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FMUP FACULDADE DE MEDICINA
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# Evolução Temporal, Colaterais e Eficácia da Autorregulação Cerebral no Acidente Vascular Cerebral Isquémico

# Time trends, collaterals and cerebral autoregulation efficacy in acute ischemic stroke

**ABRIL, 2021**

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DESIGNAÇÃO DA ÁREA DO PROJECTO

Ciências Médicas e da Saúde – Medicina Clínica

TÍTULO DISSERTAÇÃO/~~MONOGRAFIA~~ (riscar o que não interessa)

Time trends, collaterals and cerebral autoregulation efficacy in acute ischemic stroke

ORIENTADOR

Pedro Miguel Araújo Campos Castro

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**Dedicatória**

À minha família, pelo apoio inestimável que me prestou ao longo de todos os anos da minha formação.

Aos amigos e à Raquel que coloriram este percurso que finalizo com orgulho.

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**Abstract**

Cerebral autoregulation (CA) is crucial for stable blood perfusion pressure and is challenged during acute ischemic stroke. CA's efficacy and collateral arteries may play a key role in penumbral region perfusion during acute phase of ischemia. We aimed to investigate CA parameters in collateral arteries over the first 48 hours post-stroke and compare them between cerebral hemispheres.

We enrolled 46 patients with acute ischemic stroke of the middle cerebral artery territory and monitored cerebral blood flow velocity (CBFV) of the main cerebral arteries with transcranial Doppler. We assessed dynamic CA by projection pursuit regression (PPR) from the spontaneous oscillations of blood pressure and CBFV from within 6 hours until 48 hours of symptom onset.

No differences were detected throughout time. Affected middle cerebral artery showed steeper autoregulatory gain (worse dynamic CA) than its contralateral after 48 hours of onset (0.42±0.37 vs 0.37±0.30 cm/s/mmHg, $p<0.05$). Slight asymmetries were found in CA mostly outside autoregulatory regions.

Our findings advance on the knowledge of global CA impairment during acute phase of stroke. Understanding collateral arteries role and physiological mechanisms regarding their CA efficacy can be useful to personalize stroke hemodynamic management and predict stroke clinical outcomes.

**Keywords:** Cerebral autoregulation; Collateral arteries; Projection Pursuit Regression; Stroke; Transcranial Doppler.

## 1. Introduction

Cerebral vasculature has the ability to buffer blood pressure swings or other hemodynamic challenges through counterregulatory adjustments in arteriolar diameter and resistance, which refers to the so-called cerebral autoregulation (CA)[1]. It's fairly known that this mechanism is crucial for neural tissue health and when dysfunctional may have a role in various pathological conditions, such as vascular dementia[2], hemorrhagic and ischemic stroke[3, 4].

Despite its clinical significance, the full understanding of CA is still incomplete. Several physiological mechanisms have been pointed as possible intervenients in healthy individuals, such as the autonomous nervous system, myogenic, endothelial and metabolic vascular responses[5], but they fail to comprehensively explain cerebral perfusion pressure-flow relationship[6].

Transcranial Doppler sonography (TCD) has been used to assess dynamic CA non-invasively[7], by measuring real-time and dynamic changes in cerebral blood flow (based on its surrogate, cerebral blood flow velocity (CBFV)) in response to changes in cerebral perfusion pressure, either induced by certain maneuvers (such as body tilt, handgrip, squat-stand and others[8]) or taking advantage of spontaneous blood pressure fluctuations. In the acutely ill patient setting, it is preferable to determine CBFV in response to spontaneous fluctuations of arterial blood pressure[1], which is an innocuous and feasible way to evaluate dynamic cerebral autoregulation.

Pressure-flow relationship usually entails three different regions of CA effectiveness, one intermediate autoregulatory region wherein arterial pressure fluctuations are effectively counter-regulated, and two outer, more passive regions, each represented by a different slope. The lower the slope, the more active CA is, meaning that

autoregulatory mechanisms can better buffer blood pressure swings and keep cerebral blood flow constant for neural perfusion.

This non-linear relationship is observed when the CA is effective[6] and presumably during the acute stage of acute ischemic stroke (AIS). Unlike previous methodologies of CA assessment (transfer function analysis, for instance) that assume linearity between signals[9], projection pursuit regression (PPR) is a novel statistical model that was developed to overcome such linearity assumption. PPR analytic approach has demonstrated ability to reliably quantify cerebral blood pressure-flow relationship and measure cerebral autoregulation effectiveness[6]. Additionally, PPR represents pressure-flow relationship in a more physiological manner granting the possibility of inferring pathophysiological mechanisms involved in CA derangements. PPR has not yet been used to assess CA in AIS patients, though.

CA's efficacy during ischemic stroke is critical for the maintenance of stable blood flow in the ischemic penumbra and for avoidance of excessive hyperperfusion with the inherent risk of hemorrhagic transformation[10]. Additionally, in case of acute cerebral artery occlusion, collateral arteries are recruited and provide immediate diversion of blood flow, enabling blood perfusion to penumbral regions, through existing anastomoses. Thus, collateral blood flow through circle of Willis have also shown to play a role in attenuating severity of ischemic injury in AIS[11]. Collateral arteries pose as protective vascular pathways and previous research showed that CA is a crucial facilitator of collateral flow[11]. In fact, routine collateral flow evaluation has been advanced as a potential factor for risk stratification and guidance of therapeutic intervention in cerebral ischemia[12].

Cerebral autoregulation status and variation is still fairly unknown within the first hours after onset because most of previous studies on CA start monitoring blood flow at

later stages[9]. Moreover, they focus on middle cerebral artery (MCA) measurements of both hemispheres to assess CA, while collateral circulation and autoregulation remains largely unappreciated.

