

Are Optimal Cerebral Perfusion Pressure and Cerebrovascular Autoregulation Related to Long-term Outcome in Patients With Aneurysmal Subarachnoid Hemorrhage?

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Background and Objectives: Continuous assessment of the cerebrovascular autoregulation (CVA) through use of the pressure reactivity index (PRx), a moving linear correlation coefficient between mean arterial blood pressure and intracranial pressure, has been effective in optimizing cerebral perfusion pressure (CPPopt) in traumatic brain injured (TBI) patients. This study investigates the feasibility of measuring CPPopt in patients with aneurysmal subarachnoid hemorrhage (aSAH) by continuously assessing the CVA.

Methods: Twenty-nine aSAH patients were enrolled, and data from CVA status, CPPopt, and periods when CPP was below, within, or above CPPopt were computed daily. Outcome was assessed at 6 months with the Glasgow Outcome Scale. Mann-Whitney *U* test was used to analyze differences in the duration of impaired CVA and duration of CPP below CPPopt in patients with good and poor outcomes. Multivariable logistic regression analysis was used to identify independent predictors of outcome.

Results: CVA monitoring data were available for all 29 patients with a total monitoring time of 2757 h. The duration of impaired CVA was 36.5% (interquartile range: 24.6 to 49.8) of the total monitoring time in 15 patients with good outcome and 71.6% of the total monitoring time (51.2 to 80.0) in 14 patients with poor outcome (Mann-Whitney *U* test 3.295, $P = 0.0010$). PRx-based CPPopt could be identified in 26 patients (89.6%) with a total monitoring time of 2691 h. The duration of CPP below the CPPopt range was 28.0% (interquartile range: 18.0 to 47.0) of the total monitoring time in patients with good outcome and 76.0% (48.5 to 82.5) in patients with poor outcome (Mann-Whitney *U* test 2.779, $P = 0.0054$). Glasgow Coma Scale score

and duration of impaired CVA were independently associated with 6-month outcome (Glasgow Coma Scale score odds ratio: 1.95, 95% confidence interval: 1.01-3.75; duration of impaired CVA odds ratio: 0.88, 95% confidence interval: 0.78-0.99).

Conclusions: The assessment of CVA and CPPopt is feasible in aSAH patients and may provide important information regarding long-term outcome. A PRx above the 0.2 threshold and a CPP below the CPPopt range are associated with worse outcome.

Key Words: subarachnoid hemorrhage, cerebrovascular autoregulation, cerebral perfusion pressure

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Patients with aneurysmal subarachnoid hemorrhage (aSAH) may benefit from a cerebral perfusion pressure (CPP)-oriented therapy, which is tailored to prevent cerebral ischemia secondary to vasospasm.^{1,2} However, the value at which the CPP should be maintained in these patients remains undefined.^{1,3,4} CPP values that are too low or too high may respectively lead to hypoperfusion and cerebral ischemia or hyperemia with increased risk of rebleeding and secondary intracranial hypertension.^{5–7} Furthermore, a CPP threshold common to all patients is probably over simplistic. It is likely that the optimal CPP is different in patients and should be individually tailored.^{1,4}

Theoretically, the target CPP at which aSAH patients must be maintained should correspond to the level at which cerebrovascular pressure reactivity works at its best.⁸ In this manner, it is possible to identify the optimal CPP (CPPopt). In fact, this concept has been evaluated in patients with traumatic brain injury (TBI) where those with impaired cerebrovascular autoregulation (CVA) and a CPP lower or higher than CPPopt have worse outcome than patients with normal CVA or those with a CPP at CPPopt value.^{8–11} Therefore, CVA optimization has been proposed as a guide for assessing CPPopt in TBI patients.^{9,10} In fact, to our knowledge, there is no evidence of an association between CPPopt and outcome in aSAH patients.

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The purposes of this study were to investigate: (1) whether the assessment of CVA and CPPopt is feasible in aSAH; (2) whether aSAH patients with greater duration of impaired CVA status had worse neurologic outcome than patients with intact CVA; and (3) whether patients with CPP outside the CPPopt range had worse neurologic outcome than those with CPP within the CPPopt range.

MATERIALS AND METHODS

Study Design and Setting

The study was approved by the local Ethics Committee. Detailed written information was provided to the patient's next of kin. Written information was given, and consent was obtained from all surviving patients as soon as they regained mental competency.

