

CLINICAL RELEVANCE OF CEREBRAL AUTOREGULATION FOLLOWING SPONTANEOUS INTRACEREBRAL HAEMORRHAGE

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ABSTRACT

Hypertensive intracranial haemorrhage is a common neurological emergency in clinical practice. The presence of an intracranial lesion of expansive focal nature can compress vascular structures and cause ischaemic effects. It is very common for these patients to have hypertensive peaks at admission, which may progress to rebleeding and neurological worsening. The safety of blood pressure reduction in patients with hypertension and intracranial haematomas is still a debatable subject due to lack of studies on cerebral autoregulation in this situation. The aim of this study is to discuss cerebral autoregulation in patients with spontaneous intracerebral haemorrhage based on scientific and personal evidence.

Keywords: Intracranial haemorrhage, hypertensive, cerebral haemorrhage, cerebral autoregulation.

INTRODUCTION

Spontaneous intracerebral haemorrhage (SICH) accounts for 10-15% of cerebrovascular events, with a mortality rate of 35-52%; half of these deaths occur within the first 2 days after the event¹⁻³ and the haematoma volume is an independent prognostic variable.⁴ Acute haematomas with volume >150 ml can reduce cerebral perfusion pressure to zero, leading to death. If the haematoma volume is <140 ml, most patients will survive the initial stroke.^{5,6} According to the International Surgical Trial in Intracerebral Haemorrhage (STICH) there are a number of situations with little chance of a positive outcome: poor neurological condition e.g. coma or Glasgow Coma Scale (GCS) ≤5/15; age of >75 years; massive haemorrhage with significant neuronal destruction (>60 cc with GCS <8/15; >85 cc or diameter of haematoma 5.5 cm independent of GCS); large haemorrhage in dominant hemisphere; basal ganglion (putaminal) or thalamic haemorrhage.⁷ Cerebral autoregulation impairment is one of the important mechanisms in

the pathophysiology of SICH, both from the prognostic and therapeutic points of view. Therefore, the understanding of SICH functionality at the bedside represents an improvement in terms of neurological intensive care.

Cerebral autoregulation is defined by the intrinsic capacity of the cerebral vasculature to maintain a constant cerebral blood flow (CBF) (50 ml/100 g/min), considering variations in mean arterial blood pressure within the range of 60-150 mmHg in healthy subjects.⁸ These limits are not accurate in clinical practice and represent points of inflection where the association between pressure gradient and flow change significantly.⁹ Above or below the autoregulation limits, CBF has a passive behaviour in relation to mean arterial pressure (MAP) and intracranial pressure (ICP). Several mechanisms have been attributed to cerebral autoregulation, which are myogenic, neurogenic, and metabolic. However, recent studies have suggested the presence of more than one mechanism.¹⁰ Patients with chronic arterial hypertension shift the thresholds of autoregulation upward.¹¹

Cerebral autoregulation consists of fast and slow components, in terms of changes in cerebrovascular resistance, in response to pulsatility pressure and mean cerebral perfusion pressure (CPP), respectively. Quantifying the cerebral autoregulation phenomenon is a complex process, as there are many physiological variables that can interfere with CBF, either directly or through metabolic coupling.¹² Static autoregulation is considered a 'gold standard' test for the assessment of cerebral autoregulation, as it measures changes in CBF arising from CPP variations. It therefore represents the slow components of autoregulation. Dynamic autoregulation evaluates fast autoregulation components and tends to be impaired early in relation to static autoregulation.¹³ Therefore, there are technical limits for each methodology that require appropriate interpretations.^{14,15}

The concept of cerebrovascular pressure reactivity index (PRx) was introduced by Czosnyka et al.¹⁶ in 1997, based on the principle that, in the presence of mean blood pressure elevations, there would be cerebral vasoconstriction with reduced cerebral blood volume and, consequently, ICP. PRx indirectly reflects cerebral autoregulation, being used to optimise CPP.

PRx reflects the smooth muscle tone of cerebral arteries and arterioles, as well as changes in transmural pressure, being part of a more elaborate phenomenon called cerebral autoregulation. Expansive lesions alter the CPP and can decompensate the cerebral autoregulation mechanism responsible for maintaining adequate CBF. With the reduction in CPP, vasodilation occurs as a compensatory measure to keep the CBF. However, this vasodilating cascade culminates with a significant increase in cerebral blood volume and vascular collapse, due to increased cranial pressure.

