrated that x-BRS results in a lower intra- and inter-individual variability (24). xBRS method has been validated against the gold standard of phenylephrine and nitroprusside bolus injections (25). Normal values of BRS calculated with the xBRS method from a data set obtained from 21 patients (4 men and 17 women) aged 20 to 68 (source: EUROBAVAR database) yielded a mean value for xBRS of 12.4 msec/mmHg, as compared to 13.4msec/mmHg for BRS calculated locally using the sequence method (26) by the team who set the method for x-BRS calculation, and compared to 16.2msec/mmHg 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 10sec window (moved along the time axis in 10 sec steps), along with mean values of the other vital signs variables included in analysis. However, the x-BRS algorithm required sABP 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 sec (24). All the analysed physiological data were ultimately averaged over each recording.

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

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 one 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 (AIC) otherwise. In order 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 Firth (27).

For the models of interest, the area under the ROC (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's 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.

RESULTS

One hundred and one patients were included in the prospective series. From these patients, 4 were under treatment with beta-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 to 76 years old). The female/male ratio was 34/14. Median of WFNS clinical severity score upon admission was 2 (1 to 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 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 heart rate

(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 Glasgow Outcome Scale (GOS), GOS: 4-5 = good outcome and GOS 1-3: 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.

AUC for the model including only BRS as a predictor was 0.835. The model estimated an odds ratio (OR) (95%CI) 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. AUC for the model including only the heart rate (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 (OR:1.312[1.048-1.818];P=0.015) and WFNS (OR:0.382[0.171-0.706]; P=0.001) as explanatory variables, and presented an AUC of 0.900. (Figure 2)

The value of the estimated coefficients and their standard deviations are presented in Table 3.

The model composed of BRS and heart rate (HR) exhibited a worse performance, with a non-significant effect of HR on good outcome (BRS: P=0.049; HR: P= 0.909).

DISCUSSION

After aneurysmal subarachnoid haemorrhage, we have highlighted a significant association between BRS and the outcome at 3 months. Each increase of one 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 concerning the baroreflex in aneurysmal subarachnoid haemorrhage is scarce.

The consequences of changes in the autonomic nervous system with activation of the stress system are however known in this pathology. Particulary so for complications related to the activation of the sympathetic system, such as arrhythmia, cardiac ischemia, neurogenic pulmonary oedema and Tako Tsubo 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, 5, 6). Indeed, sympathetic activation is associated with increased platelet aggregation, hyperglycaemia, inflammation and increase of the blood-brain barrier's permeability (29).

Our results are in line with those of Papaioannou et al. 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 (18). They are also in line with the results of Schmidt et al. (30) who, assessed HR variability in the frequency domain in subarachnoid haemorrhage and identified an association between the LF/HF 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 highlighted an association between a HR increase above 95 /minute lasting more than 12 hours and the 3-month functional outcome (31). 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, 5, 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 unfavourable outcome after SAH.

In our study, the adjustment of the HR effect to BRS annihilated the significance of HR. The baroreflex, which is a biofeedback loop, integrates a 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 which depend on the state of baroreceptors which are known to be altered in atheromatous patients (6, 13-16); (2) 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 subarachnoid haemorrhage potentially impairs their functioning by the apoptotic mechanisms that it is believed to trigger (32); (3) the efferents which control the contractility and rate of the heart muscle, on 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 haemorrhage 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 haemorrhage and occurrence of systemic complications during hospitalization.

We did not find a significant association between BRS and vasospasm. As compared to 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. 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 due to 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 heart rate variation (33) which is assessed in our study through BRS.

Mechanical ventilation can be another factor that is able to alter baroreflex sensitivity. In a study by Andry Van de Louw et al (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 due 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 concerning 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 beta-blockers, or factors which may have such an action, as the noradrenaline. In the upcoming studies, it will be useful to integrate these patients which have not been included in the current series, in order to test the association identified between the BRS and the outcome in conditions of usual clinical care, thus accepting the limit of pharmacologic 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 non-pharmacological- assessing the impact of baroreflex improvement on outcome, in aneurysmal subarachnoid haemorrhage.

DISCLOSURES

ICM+ is a software for brain monitoring licensed by Cambridge Enterprise. Marek CZOSNYKA and Peter SMIELEWSKI have financial interest in a part of licensing fee.