This is a retrospective analysis of prospectively recorded data, derived from the enrollment of a consecutive series of acutely ill adult patients with aSAH admitted to the Neurointensive Care Unit of the Spedali Civili di Brescia, Italy, a University-affiliated teaching Hospital, between January 2005 and January 2009. Inclusion criteria were age ≥ 18 years, a diagnosis of aSAH, invasive monitoring of intracranial pressure (ICP), and arterial blood pressure (ABP). Patients were excluded if they were pregnant, had nonaneurysmal SAH, were expected to die soon after admission, or fulfilled brain death criteria.

Neurologic Evaluation and Treatment

The diagnosis of aSAH was established on the basis of computed tomography (CT), computed tomography angiography, digital subtraction angiography, or with xanthochromia of the cerebrospinal fluid if the CT scan was negative.

Neurological severity was graded according to the Glasgow Coma Scale (GCS), Hunt & Hess, and the World Federation of Neurologic Surgeons (WFNS) scores. Brain CT distribution of blood was graded according to Fisher et al.¹²

Aneurysm obliteration was performed as soon as possible after diagnosis, generally within 1 calendar day, by using either neuroradiological coiling or surgical clipping according to the local protocol. All patients were sedated, intubated, and mechanically ventilated and were managed according to current guidelines¹³: patients were maintained normovolemic and mildly hemodiluted (35% hematocrit); PaO₂ was maintained above 80 mm Hg and PaCO₂ between 35 and 40 mm Hg; nimodipine was given to all patients; CPP was initially tailored at a target above 70 mm Hg. An external ventricular drain was placed in all patients with symptomatic hydrocephalus or intraventricular hemorrhage with a level of consciousness that precluded the patient from following simple commands. Transcranial Doppler (TCD) (DWL, Stuttgart, Germany) was performed daily, and diagnosis of cerebral vasospasm was based on TCD, digital subtraction angiography, or clinically in the presence of delayed ischemic neurological deficits (DINDs). DINDs themselves were diagnosed on the basis of both clinical criteria

and brain CT findings. Triple H therapy (hypertension, hemodilution, hypervolemia) was started when the diagnosis of vasospasm was established. When significant clinical symptoms persisted for more than 2 h despite this therapy, angiography with balloon angioplasty of vasospastic vessels was performed with or without intra-arterial vasodilators, if technically feasible.

ICP was monitored through the use of intraparenchymal (Camino Intracranial Pressure Monitoring Kit, Integra NeuroSciences, San Diego, CA; CODMAN ICP Monitoring System, Johnson & Johnson Medical LTD, Raynham, MA) or intraventricular catheters (CODMAN External drains). ABP was monitored invasively (Edwards Lifesciences; Irvine, CA). For multimodal data acquisition and calculation of derived indexes, we used the Intensive Care Monitoring software system (ICM+, University of Cambridge, UK) running on bedside laptop computers. Simultaneous recordings of analogic signals from ICP and ABP signals were digitalized with an analogic-to-digital converter, sampled (sampling at 50 Hz) and averaged every 5 s. CPPopt was calculated daily from data averaged over 24 h values. Artifacts were manually detected and removed.

CVA assessment was measured continuously through calculation of the pressure reactivity index (PRx). PRx, as described by Czosnyka et al¹⁴ and Steiner et al,¹⁰ was calculated every 60 s as a moving Pearson correlation coefficient between 30 consecutive samples of mean arterial pressure and ICP. PRx is evaluated as a variable index, changing in time along with ICP, CPP, and arterial pressure. This coefficient represents an index of covariance ranging from -1 to 1 , in which a PRx above the value of 0.2 is indicative of defective CVA in TBI patients.¹⁴ We adopted this same threshold to define defective CVA, because no specific threshold was available for aSAH patients during the time period this study was conducted. When CVA is intact, to maintain a constant cerebral blood flow, the intracranial vessels react by contracting to increase resistance in case of increases in systemic ABP, thus leading to a reduction in intracranial blood volume and therefore ICP. When autoregulation is lost, systemic pressure changes are transmitted to the ICP. Consequently, the inverse correlation between ABP and ICP causes is represented by a negative value in PRx. On the contrary, when CVA is lost, a direct correlation between these 2 parameters, suggested by a positive value of PRx, represents a condition in which the cerebral resistance vessels become filled and emptied with blood passively after variations in CPP.^{8,14}

By plotting PRx versus CPP, the CPP range in which PRx is at its minimum represents values of CPP in which CVA is at its best. Hence, it is defined as the optimal CPP range.¹⁰ Finally, when there is no correlation between ICP and ABP, data points are randomly scattered; therefore, it is not possible to identify a CPPopt.