The cerebrovascular PRx^{16,17} consists of 40 measurements (every 5-15 seconds) of mean blood pressure and ICP, establishing a Pearson's correlation between these variables. Values <-0.2 represent good cerebrovascular reactivity, while values >0.2 reflect an impaired cerebrovascular reactivity. The presence of a positive correlation between MAP and ICP means impairment of cerebrovascular reactivity, and values >0.3 are correlated with a worse prognosis (increased mortality rate from 20% to 70%).¹⁸ When the range of values between MAP and ICP are independent, cerebrovascular reactivity is adequate and thus, there is a better functional outcome. After applying

it in clinical studies, Czosnyka et al. stated that a PRx >0.2 for more than 6 hours is associated with a poor prognosis.¹⁸

CASE REPORT

A female patient of 57 years suffered an acute stroke in 2013. On examination: Glasgow 4 with spontaneous breath and not intubated on admission, isochoric pupils, intracerebral haemorrhage (ICH) Score 3. Skull computed tomography (CT) showed a left frontal lobe haematoma. The calculated volume was 81 cm³ (12×4.5×3 cm) with septal deviation and signs of intracranial hypertension.

Surgical removal of intracranial haematoma was performed and the patient underwent multimodal neuromonitoring in the intensive care unit. Postoperative control skull CT on first operative day showed radical haematoma removal, but persistence of septal deviation. The patient remained in deep sedation without any changes in ICP (Figure 1).

Two days after onset of stroke, the cerebrovascular PRx was preserved with a CPP between 80-90 mmHg suggesting preserved cerebral autoregulation. The optimal perfusion pressure was determined at 85 mmHg with a PRx of -0.6. However, 5 days after stroke onset, the PRx was impaired, with a CPP between 60-80 mmHg, suggesting impaired cerebral autoregulation (Figure 2).

Six days from stroke onset, the patient started to show worsening in ventilatory status that led to worsening of cranial homeostasis, which developed into intracranial hypertension escapes with no radiological alteration. This deterioration was caused by positive water balance and associated low pulmonary exchange of oxygen. Other causes of brain oedema were ruled out. Nine days from stroke onset, the patient developed refractory intracranial hypertension, pupillary alterations, and fixed mydriasis, and underwent a decompressive craniectomy (Figure 3).

DISCUSSION

This case report shows that despite the haematoma volume and tomographic signs of intracranial hypertension, there was no loss of cerebrovascular reactivity in the initial phase, implying that cerebral autoregulation was preserved. Loss of

cerebrovascular reactivity occurred days later, implying impairment of cerebral autoregulation. The pathophysiological mechanisms of brain injury by SICH are analysed by the primary effect of vascular rupture and tissue destruction, and the side-effects of haematoma growth, intracranial hypertension, oedema formation, and toxic effects of clot substances. Despite occurring in a simultaneous and interrelated manner, these can be divided into the following steps:^{19,20}

I. Vascular rupture and haematoma formation: arterial rupture leads to rapid accumulation of blood in the cerebral tissue and an increase in local tissue pressure. The degree of tissue destruction is justified and explained by the sheer force of the expanding haematoma. In addition to the effect on mass, haematoma, by itself, induces three perilesional early pathophysiological changes in brain tissue: (a) neuronal and glial cell death due to apoptosis, and inflammation, (b) vasogenic oedema, and (c) breaking of blood–brain barrier.

II. Expansion of the haematoma: the ICH is not an event, rebleeding has been documented with the realisation of serial scans within the first 24 hours of the event. The incidence of haematoma increase decreases with the passage of time, 33-38% in 1-3 hours; 16% from 3-6 hours, and 14% within 24 hours of the initial event. The theory is in agreement resulting from persistent and recurrent bleeding from the rupture of a single arteriole.

III. Oedema formation: the perilesional hypoperfusion is probably due to reduced metabolic demand instead of ischaemia. Once ischaemia does not justify the neurological dysfunction after stroke, neurotoxic and inflammatory mechanisms have been proposed to explain the perilesional tissue injury: (a) local inflammation by cell mediators, humoral and cytotoxic associated with the leakage of osmotically active proteins and electrolytes; (b) induction of proteases such as thrombin, fibrinogen, and tissue plasminogen activator; (c) the clot factors associated with its degradation products.