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REFERENCES

1. Ferro JM, Canhão P, Peralta R. Udate on subarachnoid haemorrhage. J Neurol. 2008:465-79

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. 2011:211-40

3. D'Souza S. Aneurysmal Subarachnoid Hemorrhage. J Neurosurg Anesthesiol 2015;27:222-40.

4. Tafil-Klawe M, Klawe J, Majcherczyk S, Trzebski A. Sympatho-inhibitory baroreflex in conscious rabbits: simultaneous recordings of sympathetic and aortic nerve activity. J Auton Nerv Syst. 1989:227- 32.

5. Latinen T, Hartikainen J, Vanninen E, Niskanen L, Geelen G, LänsimiesE. Age and gender dependency of baroreflex sensitivity in healthy subjects. J Appl Physiol. 1998:576–583.

6. Nasr N, Pavy-Le Traon A, Larrue V. Baroreflex sensitivity is impaired in bilateral carotid atherosclerosis. Stroke 2005. 1891-1895

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. 1988:816-24.

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. 1996:1007–1010.

9. Robinson T, James M, Youde J, Panerai R, Potter J. Cardiac baroreceptor sensitivity is impaired after acute stroke. Stroke. 1997:1671–1676.

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.

11. Sykora M, Steiner T, Rocco A, Turcani P, Hacke W, Diedler J. Baroreflex sensitivity to predict malignant middle cerebral artery infarction. Stroke. 2012:714-9

12. Kardos A, Watterich G, De Menezes R, Csanady M, Casadei B, Rudas L. Determinants of spontaneous baroreflex sensitivity in a healthy working population. Hypertension. 2001:911–916.

13. Chao AC, Chern CM, Kuo TB, Chou CH, Chuang YM, Wong WJ et al. Non invasive assessment of spontaneous baroreflex sensitivity and heart rate variability in patients with carotid athrosclerosis. Cerebrovasc Dis. 2003:151–157.

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

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(3): 221-226.

16. - Mangin L, Lesèche G, Duprey A, Clerici C. Ventilatory chaos is impaired in carotid atherosclerosis. PLoS One. 2011; 6:e16297.

17. Abstract. Nellgard B. Changes in baroreflex sensitivity in correlation to incidence of vasospasm and outcome in patients with subarachnoid haemorrhage. Acta Anaesthesiologica Scandinavica 2007; 51 (Suppl 118): 31-32

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. Journal of Critical Care 2005: 20 (4): 394.

19. Budohoski KP1, Czosnyka M, Smielewski P, Kasprowicz M, Helmy A, et al. Impairment of cerebral autoregulation predicts delayed cerebral ischemia after subarachnoid hemorrhage: a prospective observational study. Stroke. 2012:3230-7.

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.

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. 2012:1711–1737.

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. 198:1457

23. Jennett B, Bond M. Assessment of outcome after severe brain damage. Lancet. 1975:480-4.

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. 2004:1371-80.

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. pii: 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. Firth David, Bias reduction of maximum likelihood estimates, Biometrika (1993) 80: 27-38.

28. R, Development, Core and Team (2012). R: A Language and Environment for Statistical Computing. In: R. Foundation for Statistical Computing.

29. Sykora M, Diedler J, Turcani P, Hacke W, Steiner T. Baroreflex: a new therapeutic target in human stroke? Stroke 2009:678-82.

30. Schmidt JM, Sow D, Crimmins M, Albers D, Agarwal S, Claassen J. Heart rate variability for preclinical detection of secondary complications after subarachnoid hemorrhage. Neurocrit Care. 2014 :382-9

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: 390-8.

32. Cahill J, Calvert JW, Zhang JH. Mechanisms of early brain injury after subarachnoid hemorrhage. J Cereb Blood Flow Metab. 2006:1341-53.

33. Ebert T. Sympathetic and Hemodynamic Effects of Moderate and Deep Sedation with Propofol in Humans. Anesthesiology 2005;103:20-4.

34. Andry Van de Louw Breathing cardiovascular variability and baroreflex in mechanically ventilated patients Am J Physiol Regul Integr Comp Physiol 2008; 295: R1934–R1940.