Current evidence suggests that a comprehensive understanding of CA effectiveness, which is increasingly more accessible at bed side of acutely ill patients. CA assessment may be a valuable tool in guiding hemodynamic management and predicting secondary complications of various cerebrovascular conditions, such as AIS[9, 10, 13, 14], opening the door towards individualized medicine.

The present study aims to describe time trends of CA in collateral arteries during acute phase of AIS, using PPR analysis. Additionally, we aim to compare autoregulation parameters between arteries of both affected and unaffected hemispheres and characterize global CA response to stroke derangements.

## 2. Material and methods

### **2.1.** Population studied

Our cohort includes patients admitted at Centro Hospitalar Universitário de São João (CHUSJ) stroke unit with AIS in anterior circulation from August 2012 until October 2013. They were consecutively selected if they were able to be monitored within 6 hours of symptoms onset. This cohort has been used before and is further detailed in previous research[14].

We used the following exclusion criteria: hemodynamic instability requiring vasoactive agents, other central neurological co-morbidities (e.g. tumor), acute kidney injury, myocardial infarction (either clinically suspected, or based on

electrocardiographic or serial myocardial injury markers findings) and insufficient temporal acoustic window.

CT brain scan (Siemens Somaton Emotion Duo, Erlangen, Germany), with 3 to 6 mm slices, was used at admission and repeated at 24 hours.

All the AIS patients primarily enrolled underwent cervical and transcranial duplex scan (Vivid e; GE) before evaluation, to exclude significant extra or intracranial stenosis. At presentation and on subsequent daily evaluations, all patients were clinically examined and ranked according to the National Institutes of Health Stroke Scale (NIHSS) score.

This study's protocol was approved by the local institutional ethical committee and performed in accordance with the Declaration of Helsinki ethical principles. All participants or their proxy gave written and informed consent prior to the inclusion in this study.

**2.2.** Monitoring protocol

Recording of the cerebrovascular measures was carried out in the stroke unit, with the patients' head at 0º, for 10 minutes. For cerebral blood flow velocity (CBFV) recording, we used a transcranial Doppler ultrasonograph with 2-MHz monitoring probes secured with a standard headband (Doppler BoxX, DWL, Singen, Germany) on both sides to obtain information of the three main cerebral arteries – A1 segment of anterior cerebral artery (ACA), M1 segment of middle cerebral artery (MCA – depth of 50-55 mm) and P2 segment of posterior cerebral artery (PCA). Finometer MIDI (FMS, Amsterdam, Netherlands) was used to continuously monitor arterial blood pressure (BP), estimated with a finger cuff on the asymptomatic side. Furthermore, BP was hourly assessed by as oscillometric cuff (Dash 2500, GE, UK). End-tidal carbon dioxide (CO2) was continuously recorded with nasal cannula attached to Respsense capnograph (Nonin,

Amsterdam, Netherlands). We used a DII lead of a standard 3-lead electrocardiogram to determine heart rate. All data was then synchronized at 400 Hz with Powerlab (AD Instruments, Oxford, UK), computerized and stored for further analysis. Data collection was repeated at various time points for later comparison and analysis. Time points selected were within the first 6 hours, then at 12 hours, 24 hours and 48 hours after the onset of symptoms.

**2.3.** Data analysis

All signals were reviewed, and artifacts removed. Ten minutes of normalized data were interpolated at 100 Hz.

Projection pursuit regression analysis was used to assess dynamic CA based on spontaneous CBFV and blood pressure oscillations. PPR identifies three regions wherein pressure-flow relationship changes and subsequent parametrization allows definition of five autoregulation markers of the pressure-flow curve that, together, describe the typical nonlinear pressure-flow relationship: falling and rising slopes (outside autoregulatory region), autoregulatory gain, and lower and upper limits of the autoregulatory region. We then computed another variable (autoregulatory range - ARR), which is the difference between the upper and lower limits of the autoregulatory region. This method was repeated for all major cerebral arteries of every patient at all selected time points. We excluded results referring to the occluded artery in each patient, and those in which a correct physiological interpretation of the obtained pressure-flow relationship was unachievable. The gain (i.e. slope) of each region provides a measure of CA effectiveness[6].

Data was analysed using Matlab (version 9.4; Mathworks, Natick, MA), and R-Language.

To better ascertain autoregulation, we divided our analysis in two subsets of patients, those without MCA occlusion (n=29) and those with MCA occlusion (n=17). We then observed autoregulatory markers variability over time on each of the collateral arteries (Figure 1) and compared them to the contralateral side, to see if there was a differential change in any hemodynamic marker of autoregulation. In the subset of patients without occlusion, all 6 arteries were taken into consideration, while for patients with MCA occluded we've focused our attention on the arteries that can be potential primary collaterals for the occlusion (both anterior cerebral arteries and ipsilateral posterior cerebral artery) and on the contralateral MCA to infer global cerebral autoregulation.

**2.4.** Statistical analysis

Normality was determined by Shapiro-Wilk test.

Comparison of all variables was made via Repeated-measures ANOVA to find significant differences in hemodynamic variables over time and between groups with multiple comparisons corrected by Bonferonni's post-hoc test. Spearman's rho correlation analysis was performed to evaluate the relationship between PPR parameters and continuous baseline variables. Although nonparametric tests have been used, for reasons of clearness, all continuous variables are expressed as mean (standard deviation (SD)).

Statistical analysis was conducted using SPSS statistics version 26 (IBM, Armonk, NY, USA). A p-value of $<0.05$ (two-sided) was considered statistically significant.