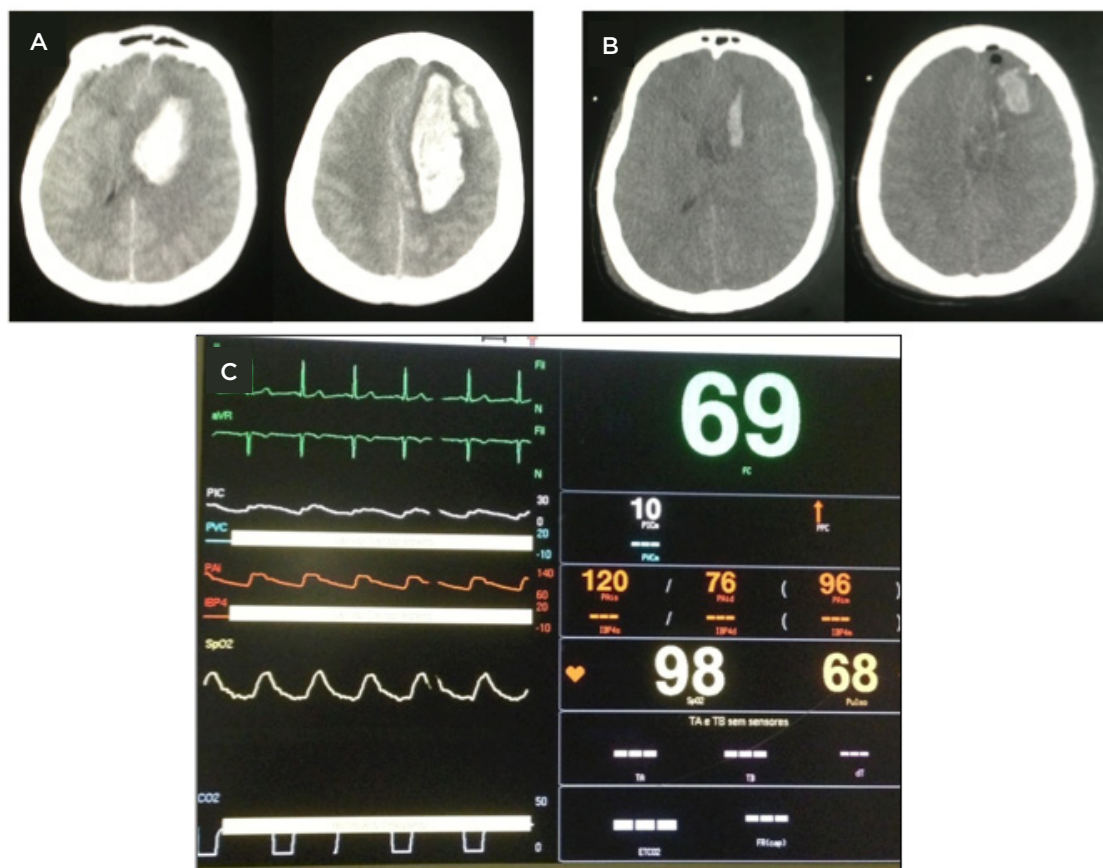


Figure 1: A: Left frontal lobe haematoma with intracranial hypertension signs; B: Postoperative control still showing septal deviation; C: Monitoring of intracranial pressure at 10 mmHg with cerebral perfusion pressure at 86 mmHg. One can also observe loss of intracranial complacency through the morphology of the intracranial pressure curve, P2>P1.

