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NEUROCRITICAL CARE SOCIETY

ORIGINAL WORK

# Early Transcranial Doppler Evaluation of Cerebral Autoregulation Independently Predicts Functional Outcome After Aneurysmal Subarachnoid Hemorrhage

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## Abstract

**Background:** Cerebral autoregulation (CA) impairment after aneurysmal subarachnoid hemorrhage (SAH) has been associated with delayed cerebral ischemia and an unfavorable outcome. We investigated whether the early transient hyperemic response test (THRT), a transcranial Doppler (TCD)-based CA evaluation method, can predict functional outcome 6 months after aneurysmal SAH.

**Methods:** This is a prospective observational study of all aneurysmal SAH patients consecutively admitted to a single center between January 2016 and February 2017. CA was evaluated within 72 h of hemorrhage by THRT, which describes the changes in cerebral blood flow velocity after a brief compression of the ipsilateral common carotid artery. CA was considered to be preserved when an increase ≥ 9% of baseline systolic velocity was present. According to the modified Rankin Scale (mRS: 4–6), the primary outcome was unfavorable 6 months after hemorrhage. Secondary outcomes included cerebral infarction, vasospasm on TCD, and an unfavorable outcome at hospital discharge.

**Results:** Forty patients were included (mean age = 54 ± 12 years, 70% females). CA was impaired in 19 patients (47.5%) and preserved in 21 (52.5%). Impaired CA patients were older (59 ± 13 vs. 50 ± 9, $p = 0.012$), showed worse neurological conditions (Hunt&Hess 4 or 5–47.4% vs. 9.5%, $p = 0.012$), and clinical initial condition (APACHE II physiological score—12 [5.57–13] vs. 3.5 [3–5], $p = 0.001$). Fourteen patients in the impaired CA group and one patient in the preserved CA group progressed to an unfavorable outcome (73.7% vs. 4.7%, $p = 0.0001$). The impaired CA group more frequently developed cerebral infarction than the preserved CA group (36.8% vs. 0%, $p = 0.003$, respectively). After multivariate analysis, impaired CA (OR 5.15 95% CI 1.43–51.99, $p = 0.033$) and the APACHE II physiological score (OR 1.67, 95% CI 1.01–2.76, $p = 0.046$) were independently associated with an unfavorable outcome.

**Conclusions:** Early CA impairment detected by TCD and admission APACHE II physiological score independently predicted an unfavorable outcome after SAH.

**Keywords:** Subarachnoid hemorrhage, Cerebral circulation, Transcranial Doppler, Cerebral autoregulation, Transient hyperemic response test

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## Introduction

Aneurysmal subarachnoid hemorrhage (SAH) is a neurological emergency usually affecting working age groups, with a great socioeconomic impact [1]. Despite advances in management [2, 3], mortality rates are still high and long-term impairment affects up to 75% of survivors [4]. More than a half the patients classified as good outcome using routine scales present cognitive and psychological impairment that impacts their quality of life [5]. Outcome after aneurysmal SAH is a function of the complex interaction between severity of the primary brain injury and the neurological and systemic complications occurring in the first weeks thereafter [6, 7].

Cerebral vasospasm, i.e., the vasoconstriction of cerebral arteries, was thought to be the main factor associated with neurological deterioration, cerebral infarction, and poor outcome after aneurysmal SAH. It usually occurs within 2 weeks from the SAH and can be suspected clinically and confirmed angiographically [8]. However, current evidence suggests that vasospasm might be only an epiphenomenon rather than the main factor responsible for the neurological complications after aneurysmal SAH [9, 10]. The pathophysiology of delayed cerebral ischemia (DCI) is much more complex than previously thought. Angiographic vasospasm might play a role in DCI pathophysiology, but other important contributors such as early brain injury (the immediate injury to the brain after SAH), cerebral microthrombosis, cortical spreading ischemia, neuroinflammation, and cerebral autoregulation (CA) impairment have all been implicated in DCI as well [11–13].

CA is the intrinsic capacity of cerebral arterial vessels to adjust their diameter in order to maintain a relatively constant cerebral blood flow [14, 15] despite changes in cerebral perfusion pressure (CPP). CA may be disturbed early during the course of aneurysmal SAH [16–18], possibly increasing the risk of DCI and negatively impacting the long-term functional outcome [12, 19–22]. The transient hyperemic response test (THRT) is a transcranial Doppler (TCD)-based technique that permits CA assessment. It investigates changes in peak flow velocity (PFV) in intracerebral arteries after a brief compression of the ipsilateral common carotid artery [23] and can be used to evaluate CA.