## 3. Results

From 50 patients, 4 were excluded because they had posterior cerebral artery (PCA) infarcts. The 46-patient cohort had a mean age of 73 ± 12 years and was composed by 25 (54%) male patients, 35 (76%) underwent intravenous thrombolysis and 17 (37%) had MCA occlusion within 6 hours post-stroke. Median NIHSS was 14 points (inter-quartile range of 9-22). None had hemodynamic significant stenosis at ICA or MCA. Further demographic and clinical characteristics are detailed in our previous study[14].

Overall, there were no major significant changes in autoregulation parameters throughout the time series when considering each artery at an individual level. The only exceptions among patients without MCA occlusion (Table 1) were noticed in the ipsilateral anterior cerebral artery falling slope at 12 hours (0.57 ± 0.43 vs 0.52 ± 0.39 cm/s/mm Hg at 6 hours, $p < 0.05$) and in contralateral anterior and posterior cerebral arteries ARR at 24 hours (with lower and higher ARR compared to 6 hours, respectively).

When looking for differences between affected and non-affected hemispheres, we observed that MCA's falling slope was significantly steeper on the contralateral side within 6 hours after stroke (0.79 ± 0.66 vs 0.70 ± 0.54 cm/s/mm Hg, $p < 0.05$). The tendency for steeper falling slopes was also noticed on contralateral side throughout all measurements and for ACA. We found a similar pattern of steeper rising slopes on anterior cerebral circulation's contralateral side, only significant for anterior cerebral artery at 12 hours (0.77 ± 0.43 vs 0.64 ± 0.58 cm/s/mm Hg) and 48 hours measurements (0.72 ± 0.41 vs 0.54 ± 0.30 cm/s/mm Hg). Autoregulatory gain was overall similar between both sides in all arteries, but was significantly higher at affected MCA compared to contralateral side at 48 hours (0.42 ± 0.37 vs 0.37 ± 0.30 cm/s/mmHg, $p < 0.05$).

In comparison to the ipsilateral anterior and posterior cerebral arteries, the recanalized MCA showed higher slopes in all autoregulatory regions - falling slope

(significant at 24 hours), autoregulatory gain (significant at 12 and 48 hours measurements) and rising slope (significant from 12 to 48 hours when compared to posterior artery). On the contralateral side, our results suggest that the posterior vascular compartment had generally lower slopes in all regions of autoregulation, than anterior and middle cerebral arteries. In comparison to unaffected MCA, contralateral ACA had similar autoregulatory markers, while contralateral PCA showed significantly lower falling slopes (0.42 ± 0.35 vs 0.75 ± 0.40 cm/s/mmHg at 12 hours; 0.43 ± 0.41 vs 0.81 ± 0.55 cm/s/mmHg at 24 hours; 0.43 ± 0.35 vs 0.76 ± 0.36 cm/s/mmHg at 48 hours).

Posterior arteries also showed a wider ARR at all time points in comparison with arteries from anterior circulation of the same side (significant at 48 hours between posterior and middle ipsilateral arteries [6.06 ± 3.74 vs 4.49 ± 4.24 mmHg]).

Similarly, in the subset of patients with middle cerebral artery occlusion (Table 2), those who didn't recanalize at the affected MCA, we didn't find any particular or sustained temporal trend for any of the autoregulation markers of each artery.

But when comparing each artery to the opposite side, we've noticed some different patterns mostly on the anterior cerebral artery, outside of autoregulatory region: falling slope tends to be higher on the contralateral side (although $p$ values > 0.10) and rising slope also appears to be steeper on the contralateral side, only significant at 48 hours (0.70 ± 0.43 vs 0.42 ± 0.38 cm/s/mmHg). Autoregulatory gain seems to be markedly increased on the contralateral artery, although not statistically significant (0.29 ± 0.20 vs 0.16 ± 0.18 cm/s/mmHg at 12 hours, $p < 0.10$; 0.30 ± 0.43 vs 0.06 ± 0.31 cm/s/mmHg at 48 hours, $p < 0.10$), which could imply a more efficient autoregulation on ipsilateral anterior artery.

Despite some occasional statistically significant difference between sides for upper and lower limits of autoregulation, autoregulatory region (ARR) is overall similar in both sides.

In consonance to our findings for the subset of patients without MCA occlusion, in this subgroup there seems to exist a different pattern between posterior and anterior cerebral circulations. When compared to the unaffected MCA (contralateral), posterior cerebral artery of the same side had lower slopes in all regions of autoregulation, and with distinguishably significance in almost every measurement, while differences with anterior cerebral artery were not found.

## 4. Discussion

In this study, we performed serial bilateral measurements of cerebral autoregulation from within 6 hours until 48 hours of symptom onset of 46 patients with MCA ischemic stroke at affected territory and neighbor arterial territories and found that there was no overall change in autoregulatory parameters throughout this critical time period. However, when compared to contralateral side, affected MCA showed steeper cerebral blood flow in response to fast reductions in blood pressure within autoregulatory region, which might aggravate ischemic lesion. A tendency for steeper slopes was noted outside autoregulatory region at the contralateral anterior cerebral circulation (anterior and middle cerebral arteries), independently of MCA's occlusion status, in comparison with ipsilateral arteries.

Additionally, we've noticed significant distinct patterns within arteries of the same side irrespective of occlusion status. Middle cerebral arteries showed worse global autoregulation with steeper slopes within all autoregulatory regions, while posterior cerebral arteries had lower slopes and wider ARR (only for patients without MCA occlusion), thus better autoregulatory markers.

Notably, slopes of anterior cerebral arteries had a more similar pattern to posterior cerebral arteries if there wasn't MCA occlusion, while in the subset of patients with MCA occlusion, contralateral ACA had closer slopes to those of unaffected MCA.