The data acquired from the patients' CVA status and CPPopt were used for research purposes only and did not influence the clinician's therapeutic strategy.

Follow-up

Neurologic outcome was evaluated 6 months after the initial aSAH episode using the Glasgow Outcome Scale (GOS). As for the monitoring data, the GOS scores were collected prospectively and analyzed retrospectively. Hence, the outcome assessor was blinded to the study results.

Data Presentation and Statistical Analysis

We expressed continuous variables as means (standard deviation) or medians (interquartile range, IQR) and discrete variables as counts (percentage).

We calculated the total monitoring time per patient and the percentage of time during which the CVA was altered (PRx > 0.2). Since patients who died had shorter total monitoring time and greater proportional duration of impaired CVA than survivors, for statistical purposes we compared the percentage of time during which the CVA was altered in patients with good or poor outcome.

We also calculated the total monitoring time and the percentage of time during which measured CPP was below (low CPP), within, or above the CPPopt range. The percentage of low CPP time in patients with good or poor outcome was compared.

GOS was dichotomized into good (good recovery and moderate disability) and poor outcomes (severe disability, vegetative state, or death).

Differences in continuous variables with abnormal distribution or unequal variance (age, duration of defective CVA, and low CPP) and in ordinal variables (GCS, WFNS, and Fisher scores) were analyzed with the nonparametric Mann-Whitney *U* test.

Differences in qualitative variables (sex and episodes of DINDs) were analyzed in contingency tables by means of the χ^2 statistics or by the Fisher exact test when the

expected values in any of the cells of the contingency table were less than 5.

To analyze the independent predictors of 6-month outcome, a multivariable logistic regression model was constructed. Predictor variables were introduced into the logistic model if they were significantly different in the bivariate analysis; to avoid the multicollinearity, we used GCS scores as the only measure of neurological severity; to avoid overfitting of a large number of predicting variables to a relatively small number of outcome events and the consequent likelihood of spurious relationships, we used the rule of 10: no more than 1 predictor for each 5 to 10 of the least frequent outcomes.¹⁵ Statistical test were 2 tailed, and *P* < 0.05 was considered as significant. The odds ratios (ORs) and 95% confidence interval (CI) were also calculated. The data were analyzed with STATA 10.0.

RESULTS

Of the 77 patients with SAH screened, 48 (62.3%) were excluded because of the following reasons: no ICP monitoring = 20 (41.7%); non-aSAH = 15 (31.2%); younger than 18 = 7 (14.6%); brain death criteria = 4 (8.3%); pregnancy = 2 (4.2%). Twenty-nine patients fulfilled the inclusion criteria and were enrolled. Of them, 15 had a good 6-month outcome (7 had good recovery; 8 had moderate disability) and 14 had a poor outcome (5 patients had severe disability, 1 patient was in a vegetative state, and 8 patients died). Vasospasm was present in two patients with good outcome, none of whom had DIND and in 6 patients with poor outcome group, 3 of whom had DIND. On bivariate analysis, patients with good outcome were significantly younger and had significantly lower GCS and WFNS scores on admission than patients with poor outcome (Table 1).

TABLE 1. Demographic Characteristics and Outcome of Enrolled Patients

| | Patients With 6-mo Good Outcome | Patients With 6-mo Poor Outcome | <i>P</i> | Total |
|--|---------------------------------|---------------------------------|----------|---------------|
| No. patients | 15 | 14 | / | 29 |
| Sex | | | | |
| No. females (%) | 10 (66.7%) | 6 (42.8%) | 0.198 | 16 (55.2%) |
| Age (y) | | | | |
| Mean (SD) | 49.7 (11.3) | 63.0 (14.9) | 0.027 | 56.1 (14.6) |
| Glasgow Coma Scale score | | | | |
| Median (IQR) | 8.0 (5.0-12.00) | 4.5 (4.00-6.00) | 0.007 | 6.0 (4.0-8.0) |
| World Federation Neurological Surgeons score | | | | |
| Median (IQR) | 4.0 (4.0-5.0) | 5.0 (5.0-5.0) | 0.005 | 5.0 (4.0-5.0) |
| Fisher score | | | | |
| Median (IQR) | 3.0 (2.0-3.0) | 3.0 (2.0-4.0) | 0.253 | 3.0 (2.0-3.0) |
| Delayed ischemic neurological deficits | | | | |
| No. events | 0 | 3 | 0.100 | 3 |
| Cerebral vasospasm | | | | |
| No. events | 2 | 6 | 0.209 | 8 |
| Treatment procedure: | | | | |
| Aneurysm clipping | 5 | 9 | 0.290 | 14 |
| Aneurysm coiling | 10 | 3 | | 13 |
| Neither | 0 | 2 | | 2 |

Good outcome indicates 6-month good recovery or moderate disability according to the Glasgow Outcome Scale; poor outcome indicates 6-month severe disability, vegetative state or death.
IQR indicates interquartile range.