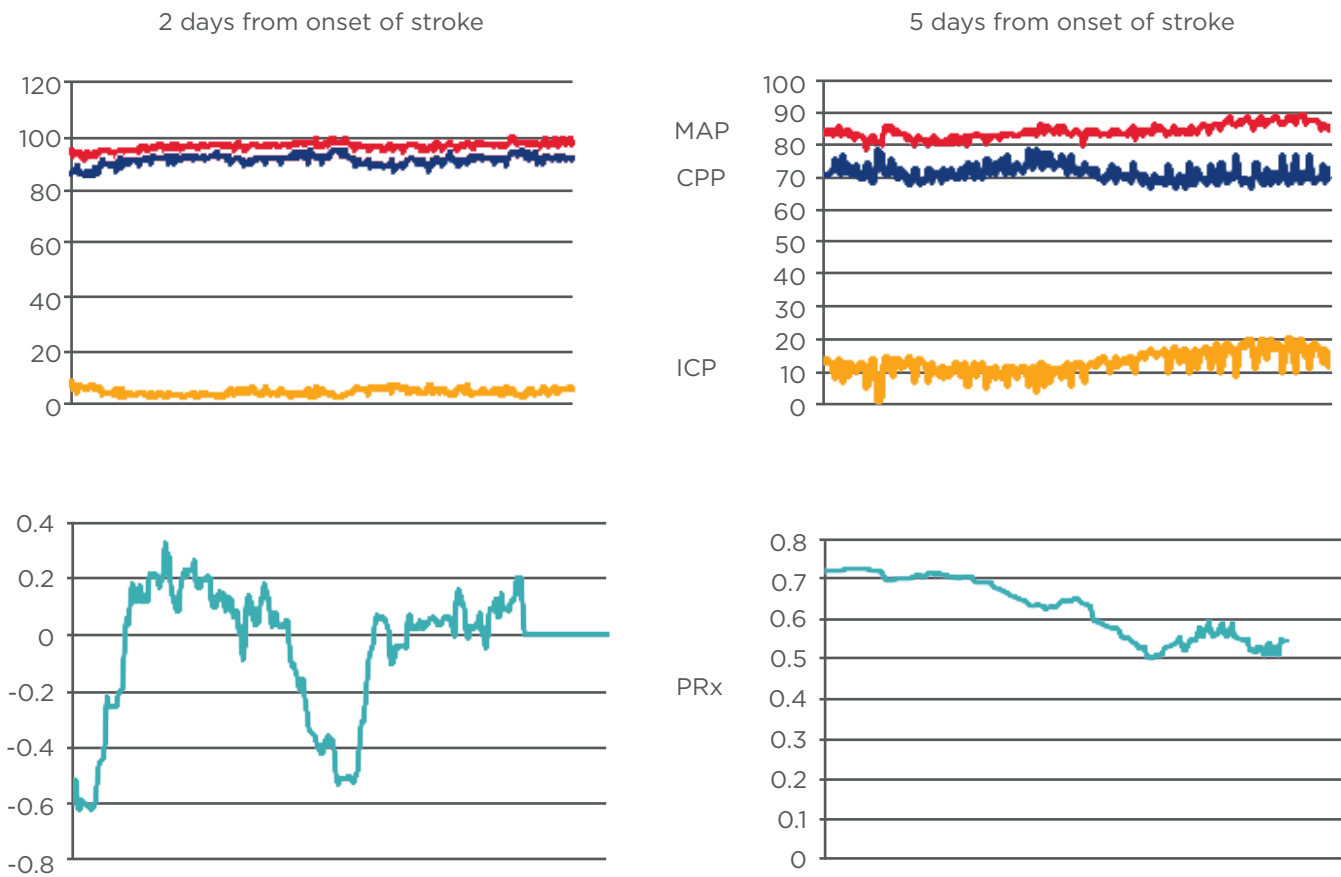


Figure 2: On the left, 1-hour multiparametric neuromonitoring performed 2 days after the onset of stroke showing a preserved cerebrovascular pressure reactivity index (PRx) with a cerebral perfusion pressure (CPP) between 80-90 mmHg. On the right, 1-hour multiparametric neuromonitoring performed 5 days from the onset of stroke, showing impaired cerebrovascular PRx, with the CPP being adjusted between 60-80 mmHg.

MAP: mean arterial pressure; ICP: intracranial pressure.