In AIS major changes occur in local perfusion pressure and vascular integrity, thus CA is particularly challenged. It has been well-stablished by previous research that autoregulation is impaired in AIS[14-16]. This weakened ability is not only pronounced in the occluded artery territory but may also be diminished in its collaterals of the same and contralateral hemispheres[9].

We didn't find any robust and sustained time trend of any of the autoregulatory markers, from 6 to 48 hours interval. It is important to notice that the present study first measurements took place at earlier phases (within 6 hours of onset - hyperacute phase) of AIS than most previous studies on CA that start monitoring cerebrovascular parameters and report CA impairment from 24 hours onward[17-19]. This being said, our results' apparent homogeneity from 6 to 48 hours, in all arteries of both subset of patients, may be interpreted as one of following two manners: either that CA impairment reported by previous studies, is as well present in the hyperacute phase, particularly outside of autoregulatory region (i.e. for more extreme blood pressure values); or that CA differences over time, in the autoregulatory region, would only be evidenced after 48 post-stroke.

Some controversy remains in whether dynamic CA impairment is global or predominates on the ipsilateral side to the occlusion. On one hand previous studies, using different methodologies regarding MCA autoregulation assessment, indicate a global impairment of CA involving not only the infarcted, but also the unaffected side, independent of stroke type[10, 17, 18, 20] . On the other hand, there is evidence suggesting that the territory of dynamic CA loss is dependent on AIS subtype showing that large vessel

occlusion mainly affects the ipsilateral hemisphere, while lacunar stroke impairs CA bilaterally[21, 22]. Therefore, this global effect doesn't seem directly caused by the type of infarct, but rather the reflection of pre-existing endothelial dysfunction associated with hypertension and other cerebrovascular risk factors, that may be exacerbated as a response to an ischemic event, mediated by inflammatory and autonomic changes[23].

To be noticed, most of previous research take only MCA's measures into consideration to obtain information on hemispheric CA. Oppositely, besides MCA, we took a closer look at anterior and posterior cerebral arteries of both hemispheres, attempting to further investigate pressure-flow relationship asymmetry. Our results don't suggest sustained differences between affected and unaffected sides regarding autoregulatory gain in collateral arteries. However, in patients without occlusion, we found that contralateral MCA had lower autoregulatory gain than ipsilateral side only after 48 hours of onset, which implies a less effective CA on affected MCA at this time. This tendency for symmetry in autoregulatory gain of collateral arteries favors the concept of global CA impairment.

Our results suggest slight asymmetry outside of autoregulatory region, especially regarding rising and falling slopes of anterior and middle cerebral arteries. Although not always significant, there's a tendency for steeper slopes on the contralateral side, which is consistent with a substantial variation in flow in response to transient fluctuations towards extreme blood pressure values.

*Reinhard et al* showed that dysautoregulation tends to worsen and spread to contralateral side over the first days after AIS[24]. This study included two measurements: the first took place within 48 hours and the second between 5-7 days post-stroke and was based on bilateral MCA's dynamic autoregulation assessment through time correlation and transfer function analysis, that defines CA efficacy by global parameters (Mx and

phase shift, respectively). Our PPR approach allowed us to decompose blood pressure-flow relationship in 3 different regions of autoregulation and to draw conclusions to each one of them. Having this previous study's results in mind, after comparing both MCA's of the non-occluded subset of patients, we can suggest that spreading of CA impairment to the contralateral side may start sooner than 48 hours post-stroke, and that steeper slopes outside of autoregulatory region may underpin the global autoregulatory dysfunction *Reinhard et al* also described.

An interesting approach to address how different physiological systems work in concert to shape the pressure-flow relationship in healthy individuals, conducted by Hammer et al, suggests that myogenic response is the most important contributor behind it[6, 25]. In fact, myogenic effects appeared to be the most prominent determinant of cerebrovascular response outside of the more active autoregulatory region (i.e. falling and rising slopes of flow-pressure curve). These were exactly the same autoregulatory markers in which we found pattern differences between infarcted and contralateral side (on ACA and MCA), making it plausible to admit that differential impairment in myogenic mechanisms may justify this asymmetry.

Furthermore, our findings also suggest that these seemingly more passive regions of autoregulation, are not as passive as commonly conceived and can indeed buffer rapid changes in perfusion pressure. The apparent steeper falling and rising slopes on contralateral ACA and MCA could imply a higher risk for ischemia or hemorrhage in their territories[6]. However, this conclusion is clearly limited since pathophysiologic alterations in stroke patients may differ from those induced by pharmacologic blockades in healthy individuals, conducted in that study. Further research using PPR methodology in CA assessment of stroke patients would be needed to consolidate these correlations.

Nonetheless, in consonance with this theoretical disturbed myogenic autoregulatory capacity, previous research in animal models showed myogenic disfunction bilaterally after MCA occlusion that tended to decline only after longer periods of reperfusion[26]. However, it remains unclear why only contralateral arteries show apparent CA impairment outside of autoregulatory region.

The fact that posterior cerebral arteries displayed better autoregulatory markers, in general, than those of the anterior cerebral circulation (mostly in the subset of patients with MCA occluded) may be interpreted considering previously reported differences in regional sympathetic innervation[27], that observed denser sympathetic nerve fibers in the anterior circulation than those in the posterior circulation. Additionally, it has been demonstrated that impaired autonomic function secondary to sympathetic hyperactivity, is common in patients with AIS[28]. Hence, differential sympathetic activity could justify the apparent regional heterogeneity we observed in cerebral vasomotor control, in favor of the posterior vascular compartment.