We designed the present prospective study based on our previous clinical empirical observations. We hypothesized that impaired CA assessed early during the course of aneurysmal SAH by the THRT could predict an unfavorable outcome within 6 months, as well as cerebral infarction, vasospasm on TCD, and an unfavorable outcome at hospital discharge.

## Methods

We performed a prospective observational study of all aneurysmal SAH patients consecutively admitted to a single high-volume SAH reference hospital in Porto Alegre, Brazil, between January 2016 and February 2017. Inclusion criteria were: (a) adult patients ($\geq$ 18 years), (b) SAH confirmed by noncontrast computed tomography (CT) or lumbar puncture, (c) ruptured cerebral aneurysm confirmed by CT angiography (CTA) or digital subtraction angiography (DSA), and (d) admission to the study hospital within 72 h of hemorrhage. Exclusion criteria were: (a) admission to the hospital $\geq$ 72 h after aneurysm rupture (which prevented an early evaluation of CA), (b) impossibility to perform the TCD study due to the absence of a readable acoustic temporal bone window, (c) previous neurological disease that could affect CA (i.e., ischemic stroke, carotid stenosis, or severe traumatic brain injury), (d) early angiographic vasospasm in the initial CTA or DSA imaging (which could prevent adequate CA evaluation) [24], (e) clinical instability at admission precluding aneurysmal investigation (i.e., DSA), or (f) death before aneurysm investigation. Patients were managed according to the institutional SAH protocol which is based on current international guidelines [25–27]. The first step in DCI management was the correction and maintenance of euvolemic status. Eventually, noradrenaline was used to increase blood pressure, targeted on neurological improvement, up to a systolic blood pressure of 220 mmHg after aneurysmal treatment [27]. The patients did not have access to rescue therapy with cerebral angioplasty or an intra-arterial vasodilator. The study was approved by the local Research Ethics Committee (CAAE: 49998115.1.0000.5530).

The primary outcome was functional outcome assessed by the modified Rankin Scale (mRS) evaluated 6 months after SAH. All patients were assessed during visits to the neurosurgical outpatient clinic. The functional assessment was performed by one neurosurgeon, who was blind to the CA evaluation results. Outcome was dichotomized into favorable (mRS = 0–3) and unfavorable (mRS = 4–6).

Secondary outcomes included: (a) mRS upon hospital discharge; (b) cerebral infarction on neuroimaging as a measure of DCI, defined as image diagnosis of cerebral infarction identified on CT or magnetic resonance imaging (MRI) within 6 weeks after SAH or on the latest CT or MRI scan before death within 6 weeks and not present on the scan between 24 and 48 h after early aneurysm occlusion. The hypodensity of the cerebral image was not attributable to surgical clipping, endovascular treatment, ventricular catheter, or reabsorbed intraparenchymal hematoma. The other secondary outcomes were: (c) arterial narrowing on CTA or DSA; (d) vasospasm on TCD,

defined by a middle cerebral artery (MCA) mean flow velocity (FV) exceeding 120 cm/s with a concomitant Lindegaard Ratio ($MCA_{fv}$/internal carotid artery $[ICA]_{fv}$) greater than 3.0 and corresponding vasospasm criteria for anterior and posterior cerebral arteries, as well as vertebral and basilar arteries [28]; (e) length of hospital stay. These concepts are in agreement with the current international definitions of SAH outcomes [29].

### CA Assessment

TCD examination was performed with a 2 mHz probe Digi-Lite™ equipment (Rimed®, Israel) by a single operator (CBR) to minimize inter-observer variation. All examinations were performed by about the third day of hemorrhage, always before aneurysmal treatment. CA was assessed by THRT, a TCD-based CA evaluation method, which describes the changes in peak cerebral blood FV after a brief compression of the common carotid artery as previously described [23, 30, 31]. In short, CA is preserved when a brief hyperemic response occurs, i.e., an increase greater than 9% (the transient hyperemic response ratio $\geq 1.09$, the ratio between the hyperemic response and the baseline FV) of the baseline MCA PFV following a transient (3–5 s) ipsilateral common carotid artery compression in the neck (Giller maneuver) [23, 30]. A reduction $\geq 30\%$ of the baseline PFV is considered to reflect adequate carotid compression. After compression release, the first cardiac cycle was discarded and three cardiac cycles were averaged to calculate the transient hyperemic response ratio. When MCA PFV did not increase $\geq 9\%$ (i.e., the transient hyperemic response ratio was $< 1.09$), or eventually decreased, the test was repeated at least 3 times at 2-min intervals in order to guarantee that the result was not a false negative due to a technical problem. Last, the PFV should return to baseline values within 10 to 20 s after release of the carotid artery, as a marker of good test quality. CA was preserved if both sides presented a hyperemic response. The absence of a hyperemic response on both sides, or on at least one side, was consistent with impaired CA [31]. Each side was tested separately. During TCD evaluation, patients were eupneic and those under mechanical ventilation were kept normocapnic ($PaCO_2 = 35$–$40$ mmHg) as recommended for CA evaluation [30]. While the THRT was performed, the mean arterial pressure (MAP) of the patients should be above 70 mmHg, without bradycardia or tachycardia and without fever or hypothermia. If needed, vasopressors were used to maintain MAP above 70 mmHg [30].