CVA monitoring data were available for all 29 patients with a total monitoring time of 2757 h [patients with good outcome: 1413 h, median (IQR) 115 (48 to 140); patients with poor outcome 1344 h, 36 (20 to 120)]. Duration of impaired CVA was 36.5% (IQR: 24.6 to 49.8) of the total monitoring time in patients with good outcome and 71.6% of the total monitoring time (51.2 to 80.0) in patients with poor outcome (Mann-Whitney *U* test 3.295, *P* = 0.0010) (Fig. 1).

A PRx-based CPPopt could be identified and was available in 26 of 29 patients (89.6%), with a total monitoring time of 2691 h [patients with good outcome: 1389 h, median (IQR) 117 (48.0 to 140.0); patients with poor outcome: 1302 h, 59 (20.5 to 168.0)]. The CPPopt range was comparable in patients with good and poor outcomes (median 76 mm Hg, IQR: 73 to 85 mm Hg; 78 mm Hg, IQR: 67 to 88 mm Hg; Mann-Whitney *U* test 0.339, *P* = 0.7346). However, the fraction of the time spent below CPPopt was significantly greater in patients with poor outcome (76.0%, IQR: 48.5% to 82.5%) than in patients with good outcome (28%, IQR: 18.0 to 47.0 Mann-Whitney *U* test 2.779, *P* = 0.0054) (Fig. 2). Median CPPopt was 76.7 mm Hg. CPPopt ranges between 71 and 90 mm Hg were the most common CPPopt ranges. The least represented CPPopt range was also the lowest range and was comprised between 51 and 60 mm Hg (Fig. 3).

On multivariate logistic regression using age, GCS score and duration of impaired CVA as predictor variables, these 2 latter were independently associated with 6-month outcome (GCS score OR: 0.51, 95% CI: 0.27-0.99; duration of impaired CVA OR: 1.14, 95% CI: 1.01-1.29), whereas age was not (OR: 1.10, 95% CI: 0.98-1.23).

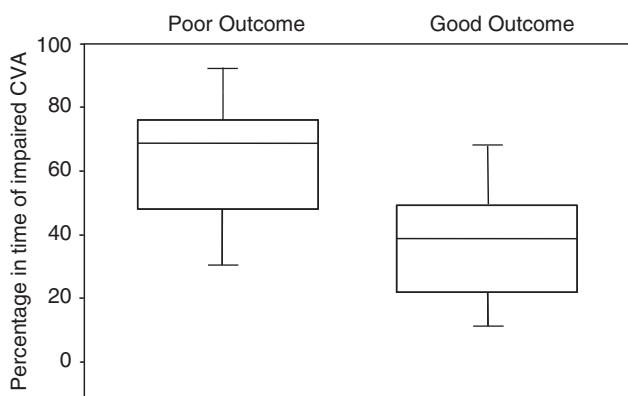


FIGURE 1. Box and whisker plots showing the duration of impaired cerebrovascular autoregulation (CVA) in patients with poor and good outcomes. The bottom and top of the box are respectively the 25th and 75th percentile and the middle band is the median. The ends of the whiskers represent the second and 98th percentile. Duration of impaired CVA was 36.5% (interquartile range: 24.6 to 49.8) of the total monitoring time in the 15 patients with good outcome and 71.6% (51.2 to 80.0) of the total monitoring time in the 14 patients with bad outcome (Mann-Whitney *U* test 3.295, *P* = 0.0010).