Despite inexistence of gold standard method to measure dynamic CA and the considerable heterogeneity between previous studies on CA assessment in AIS in terms of methodology and time points of measurements[29], we believe PPR is a tool that can provide unique perception of integrated cerebrovascular control by drawing various autoregulatory markers of the pressure-flow relationship. These allow diagnosis of pathophysiological alterations underlying cerebral autoregulation impairment in acutely ill patients and have already shown ability to predict clinical outcomes in subarachnoid hemorrhage setting[30].

The main limitation of this study is the small cohort. Our approach would also benefit from the use of controls that would allow establishment of basal autoregulatory markers to compare with those from patients and better understand the grade of CA

impairment. Finally, we cannot rule out the influence of size of infarct which have been associated to CA impairment[24]; the use of chronic medications, such as beta-blockers that may affect dynamic CA through autonomic modulation and decreased sympathetic activity[31]; nor the history of chronic hypertension, which has been linked to impaired autoregulation, especially its lower and upper limits[32]. Our study was mainly explorative, thus some of the associations here suggested should be interpreted with caution and better confirmed in larger cohorts.

## Conclusions

Autoregulation parameters were overall stable over acute stroke phase in collateral arteries. Recanalized MCA showed less effective CA than contralateral MCA and asymmetry in collaterals was found mainly outside of autoregulatory region. Future research on collateral and infarcted arteries using PPR is warranted to understand the physiological mechanisms altered during acute ischemia, that can be useful to identify potential therapeutic strategies that might prolong the ischemic penumbra survival.

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**Author Contributions**: Conceptualization, P.C.; methodology, P.C.; software, C.O.T.; validation, P.C.; formal analysis, N.G., P.C.; investigation, N.G., P.C.; resources P.C.; data curation, N.G., P.C.; writing—original draft preparation, N.G; writing—review and editing, N.G, P.C.; visualization, N.G, P.C. and C.O.T.; supervision, P.C.; project administration, P.C. All authors have read and agreed to the published version of the manuscript.

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**Figures**

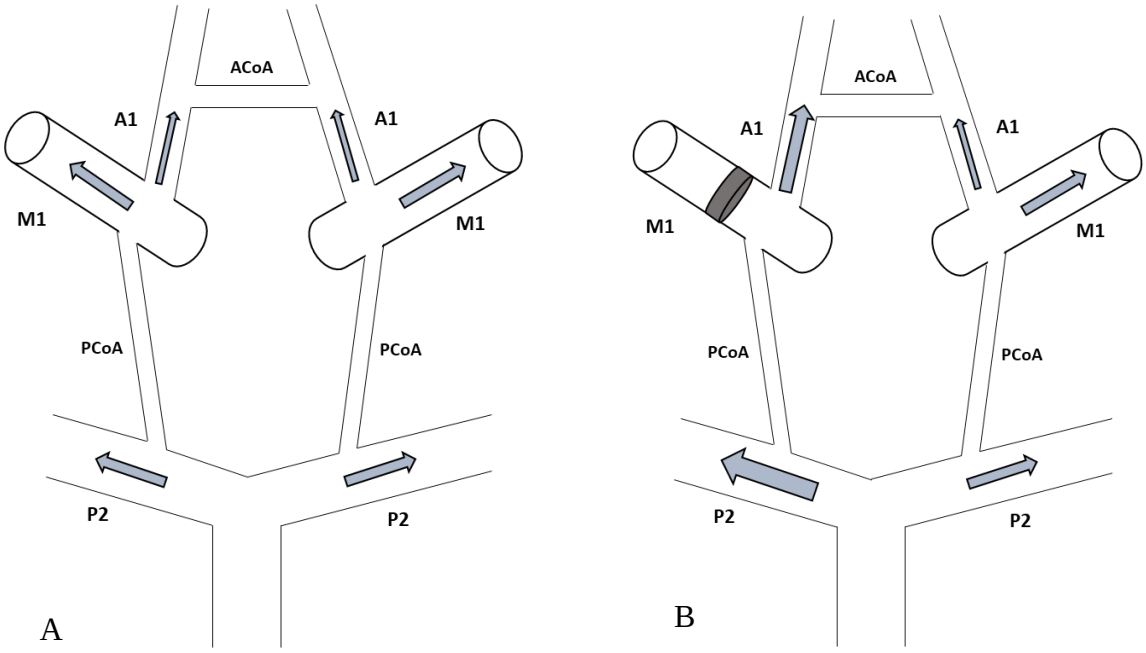


**Figure 1.** Regions in which cerebral blood flow velocity was assessed with Transcranial Doppler in **A:** patients without occlusion at 6 hours post-stroke. **B:** patients with occlusion at 6 hours post-stroke on the affected medial cerebral artery. Filled arrows represent flow direction. Wider arrows represent main collateral pathways upon MCA occlusion.

Abbreviations: A1 - A1 segment of Anterior cerebral artery; M1 – M1 segment of Middle cerebral artery; P2 – P2 segment of Posterior cerebral artery; ACoA – anterior communicating artery; PCoA – Posterior communicating artery.