### Statistical Analysis

Data are presented as mean ± standard deviation (SD) or median and interquartile range (IQR).

Patients with unilateral or bilateral failure in the CA test were diagnosed as having CA impairment. Patients with unilateral or bilateral cerebral infarction on imaging were diagnosed as having cerebral infarction. The Shapiro–Wilk test was used to test normality. Continuous variables were analyzed by the Student $t$ test or Mann-Whitney U test depending on the normality of data distribution. The Chi-squared or Fisher's exact test was used for categorical variables, and the results are expressed as odds ratio (OR) with 95% confidence interval (CI). Clinical characteristics and common predictors of outcome were selected from previous studies [32, 33] and were analyzed by univariate analysis. Variables with $p < 0.10$ identified during univariate analysis were included in a multivariate logistic regression to determine factors independently associated with an unfavorable long-term outcome (mRS score 4–6). The analysis was performed using SPSS software (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, version 21.0. Armonk, NY: IBM Corp). The level of significance was set at $p < 0.05$ in all analyses. Based on our previous empirical unpublished observations and considering that 50% of patients with impaired CA and 10% with preserved CA would evolve to unfavorable outcome, the inclusion of 38 patients would result in a study with an error beta of 0.2, power of 0.8, with alpha = 0.05.

## Results

Ninety-eight aneurysmal SAH patients were admitted during the study period, and 40 of them were included in the final analysis (mean age = 54 ± 12 years, 72.5% females). The main reasons for exclusion were: (a) hospital admission $\geq 3$ days after the hemorrhage, (b) clinical instability at hospital admission that precluded aneurysmal investigation (i.e., DSA), (c) death before aneurysm treatment and (d) no readable temporal bone acoustic window (Fig. 1). The mean time for THRT was 2.87 ± 0.34 days. No patient needed a vasopressor during THRT because all of them spontaneously maintained MAP above 70 mmHg.

Table 1 summarizes the baseline characteristics of the impaired vs. preserved CA groups. Most of the aneurysms were located in the anterior circulation: 14 cases in the MCA (14/40–35%) (7 in the preserved and 7 in the impaired CA group), 11 cases in the anterior communicating artery (11/40–27.5%) (7 in the preserved and 4 in the impaired CA group), 2 cases in the ICA (2/40–5%) (1 in the preserved and 1 in the impaired CA group), 1 case in the anterior communicating artery (1/40–2.5%) (preserved CA). In the posterior circulation, 11 cases were located in the posterior communicating artery (11/40–27.5%) (5 in the preserved and 6 in the impaired CA group) and 1 case in the posterior

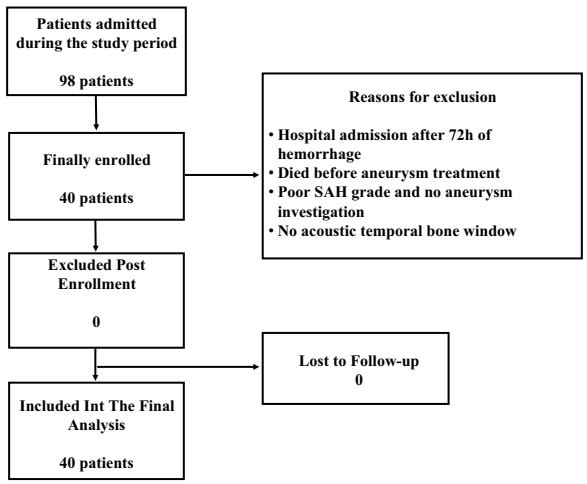


**Fig. 1** Flowchart of the entire cohort admitted between January 2016 and February 2017

49.5 ± 9.3, $p = 0.012$), arrived at the hospital in worse neurological condition upon admission (Hunt&Hess [H&] 4 or 5–47.4% vs. 9.5%, $p = 0.012$) and presented higher APACHE II physiological score when compared to patients in the preserved CA group (12 vs. 3.5, $p = 0.001$).