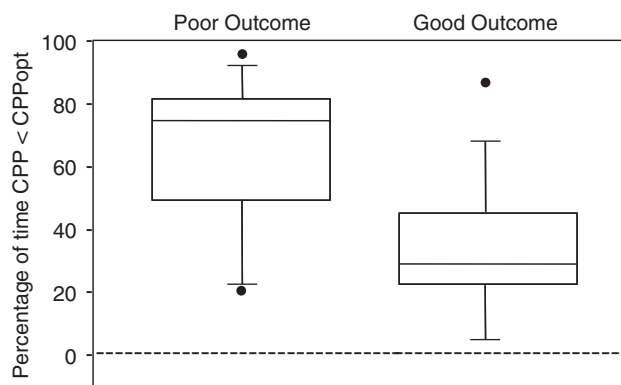


FIGURE 2. Box and whisker plots showing the percentage in time cerebral perfusion pressure (CPP) spent below optimal CPP (CPPopt) value in patients with good and poor outcomes. The bottom and top of the box are respectively the 25th and 75th percentile and the middle is the median. The ends of the whiskers represent the second and 98th percentile and the dots are the outliers. The fraction of the time spent below CPPopt was significantly greater in the 14 patients with poor outcome [76.0%, interquartile range (IQR): 48.5% to 82.5%] than in the 15 patients with good outcome (28.0%, IQR: 18.0 to 47.0 Mann-Whitney *U* test 2.779, *P* = 0.0054).

DISCUSSION

One of the mainstay of intensive care of neurologically injured patients is avoiding secondary brain damage resulting from cerebral metabolic and hemodynamic impairment.¹⁶ Available evidence suggests that CVA may be impaired after aSAH, increasing the risk of

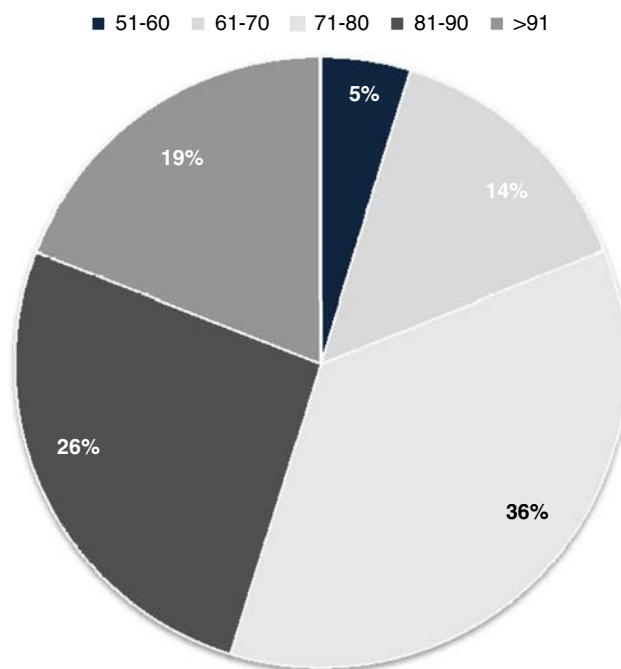


FIGURE 3. Optimizing cerebral perfusion pressure ranges in the study population.

secondary ischemic injury and DINDs.^{17,18} When CVA is impaired, the brain is vulnerable to ischemic damage, as a fall in ABP or rise of intracranial hypertension cannot be compensated by vasodilation of the cerebrovascular bed to maintain constant cerebral blood flow.^{19–21} An important tool at hand for the clinician caring for these patients is the capability to continuously assess CVA status through PRx calculation.^{8,10,14,19,20,22} In this study, we found that neurological severity and the duration of impaired CVA were both independent predictors of 6-month outcome in aSAH patients. This confirms that a PRx above 0.2 threshold, which we derived from TBI literature, is also valid for aSAH patients, as also showed by Diedler et al.¹³ Furthermore, the longer the time spent with a CPP below the CPPopt range, the worse the outcome.

Recent literature suggests avoiding the use of triple H therapy, especially in the absence of vasospasm, as hemodilution and hypervolemia have been associated with important complications (reduction in brain tissue PO₂, disturbed CVA, Acute Respiratory Distress Syndrome).^{23,24} Instead, induced hypertension has been shown to increase brain tissue PO₂ in SAH patients with vasospasm.²⁵ However, it remains uncertain to what extent should the clinician increase the blood pressure in the individual patient. CPPopt may itself vary over time, as shown in a recent study.²⁶ Therefore, continuous monitoring of CPPopt and its variations might provide the clinician with an individually tailored CPP and could represent a safe and useful complement in assessing the outer limits of an acceptable CPP by reducing the risk of cerebrovascular hypoperfusion and hyperperfusion.

The CPPopt range was comparable in patients with good and poor outcomes, indicating that CPPopt is an achievable target. Future studies are needed to show whether the outcome can be improved by avoiding a low CPP.