## Tables

**Table 1** – Cerebral autoregulation markers in patients without occlusion of MCA (n=29). Values are represented as mean (SD).

| | Time (h) | A1 | | M1 | | P2 | |
|---|---|---|---|---|---|---|---|
| | | ipsilateral | contralateral | ipsilateral | contralateral | ipsilateral | contralateral |
| **Falling Slope ($cm \cdot s^{-1} \cdot mm\ Hg^{-1}$)** | 06 | 0.52 (0.39) | 0.55 (0.39) | 0.70 (0.54) | 0.79 (0.66) [a] | 0.46 (0.29) | 0.48 (0.41) |
| | 12 | 0.57 (0.43) [b] | 0.84 (1.52) | 0.68 (0.43) | 0.75 (0.40) | 0.48 (0.35) | 0.42 (0.35) [c] |
| | 24 | 0.42 (0.49) [c] | 0.62 (0.36) | 0.67 (0.42) | 0.81 (0.55) | 0.45 (0.37) [c] | 0.43 (0.41) [c] |
| | 48 | 0.50 (0.46) | 0.63 (0.48) | 0.69 (0.33) | 0.76 (0.36) | 0.48 (0.40) | 0.43 (0.35) [c] |
| **Lower limit of autoregulation (mm Hg)** | 06 | -1.07 (2.47) | -2.01 (3.27) | -1.75 (2.89) | -1.16 (2.75) | -1.87 (3.31) | -2.15 (2.66) |
| | 12 | -2.35 (3.67) | -1.47 (3.65) [a] | -1.41 (2.66) | -1.95 (2.83) | -3.28 (3.18) | -2.41 (3.75) |
| | 24 | -2.24 (3.15) | -1.63 (3.14) | -2.00 (2.56) | -2.31 (2.48) | -2.07 (3.26) | -2.38 (3.31) |
| | 48 | -1.39 (3.55) | -0.73 (3.92) | -1.64 (3.68) | -1.44 (3.47) | -1.98 (3.67) | -1.58 (2.84) |
| **Autoregulatory gain ($cm \cdot s^{-1} \cdot mm\ Hg^{-1}$)** | 06 | 0.29 (0.42) | 0.27 (0.38) | 0.32 (0.34) | 0.33 (0.33) | 0.25 (0.21) | 0.19 (0.18) |
| | 12 | 0.22 (0.27) [c] | 0.29 (0.32) | 0.41 (0.25) | 0.35 (0.29) | 0.15 (0.19) [c] | 0.11 (0.11) |
| | 24 | 0.49 (1.71) | 0.21 (0.28) | 0.19 (0.33) | 0.31 (0.38) | 0.19 (0.28) | 0.11 (0.19) |
| | 48 | 0.12 (0.23) [c] | 0.25 (0.33) | 0.42 (0.37) | 0.37 (0.30) [a] | 0.16 (0.20) [c] | 0.17 (0.21) |
| **Upper limit of autoregulation (mm Hg)** | 06 | 3.47 (2.45) | 3.08 (3.80) | 3.02 (3.10) | 2.95 (2.94) | 3.78 (3.64) | 2.54 (2.97) |
| | 12 | 3.41 (2.70) | 3.65 (3.78) | 3.46 (2.27) | 3.21 (2.55) | 2.06 (3.99) | 3.99 (3.81) [a] |
| | 24 | 2.38 (3.51) | 2.92 (3.63) | 2.10 (2.83) | 1.71 (2.98) | 3.68 (3.55) | 2.82 (4.07) |
| | 48 | 2.58 (3.92) | 3.38 (3.82) | 2.84 (4.21) | 2.62 (3.97) | 4.09 (4.13) | 3.85 (3.04) |
| **Rising Slope ($cm \cdot s^{-1} \cdot mmHg^{-1}$)** | 06 | 0.58 (0.44) | 0.64 (0.54) | 0.69 (0.39) | 0.80 (0.36) | 0.48 (0.29) | 0.42 (0.24) |
| | 12 | 0.64 (0.58) | 0.77 (0.43) [a] | 0.76 (0.35) | 0.87 (0.56) | 0.42 (0.25) [c] | 0.38 (0.23) |
| | 24 | 0.57 (0.33) | 0.73 (0.46) | 0.75 (0.44) | 0.89 (0.54) | 0.53 (0.41) [c] | 0.48 (0.33) |
| | 48 | 0.54 (0.30) | 0.72 (0.41) [a] | 0.81 (0.49) | 0.84 (0.39) | 0.48 (0.30) [c] | 0.47 (0.30) |
| **ARR (mm Hg)** | 06 | 4.53 (2.49) | 5.08 (3.28) | 4.77 (3.68) | 4.11 (2.58) | 5.64 (3.87) | 4.69 (2.84) [a] |
| | 12 | 5.76 (4.16) | 5.13 (4.49) | 4.87 (3.41) | 5.15 (3.84) | 5.34 (4.35) | 6.39 (4.73) |
| | 24 | 4.62 (3.70) | 4.55 (4.06) [b] | 4.10 (2.21) | 4.02 (2.19) | 5.75 (4.34) | 5.21 (4.29) [a, b] |
| | 48 | 3.96 (3.48) | 4.11 (3.61) | 4.49 (4.24) | 4.06 (4.24) | 6.06 (3.74) [c] | 5.43 (3.95) |

Abbreviations: Autoregulatory range (ARR), Middle cerebral artery (MCA), standard deviation (SD), A1 segment of Anterior cerebral artery (A1), M1 segment of Middle cerebral artery (M1), P2 segment of Posterior cerebral artery (P2).