### Primary Outcome

Nineteen patients out of forty (47.5%) had impaired CA, while 21 (52.5%) had preserved CA according to TRHT (Fig. 2). In the long-term assessment (mean time of 4.95 ± 1.26 months), 14 patients (14/19) in the impaired CA group vs. only one patient (1/21) in the preserved CA group had an unfavorable outcome, i.e., mRS 4–6 (73.7% vs. 4.7%, $p = 0.0001$, respectively—Table 2). In our sample, the long-term mortality (mRS = 6) was 5% (2/40). Actually both patients died before hospital discharge and belonged to the impaired CA group. The bilateral absence of a hyperemic response occurred in 42% (8/19) of the patients in the impaired CA group and only one of those cases had a favorable outcome. Two of the patients in the impaired CA group with unilateral absence of a hyperemic response (11/19) had a favorable outcome.

**Table 1 Baseline characteristics according to cerebral autoregulation**

| | All patients | Preserved CA ($n = 21$) | Impaired CA ($n = 19$) | *p* value |
|---|---|---|---|---|
| Age, years | 53.92 ± 12.10 | 49.5 ± 9.3 | 58.9 ± 13.1 | 0.012 |
| Female (%) | 28 (70) | 13 (61.9) | 15 (78.9) | 0.311 |
| Hypertension (%) | 19 (47.5) | 7 (33.3) | 12 (63.2) | 0.112 |
| Smoking (%) | 23 (57.5) | 14 (66.7) | 9 (47.4) | 0.337 |
| LOC at presentation (%) | 24 (60) | 12 (57.1) | 12 (63.2) | 0.755 |
| APACHE II physiological sub-score | 5 (5–12) | 3.5 (3–5) | 12 (5.57–13) | **0.001** |
| Hunt&Hess 4 or 5 (%) | 11 (27.5) | 2 (9.5) | 9 (47.4) | **0.012** |
| Fisher grade 3 or 4 (%) | 37 (92.5) | 18 (85.7) | 19 (100) | 0.233 |
| Intraventricular hemorrhage (%) | 8 (20) | 3 (14.3) | 5 (26.3) | 0.209 |
| Intraparenchymal hematoma (%) | 11 (27.5) | 3 (14.3) | 8 (42.1) | 0.078 |
| External ventricular drain (%) | 13 (32.5) | 5 (23.8) | 8 (42.1) | 0.314 |
| Intracranial pressure monitoring (%) | 9 (22.5) | 5 (23.8) | 4 (21) | 1.0 |
| Aneurysmal treatment: | | | | |
| Surgery (%) | 38 (95) | 20 (95.3) | 18 (95) | 0.942 |
| Endovascular procedure (%) | 2 (5) | 1 (4.7) | 1 (5) | 1 |

Data are presented as *N* (%), mean ± SD (standard deviation) and median [interquartile range]

Statistically significant differences are highlighted in bold

Scale 0 = no physiological derangement, 44 = maximal physiological derangement

*APACHE* acute physiology and chronic health evaluation, *CA* cerebral autoregulation, *LOC* loss of consciousness

inferior cerebellar artery (1/40–2.5%) (impaired CA). The majority of patients were treated with surgical clipping (38/40–95%) because of lack of neuroradiology availability in the hospital at the time of the study. The median time for aneurysm treatment was 4 days [2–5]. Nine patients (22.5%) needed intracranial pressure monitorization (4 in the impaired CA and 5 in the preserved CA group). In this sample, no control DSA was performed. Patients with impaired CA were older (58.9 ± 13.1 vs.