Limitations of PRx in aSAH Monitoring

PRx is calculated as the correlation coefficient between spontaneous changes in ABP and vasogenic changes in ICP. The assumption made is that vasogenic waves in ICP are an adequate surrogate of changes in cerebral blood volume and therefore of vascular diameter. This assumption holds true in the case of finite volume buffering reserve of the intracranial compartment (ie, if cerebral vessels dilate, ICP increases), as in physiologic condition or in states of reduced intracranial compliance with maintained skull integrity. This is not the case in patients with open ventricular drainage in whom ICP does not increase (or ICP changes are significantly dampened) in response to changes in cerebral blood volume. Caution should, therefore, be exercised when monitoring PRx in patients with increased compliance, such as open external ventricular drains and open bone flaps.

The main limitation of the PRx-based CPPopt paradigm proposed here can be expressed by the following question: “Is it possible to define the adequacy

of CPP or cerebral blood flow on the basis of a single number?” The question is particularly pressing in the context of aSAH, in which vasospasm, asymmetry of blood flow, and regional hypoperfusion are common. As an example, it is not unlikely to have a vasospastic MCA territory that is hypoperfused on 1 side and to have, at the very same time, a contralateral MCA territory that is hyperemic. PRx averages out cerebral vasoreactivity and provides a global index of cerebrovascular performance. The data shown here and in other recent studies show that despite its lack of spatial discrimination, PRx retains valuable information on the overall status of cerebrovascular reactivity and it has a strong prognostic significance after aSAH.^{10,13,26} In contrast, imaging perfusion studies, such as computerized tomography perfusion studies (CTPs), can identify regions of ischemia and regions of potentially salvageable penumbra (showed as areas of reduced cerebral blood flow with maintained cerebral blood volume) and are therefore gaining increasing popularity in the management of aSAH. However, CTPs have their own limitations. CTPs are expensive and time consuming; they require the transport of unstable patients to the radiology department and intravenous injection of contrast media. Moreover, CTPs provide a static image and are unable to provide a value for optimal perfusion. For example, if a patient has an ABP of 90 mm Hg at the time of the perfusion scan and an area of CBF/CBV mismatch is identified, it can be concluded that this patient has a significant area of salvageable penumbra. However, the target of ABP remains unclear: should we push ABP to 100, 110, 120, or 130 mm Hg? Despite its intrinsic limitations, continuous PRx monitoring could complement TCD and brain perfusion investigations and quite possibly provide usable targets for rapid CPP optimization.

Study Limitations

In our study population, GCS score and duration of impaired CVA were the only independent predicting variables of long-term outcome, whereas other factors such as vasospasm, pupillary light response, hypotension, and brain CT features were not. The small sample size conceivably prevented an adequate analysis of the interplay between aSAH and other outcome variables. Overfitting of a larger number of predicting variables to a relatively small number of outcome events produces a model that is overly sensitive to chance fluctuations in the data.²⁶ Therefore, we cannot exclude that our results were due to chance alone. Predictive modeling is particularly difficult when considering the numerous complex clinical elements that occur after aSAH and their interplay. It requires large clinical datasets together with specialized statistical tools, which still need to be fully explored.²⁷ As newly identified prognostic factors need to be validated in independent “test sets” of patients,²⁸ future studies regarding patients with aSAH should be prospectively performed using multivariable models to predict the long-term outcome of these patients and the relationship with CVA and CPPopt.

A crucial question is whether CVA performance during the first few hours of monitoring was predictive of outcome, as early identification of patients with good or poor outcome would be a major achievement to fully take advantage of the available resources. However, the statistical power of the study did not permit us to explore this aspect with the currently available sample size.

CPPopt could be identified only in 26 of 29 patients (89.6%). Therefore, technical difficulties should be considered when evaluating this monitoring in clinical practice. As a final study limitation, it should be mentioned that data were retrospectively analyzed, which might weaken results. However, the data were collected prospectively with daily surveillance and manual correction of artifacts. In addition, the outcome was assessed as part of routine clinical practice, and assessors were blinded to the study results, thus preventing expectation bias, a common and serious problem in clinical research because of the strong propensity of the treating physician to expectation bias.²⁹

CONCLUSIONS

Within the limitations of a small study population, the assessment of CVA and CPPopt is feasible in aSAH patients, and their analysis may provide important information regarding long-term outcome in aSAH patients. Longer periods with a PRx above the 0.2 threshold and a CPP below the CPPopt range are associated with worse outcome. The efficacy of a PRx-based CPP optimization strategy warrants further evaluation.

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