Variables	Total (n=48)	GOS 1-3 (n=9)	GOS 4-5 (n=39)	Simple logistic regression OR(95%CI) P
BRS (msec/mmHg)	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	58 (36-76)	60 (47-74)	57 (36-76)	0.977(0.910, 1.049) 0.521
Gender				
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* *Yes*	 42 (87.5) 6 (12.5)	 7 (77.8) 2 (22.2)	 35 (89.7) 4 (10.3)	 1.0 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 (beats/mn)	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* *yes*	 36 (75.0) 12 (25.0)	 5 (55.6) 4 (44.4)	 31 (79.5) 8 (20.5)	 1.0 0.323(0.070, 1.486)	 0.147
Vasospasm *no* *yes*	 *27 (56.3)* *21 (43.7)*	 *3 (33.3)* *6 (66.7)*	 *24 (61.5)* *15 (38.5)*	 *1.0* *0.312 (0.068, 1.441)*	 *0.136*
ABP-LF (mmHg^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*

Table 1: Univariate analysis evaluating the association between a good outcome (GOS 4 or 5) and the potential explanatory variables considered. The qualitative variables are described by the absolute (relative) frequencies of their categories and the quantitative variables are expressed as medians (minimum - maximum). The abbreviations used in the table are: GCS: Glasgow coma score; BRS: baroreflex sensitivity; ABP: arterial blood pressure; DID: delayed ischemic deficiency. Vasospasm refers to mean flow velocity > 120cm/sec 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 has been calculated as spectral power of ABP in the low frequency range (0.04-0.15Hz). The variables significantly associated with 3 month outcome were indicated in bold print.

		BRS	p-value
Categorical Variables		***Median (min - max)***	
Sex	*Female*	*11.7 (3.2 – 24.5)*	*0.867*
	Male	*10.6 (1.5 – 38.7)*	
Location of SAH	*Left*	*10.4 (2.5 – 24.5)*	*0.152*
	Right	*13.6 (2.6 – 38.7)*	
	Median	*10.9 (1.5 – 18.4)*	
Treatment of ruptured aneurysm at the time of BRS measurement	*Not treated*	*11.5 (2.6 – 24.5)*	*0.932*
	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	*no*	*12.1 (1.5 – 38.7)*	*0.314*
	yes	*8.7 (2.6 – 13.9)*	
Vasospasm on transcranial Doppler	*no*	*12.0 (3.2 – 29.3)*	*0.885*
	yes	*11.3 (1.5 – 38.7)*	

External derivation	*no*	*12.0 (2.5 – 38.7)*	*0.408*
	yes	*10.5 (1.5 – 13.9)*	
Continuous Variables		***Spearman correlation coefficient***	***p-value***
Age		*-0.186*	*0.206*
WFNS		*-0.371*	*0.015*

Table 2 *Statistical description of the (univariate) association between BRS and variables of interest pertaining to SAH. 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.*

Variable	Coefficient (Std Error)	OR (95% CI)	p-value
Intercept	1.498 (1.416)	-----	-----
BRS (ms/mmHg)	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