### Secondary Outcomes

Sixteen patients (16/19) in the impaired CA group vs. three patients (3/21) in the preserved CA group were discharged with an unfavorable functional outcome

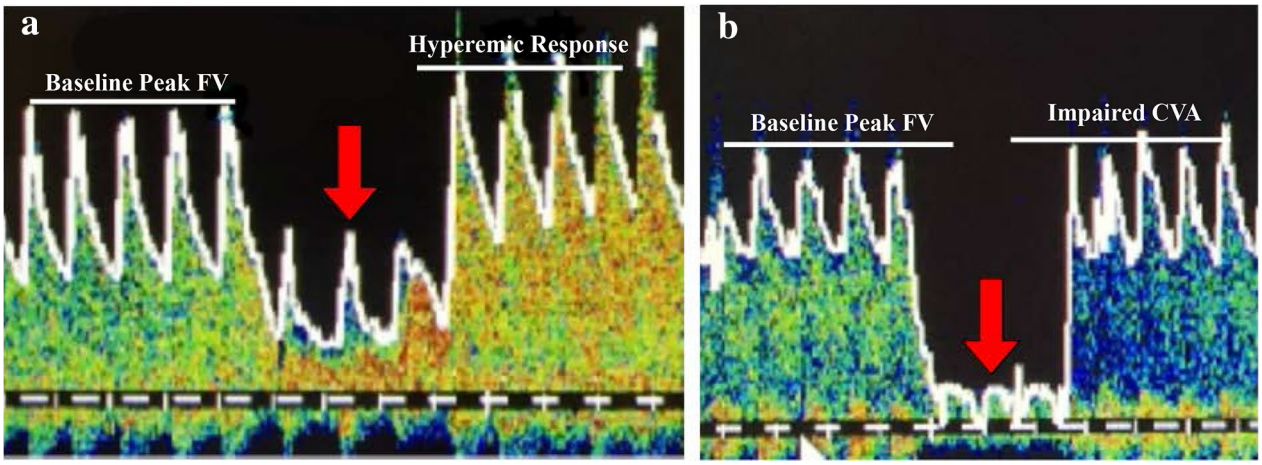


**Fig. 2** **a** Example of the hyperemic response (PFV increase over 10% of baseline) after carotid compression (red arrow) in a transient hyperemic response test with preserved cerebral autoregulation. **b** Example of no hyperemic response (the same PFV as at baseline) (Color figure online)

**Table 2 Outcomes according to cerebral autoregulation**

| | Preserved CA ($n=21$) | Impaired CA ($n=19$) | $p$ value |
|---|---|---|---|
| Primary outcome | | | |
| Unfavorable outcome—within 6 months | 1 (4.8) | 14 (73.7) | **0.0001** |
| Description of mRS within 6 months | | | |
| 0 | 4 | 0 | |
| 1 | 11 | 2 | |
| 2 | 4 | 1 | |
| 3 | 1 | 1 | |
| 4 | 1 | 4 | |
| 5 | 0 | 8 | |
| 6 | 0 | 2 | |
| Secondary outcomes | | | |
| Unfavorable outcome—hospital discharge | 3 (14.3) | 16 (84.2) | **0.0001** |
| Cerebral infarction | 0 | 7 (36.8) | **0.003** |
| Vasospasm on TCD | 5 (23.8) | 6 (31.6) | 0.727 |
| Median number of days to vasospasm on TCD | 8.25 (7–9) | 10.2 (8–11) | 0.413 |
| Median number of days of hospital stay | 30 (18–34) | 43 (25.5–71.5) | **0.020** |

Data are presented as *N* (%) and median (interquartile range)

Statistically significant differences are highlighted in bold

*CA* cerebral autoregulation, *MRS* modified Rankin Scale, *TCD* transcranial Doppler

(84.2% vs. 14.3%, $p=0.0001$, respectively—Table 2). In the preserved CA group, the median mRS improved from $1.9\pm1.33$ at hospital discharge to $1.2\pm0.99$ within 6 months after SAH ($p=0.031$), but no improvement occurred in the impaired CA group (respectively: $4\pm1.54$ to $4.2\pm1.74$ mRS; $p=0.096$) (Fig. 3). Seven patients (7/19–36.8%) in the impaired CA group developed cerebral infarction vs. no patient in the preserved CA group ($p=0.003$) (Table 2). There was no relationship between the side of impaired CA and cerebral infarction ($p=0.105$). Six patients (6/19–31.6%) in the impaired CA group vs. 5 patients (5/21–23.8%, $p=0.727$) in the preserved CA group developed vasospasm on TCD (Table 2). No patient showed an early vasospasm on TCD (within 72 h of hemorrhage). Vasospasm on TCD was diagnosed on average 8.3 days after the hemorrhagic ictus (range: 6–13 days) in the preserved CA group vs. 10.2 days (range: 6–15 days) in the impaired CA group (8.3 vs. 10.2 days, $p=0.413$). Furthermore, patients with impaired CA also had a longer hospital stay compared