[a] Pairwise comparison $p < 0.05$ vs ipsilateral artery

[b] Pairwise comparison $p < 0.05$ vs baseline (6 hours)

[c] Pairwise comparison $p < 0.05$ vs MCA of the same side

**Table 2** – Cerebral autoregulation markers in patients with ACM occlusion (n=17). Values are represented as mean (SD).

| | Time (h) | A1 | | M1 | | P2 | |
|---|---|---|---|---|---|---|---|
| | | ipsilateral | contralateral | ipsilateral | contralateral | ipsilateral | contralateral |
| **Falling slope ($cm \cdot s^{-1} \cdot mm\ hg^{-1}$)** | 06 | 0.36 (0.33) | 0.49 (0.28) | - | 0.71 (0.38) | 0.41 (0.19) | 0.44 (0.34) |
| | 12 | 0.33 (0.36) [b] | 1.28 (2.55) | - | 0.63 (0.29) | 0.57 (0.38) | 0.49 (0.43) [c] |
| | 24 | 0.37 (0.35) | 0.68 (0.30) | - | 0.77 (0.61) | 0.54 (0.57) | 0.45 (0.32) [c] |
| | 48 | 0.26 (0.24) | 0.46 (0.46) | - | 0.83 (0.48) | 0.46 (0.42) | 0.38 (0.18) [c] |
| **Lower limit of autoregulation (mm Hg)** | 06 | -2.63 (2.50) | -3.31 (3.90) | - | -0.92 (3.21) | -2.54 (3.96) | -2.23 (3.03) |
| | 12 | -3.36 (2.77) | -3.27 (3.20) [a] | - | -2.43 (3.48) | -3.69 (3.36) | -3.12 (4.21) |
| | 24 | -4.43 (3.30) | -2.41 (4.20) | - | -3.13 (2.74) | -2.26 (3.6) | -2.63 (4.29) |
| | 48 | -1.89 (4.90) | -1.18 (4.76) | - | -2.11 (3.98) | -1.76 (4.06) | -1.89 (3.07) |
| **Autoregulatory gain ($cm \cdot s^{-1} \cdot mm\ hg^{-1}$)** | 06 | 0.19 (0.14) | 0.23 (0.22) | - | 0.39 (0.30) | 0.22 (0.14) | 0.20 (0.19) [c] |
| | 12 | 0.16 (0.18) | 0.29 (0.20) | - | 0.27 (0.20) | 0.18 (0.19) | 0.11 (0.09) [c] |
| | 24 | 0.17 (0.23) | 0.28 (0.32) | - | 0.39 (0.38) | 0.28 (0.32) | 0.10 (0.25) |
| | 48 | 0.06 (0.31) | 0.30 (0.43) | - | 0.44 (0.30) | 0.16 (0.22) | 0.20 (0.24) |
| **Upper limit of autoregulation (mm Hg)** | 06 | 3.48 (2.64) | 2.68 (3.88) | - | 3.64 (2.20) | 4.16 (3.43) | 2.77 (3.17) [a] |
| | 12 | 3.28 (3.07) | 3.50 (3.72) | - | 3.82 (2.63) | 3.60 (4.35) | 4.05 (3.82) |
| | 24 | 2.19 (3.74) | 4.37 (4.51) | - | 0.50 (3.33) | 5.45 (3.42) | 2.54 (5.39) [b] |
| | 48 | 3.21 (5.28) | 3.54 (4.54) | - | 2.55 (4.67) | 3.53 (3.56) | 3.90 (3.80) [b] |
| **Rising slope ($cm \cdot s^{-1} \cdot mm\ hg^{-1}$)** | 06 | 0.43 (0.39) | 0.72 (0.66) | - | 0.78 (0.37) | 0.44 (0.32) | 0.37 (0.16) [c] |
| | 12 | 0.34 (0.33) | 0.70 (0.44) | - | 0.97 (0.87) | 0.53 (0.30) | 0.36 (0.19) [c] |
| | 24 | 0.45 (0.40) | 0.91 (0.66) | - | 0.81 (0.46) | 0.66 (0.47) | 0.55 (0.37) [c] |
| | 48 | 0.42 (0.38) | 0.70 (0.43) [a] | - | 1.01 (0.44) | 0.40 (0.39) | 0.51 (0.34) [c] |
| **ARR (mm Hg)** | 06 | 6.11 (2.92) | 5.99 (3.52) | - | 4.56 (2.81) | 6.70 (4.66) | 5.00 (2.61) |
| | 12 | 6.64 (4.47) | 6.78 (5.44) | - | 6.26 (4.98) | 7.29 (5.35) | 7.17 (5.25) |
| | 24 | 6.62 (5.30) | 6.78 (5.31) | - | 3.63 (1.94) | 7.71 (4.81) | 5.17 (4.75) |
| | 48 | 5.10 (4.06) | 4.71 (5.02) | - | 4.65 (5.56) | 5.29 (3.99) | 5.79 (4.51) |

Abbreviations: Autoregulatory range (ARR), Middle cerebral artery (MCA), standard deviation (SD), A1 segment of Anterior cerebral artery (A1), M1 segment of Middle cerebral artery (M1), P2 segment of Posterior cerebral artery (P2).

[a] Pairwise comparison $p < 0.05$ vs ipsilateral artery.

[b] Pairwise comparison $p < 0.05$ vs baseline (6 hours).

[c] Pairwise comparison $p < 0.05$ vs MCA of the contralateral side.

# Anexos

- Normas de publicação da Revista *Journal of Cerebral Blood Flow and Metabolism*

- *STROBE reporting guidelines for cohort studies*

Journal of Cerebral Blood Flow & Metabolism

“Manuscript Submission Guidelines:

**Manuscript Submission Guidelines & Editorial Policies *Journal of Cerebral Blood Flow and Metabolism***

This journal is a member of the Committee on Publication Ethics.

The *Journal of Cerebral Blood Flow & Metabolism (JCBFM)* features international peer-reviewed contributions highlighting experimental, theoretical, and clinical aspects of brain circulation, imaging and metabolism. It is truly relevant to any physician or scientist with an interest in brain function, including neurologists, neurochemists, physiologists, pharmacologists, anesthesiologists, neuroradiologists, neurosurgeons, neuropathologists, and neuroscientists. *JCBFM* stands at the interface between basic and clinical neurovascular research.