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.*

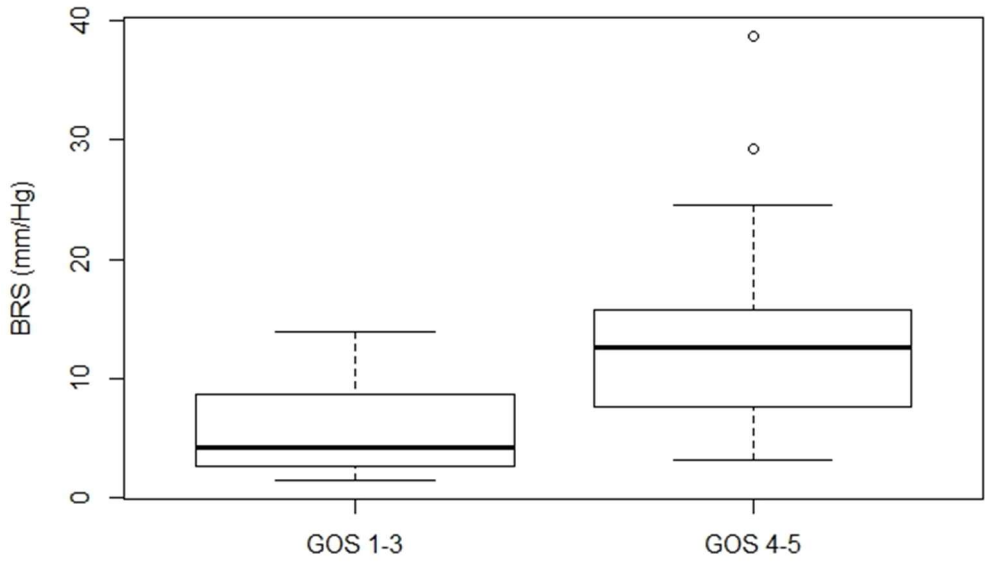

Figure 1:

Distribution of baroreflex sensitivity (BRS) early after admission for poor outcome (GOS 1-3) and good outcome (GOS 4-5).

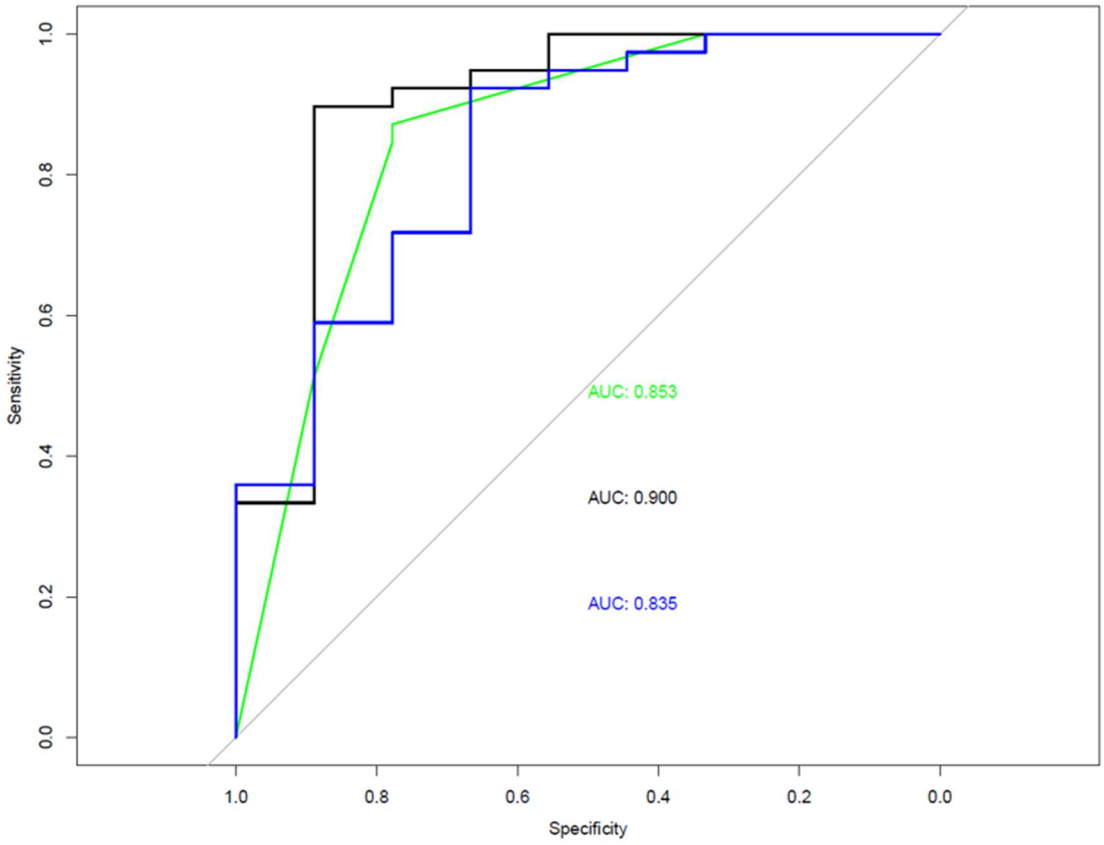

Figure 2:

ROC curves for the regression models predicting poor/good outcome from: BRS alone (AUC=0.835) in blue color, WFNS alone (AUC=0.853) in green color, and BRS+WFNS in black color (AUC=0.900).