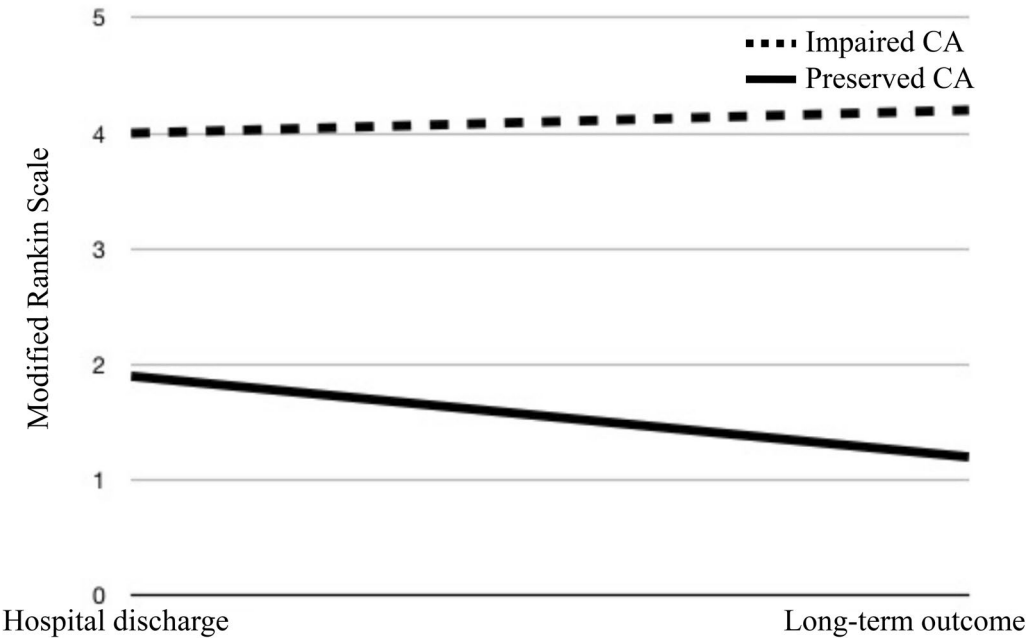


**Fig. 3** Patients with preserved cerebral autoregulation (CA) showed improvement in the modified Rankin scores. Solid line is comparing mrs of patients with preserved CA at hospital discharge with mRS of patients 6 months after SAH (Median 1.9 ± 1.33 to 1.2 ± 0.99; $p = 0.031$). Dashed line is showing that patients with impaired CA showed no improvement in the same period of time (median 4 ± 1.54 to 4.2 ± 1.74; $p = 0.096$)

**Table 3 Univariated analysis with risk factors for unfavorable long-term outcome**

| | Odds ratio (95% CI) | *p* value |
|---|---|---|
| Univariate analysis | | |
| Hypertension | 1.65 (0.726–3.78) | 0.230 |
| Age | 1.05 (1.02–1.08) | **0.001** |
| Smoking | 0.64 (0.29–1.43) | 0.284 |
| LOC | 0.76 (0.34–1.68) | 0.502 |
| APACHE II physiological score | 1.41 (1.17–1.78) | **0.0001** |
| Hunt&Hess 4 or 5 | 3.31 (1.43–6.31) | **0.003** |
| Intraparenchymal hematoma | 1.63 (0.79–3.37) | 0.182 |
| Intraventricular hemorrhage | 2.25 (1.08–4.67) | **0.030** |
| Cerebral infarction | 3.14 (1.66–5.92) | **0.0001** |
| Vasospasm on TCD | 0.96 (0.38–2.38) | 0.928 |
| Cerebral autoregulation impairment | 15.47 (2.24–106.76) | **0.005** |

Statistically significant differences are highlighted in bold

*APACHE* acute physiology and chronic health evaluation, *CI* confidence interval, *LOC* level of consciousness, *TDC* transcranial Doppler

to patients in the preserved CA group (43 vs. 30 days, p = 0.02) (Table 2).