Although the Editors and referees make every effort to ensure the validity of published manuscripts, the final responsibility rests with the authors, not with *JCBFM*, its Editors, or the publisher. For further details on how to layout the article please see 2.4 Journal layout.

| Article Type | Word Limit | Tables/Figures |
|---|---|---|
| **Original Articles** are full-length reports of current research. | Abstract: 200 words maximum<br>Article: 6,000 words including abstract and acknowledgement but excluding author contributions statement, disclosure, references, figure legends tables and figures | Up to 7 in total<br><br>(figures + tables ≤ 7) |

**2. Preparing your manuscript**

**2.1 Word processing formats**

Main document files, including tables, must be submitted in editable format, not in PDF. Preferred formats for the text and tables of your manuscript are Word DOC, RTF, XLS. LaTeX files are not accepted. The text should be double-spaced throughout and with a minimum of 3cm for left and right hand margins and 5cm at head and foot. Text should be standard 10 or 12 point.

**2.2 Artwork, figures and other graphics**

For guidance on the preparation of illustrations, pictures and graphs in electronic format, please visit SAGE’s Manuscript Submission Guidelines.

Figures supplied in colour will appear in colour online and in the print issue. Colour reproduction of images in print is covered by the page charges for publication of a manuscript.

### 2.3 Supplemental material

The Journal is able to host additional materials online (e.g. datasets, podcasts, videos, images, etc.) alongside the full-text of the article. These will be subjected to peer review alongside the article, but are not published in print.

Authors should submit supplementary information files in the final format as they are not edited and will appear online exactly as submitted. Supplementary material should be uploaded if possible as one supplementary file including figure and movie legends. Movies and extensive tables should be uploaded in separate supplementary files.

### 2.4 Journal layout

*JCBFM* conforms to the SAGE House Style.

Components of original articles should be in the following order:

- Title page
- Unstructured abstract
- Five key words
- Introduction
- Material and Methods
- Results
- Discussion
- Acknowledgements
- Author contribution statement (only for original research papers, not for reviews)
- Disclosure/conflict of interest
- Sentence regarding supplementary information on *JCBFM* website, if any
- References
- Figure legends
- Tables (in editable format, either in main document or as separate main document files)
- Figures (in separate image files, not inserted in main document)

**Title page of manuscript**
The title page should include (a) the complete manuscript title; (b) all authors' full names (listed as first name, middle initial, last name) and affiliations; (c) the name, postal address for correspondence, telephone number and e-mail address; and (d) a running headline of no more than 50 characters (including spaces) should be supplied which conveys the essential message of the paper.

If authors regard it as essential to indicate that two or more co-authors are equal in status, they may be identified on the manuscript title page by an asterisk symbol with the caption "These authors contributed equally to this work" immediately under the author affiliations list.

Please note that the title, keywords and abstract are key to ensuring that readers find your article online through online search engines such as Google. Please refer to the information and guidance on how best to title your article, write your abstract and select your keywords by visiting the SAGE Journal Author Gateway for guidelines on How to Help Readers Find Your Article Online.

**Unstructured abstract and keywords on a separate page, following title page.**
The abstract should be unstructured, factual and comprehensive. The use of abbreviations and acronyms should be limited and general statements (e.g. "the significance of the results is discussed") should be avoided. Five keywords should be provided in alphabetical order below the abstract.

**Materials/subjects and methods section**
This section should contain sufficient detail, so that all experimental procedures can be reproduced, and include references. Methods, however, that have been published in detail elsewhere should not be described in detail. Authors should provide the name of the manufacturer and their location for any specifically named medical equipment and instruments, and all drugs should be identified by their pharmaceutical names, and by their trade name if relevant.

**2.5 Reference Style**

JCBFM adheres to the SAGE Vancouver reference style. Please review the guidelines on SAGE Vancouver to ensure your manuscript conforms to this reference style."

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

| | Item No | Recommendation | Page No |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 2 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 3-5 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 5 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 5 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 5-7 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 5-7 |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed | NA[1] |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 5 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 6 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 6 |
| Study size | 10 | Explain how the study size was arrived at | 5 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 7 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 8 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 8 |
| | | (*c*) Explain how missing data were addressed | 8 |
| | | (*d*) If applicable, explain how loss to follow-up was addressed | NA[2] |
| | | (*e*) Describe any sensitivity analyses | NA[3] |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 8 |
| | | (b) Give reasons for non-participation at each stage | 8 |
| | | (c) Consider use of a flow diagram | NA |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 8-9 |
| | | (b) Indicate number of participants with missing data for each variable of interest | NA[2] |
| | | (c) Summarise follow-up time (eg, average and total amount) | NA[2] |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | 19-20 |

| | | | |
|---|---|---|---|
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 19-20 |
| | | (*b*) Report category boundaries when continuous variables were categorized | NA[5] |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | NA[1] |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | NA[6] |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 11 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 15 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 12-15 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 15 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | NA[7] |

*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

NA[1] – Not applicable, because the present study doesn't involve matched groups or calculation of the risk of exposure.
NA[2] – Not applicable, because follow-up period of 48 hours was included in a single hospitalization, and accomplished by all patients.
NA[3] – Not applicable, since we only used Projection Pursuit regression for analysis.
NA[4] – Not applicable, because we've only excluded patients that were diagnosed with posterior cerebral artery, and we chose not to include this information in a flow diagram.
NA[5] – Not applicable because we didn't categorize our results based on a continuous variable.
NA[6] – Not applicable because the subgroups we defined were analysed separately.
NA[7] – Not applicable, because this research received no specific funding

## Agradecimentos

Uma palavra final para todos aqueles que me acompanharam durante a realização deste projeto, e me concederam a oportunidade de criar um trabalho científico, através de conselhos, partilha de experiências vividas ou conhecimentos.

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