### Logistic Regression Analysis

In the univariate analysis (Table 3), older age (OR 1.05, 95% CI 1.02–1.08, $p = 0.001$), higher APACHE physiological score (OR 1.41, 95% CI 1.17–1.78, $p = 0.0001$), poor-grade SAH, i.e., Hunt&Hess 4 or 5, (OR 3.31, 95% CI 1.43–6.31, $p = 0.003$), intraventricular hemorrhage (OR 2.25, 95% CI 1.08–4.67, $p = 0.03$), cerebral infarction (OR 3.14, 95% CI 1.66–5.92, $p = 0.0001$), and impaired CA (OR 15.47, 95% CI 2.24–106.76, $p = 0.005$) were associated with an unfavorable outcome. In the multivariate analysis (Table 4), only impaired CA (OR 5.15, 95% CI 1.43–51.99, $p = 0.033$) and higher APACHE physiological score (OR 1.67, 95% CI 1.01–2.76, $p = 0.046$) remained independently associated with an unfavorable outcome.

## Discussion

In this prospective cohort study, we observed that early impairment of CA (occurring within 72 h of hemorrhage) detected by THRT was an independent predictor of an unfavorable long-term functional outcome after aneurysmal SAH. Also, patients with impaired CA had longer hospital stay, worse clinical course, and higher rates of cerebral infarction than patients with preserved CA.

SAH is a complex disease that can disturb CA [17, 34]. When CA is impaired, there is a failure of this intrinsic mechanism to maintain constant CBF, independent of CPP fluctuation. This phenomenon renders the brain susceptible to hyperemia and hypoperfusion and consequently to secondary brain damage and an unfavorable outcome [22]. In our cohort, 74% of patients with impaired CA progressed to an

**Table 4 Logistic regression with independent risk factors for long-term unfavorable outcome**

| Variables | Crude odds ratio (95% CI) | *p* | Adjusted odds ratio (95% CI) | *p* |
|---|---|---|---|---|
| Age | 1.05 (1.02–1.08) | **0.001** | 0.98 (0.87–1.10) | 0.714 |
| APACHE II physiological score | 1.41 (1.17–1.78) | **0.0001** | 1.67 (1.01–2.76) | **0.046** |
| Hunt&Hess 4 or 5 | 3.31 (1.43–6.31) | **0.003** | 6.28 (0.08–47.5) | 0.405 |
| Intraventricular hemorrhage | 2.25 (1.08–4.67) | **0.030** | 0.69 (0.01–19.6) | 0.872 |
| Cerebral infarction | 3.14 (1.66–5.92) | **0.0001** | 0.33(0.01–16.7) | 0.581 |
| Cerebral autoregulation impairment | 15.47 (2.24–106.76) | **0.005** | 5.15 (1.43–51.99) | **0.033** |

Statistically significant differences are highlighted in bold

*APACHE* acute physiology and chronic health evaluation, *CI* confidence interval

unfavorable long-term outcome. More importantly, we found that impaired CA remained independently associated with an unfavorable outcome, after the adjustment for known predictors of outcome, such as initial clinical grade (Hunt&Hess), the volume of subarachnoid blood on initial CT (Fisher grade), and age.

Our results are in line with other previous studies that showed an association between impaired CA and an unfavorable outcome, using different methods to evaluate CA [17, 22, 34–36]. The study by Budohoski et al. showed that bilateral CA failure was an independent predictor of an unfavorable long-term outcome [20]. Also, previous studies have demonstrated that CA derangement was associated with DCI [12, 37]. In a prospective cohort study of 98 patients, Budohoski et al. [16] evaluated CA using the systolic FV TCD-derived index and the near-infrared spectroscopy–based index showing that CA disturbances detected within 5 days of hemorrhage were independently predictive of DCI.

Other pathological processes independent of large-vessel narrowing, such as early brain injury (i.e., global cerebral ischemia due to increased intracranial pressure following initial bleeding), microcirculatory vasospasm, cerebral microthrombosis, cortical spreading ischemia, and CA impairment have all been implicated in the development of DCI after aneurysmal SAH [11, 13]. Whether these processes function as separate entities or they are different expressions of the same cerebrovascular failure has not been determined.

A previous meta-analysis of randomized clinical trials and the results of the CONSCIOUS trials have raised the hypothesis that angiographic vasospasm is neither the sole nor the sufficient mechanism to explain the occurrence of DCI and the poor outcomes after aneurysmal SAH [29, 38]. In our study, detection of vasospasm on TCD did not correlate with an unfavorable outcome, a finding in line with previous studies [16, 35, 39, 40]. Moreover, CA impairment was not associated with vasospasm on TCD. As DCI pathophysiology moves towards a complex and multifactorial process, CA might play a role as a possible and important contributor to the development of DCI.

Several methods of CA evaluation have been described [21, 22]; although there is no consensus about the ideal method for the assessment of CA, TCD continues to be frequently used and validated method for the noninvasive evaluation of CA [22]. This advanced methods use specific technology with software that analyze data originated from continuous monitoring. Those data are converted in different indexes and then interpreted. Besides peculiarities related to the quality of sign generated, it can be time-consuming and dependent on an expert opinion for results interpretation [21].

THRT is a real-time, bedside TCD-based technique for the assessment of CA [30, 41], previously used to assess CA in SAH. The possible operator-dependent variations of a TCD method are diminished since THRT depends on a relative change of PSV and not exactly on the absolute velocity value. The test can be used in a "summary form" with yes or no results. Although being one of the first methods described for this purpose [30, 41], it is not so frequently used in current practice. This may be due to the fact that THRT needs a manual intervention from an operator for carotid compression while other methods are more practical, using data from spontaneous oscillations during monitoring. Another point is that continuous data provide more complex information, with a graduation of CA impairment, while THRT in this "summary form" directly shows a simple result. Studies using THRT methodology also described the association between CA impairment and the development of DCI [35, 39]. Our results are consistent with findings from previous studies showing an association between CA derangement and cerebral infarction, as DCI outcome [18, 19]. As previously reported in other investigations

[42–45], we also found that cerebral infarction was associated with an unfavorable long-term outcome.

In our study, worse initial clinical severity as evaluated by APACHE II physiological sub-score at admission was also associated with unfavorable long-term outcome. Although APACHE II was not designed specifically for neurocritical patients, the admission APACHE II physiological sub-score has been used as a prognostic factor in SAH patients [46, 47].

It is still not completely understood if changing CA status could modify the outcome in SAH. CA information can contribute to the optimization of SAH treatment strategies [36]. Data obtained with advanced methods can provide the specific level of CA response to different types of therapeutic management. Previous studies on SAH patients have demonstrated the effect of different drugs and arterial pressure adjustment over CA and its association with outcome [36, 48]. Perhaps, improving the initial impaired CA status by guided therapy could change the long-term outcome of SAH.

Our study has several strengths. All CA evaluations were performed before aneurysmal treatment to prevent any influence that vessel manipulation could exert on the CA test response. In addition, we chose the early time window to evaluate CA, i.e., within 72 h of hemorrhage, in order to avoid the period of angiographic cerebral vasospasm. During vasospasm, exhaustion of the distal vasodilatation mechanism is expected to occur in response to the reduction of CPP, making it difficult to interpret CA result in this context [34, 49].

On the other hand, our study has limitations that should be recognized. First, our sample consisted of patients from a single center who were mostly submitted to surgical aneurysmal treatment. Two patients were treated with coils. The results might not be equal for those patients with coiled aneurysms. Second, a possible selection bias for our sample could be the exclusion of patients who were in poor neurological and clinical conditions and who could not be submitted to a complete early investigation for the detection of a cerebral aneurysm. Also excluded were moribund patients and those who died before aneurysm treatment. Third, due to logistic and financial constraints, we could not assess all patients at the exact time points scheduled (i.e., 3, 6, and 12 months). Forth, THRT was applied at a single point, not continuous or daily as previously described [16, 18, 39]. Fifth, our median time for aneurysm treatment was slightly later than recommended by current guidelines, in view of most of our cases is referred from other primary care centers. Additionally, we used THRT to provide only qualitative (yes/no) information, without determining a quantitative index of CA [20, 35]. Thus, some of our observations should be considered in the light of these facts and additional studies are necessary to corroborate our initial observations.

## Conclusions

In conclusion, early CA assessment can contribute to early prognostication after aneurysmal SAH. In our study, early CA impairment detected by THRT and APACHE II physiological score at intensive care unit admission were independently associated with an unfavorable long-term outcome in patients with aneurysmal SAH.

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**Authors' Contributions**

CBR contributed to the conception and design, acquisition, analysis and interpretation of data, drafting the article. ALOM contributed to statistical analysis, critically revising and drafting the article. MMR contributed to the design, acquisition, and analysis of data. CP contributed to conception and design, analysis and interpretation of data, critically revising the article. PVW contributed to acquisition, analysis, and interpretation of data. DZ contributed to acquisition and analysis of data. MMB contributed to conception and design, analysis, and interpretation of data, critically revising the article and supervising the study.

**Source of Support**

None.

**Conflict of interest**

The authors declare that they have no conflict of interest.

**Ethical Approval**

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed Consent**

Informed consent was obtained from each participant in the study.

## Publisher's Note



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