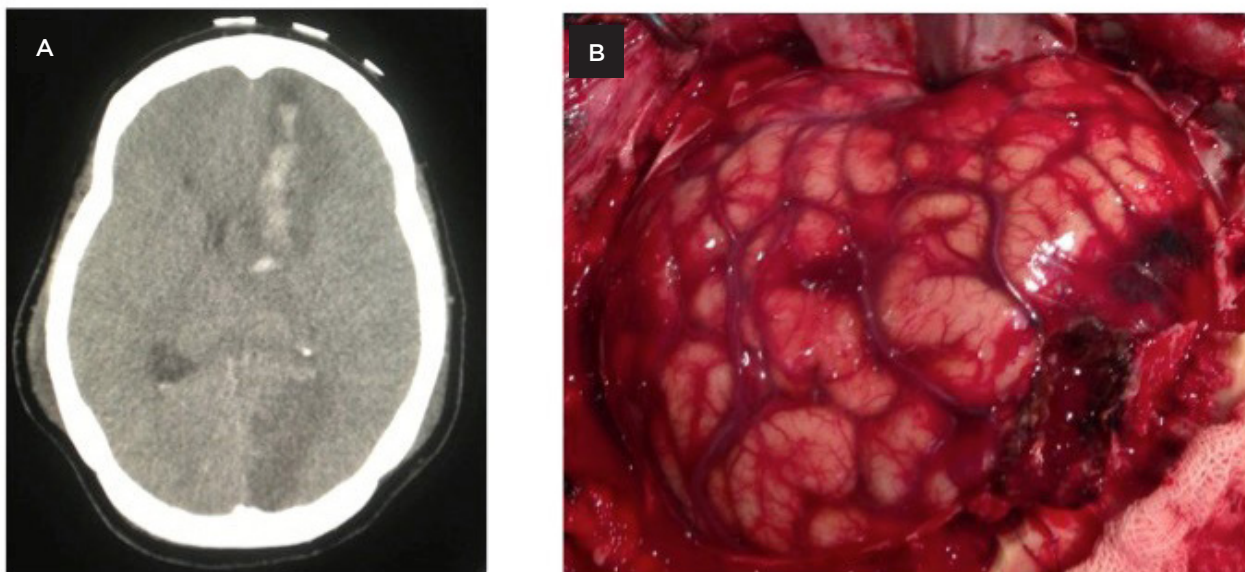


Figure 3: A: skull computed tomography performed 9 days after the onset of stroke, showing indirect signs of herniation with ischaemia in the anterior cerebral artery and left posterior artery territory. B: Brain swelling aspect after decompressive craniectomy.

Thus, the monitoring of cerebral auto-regulation is necessary, as it has a dynamic behaviour. Studies that have analysed cerebral autoregulation in patients with SICH are scarce and use different methodologies (static or dynamic):

- Zazulia et al.²¹ and Powers et al.²² studied cerebral autoregulation in 19 patients by positron emission tomography, and observed that patients with small and medium haematomas (1-45 ml) evaluated within hours after the neurological stroke (6-22 h) had preserved cerebral autoregulation in the peri-haematoma region.
- Diedler et al.²³ evaluated dynamic cerebral autoregulation in 20 patients with SICH through the cerebrovascular PRx (correlation between the ICP and MAP), observing impairment of the dynamic cerebral autoregulation, justifying it due to CPP fluctuations.
- Diedler et al.²⁴ assessed dynamic cerebral autoregulation in 5 patients with ganglionic intracerebral haemorrhage, observing that the perilesional region showed regional autoregulation involvement (PRx, correlation between $P_{br}O_2$ and CPP) whereas the overall autoregulation impairment (PRx, correlation between ICP and MAP) only occurred in one patient. In spite of the few cases, the hypothesis that PRx represents overall cerebrovascular reactivity (macrovasculature) was raised, but the authors were not able to assess local cerebrovascular reactivity (microvasculature) located in the perilesional region.
- Reinhard et al.²⁵ assessed dynamic cerebral autoregulation in 26 patients with SICH, observing that cerebral autoregulation is preserved initially; however, worsening that is ipsilateral to the haematoma can occur secondarily (between 3-5 days post-neurological stroke), being associated with a severe clinical outlook, intraventricular haemorrhage, low CPP, and poor functional outcome.
- Nakagawa et al.²⁶ evaluated dynamic cerebral autoregulation (Doppler) in 21 patients with early (<72 hours) lobar or basal ganglia ICH, observing that patients with ICH had higher gains in a wide range of frequency ranges compared with controls. These findings suggest that dynamic cerebral autoregulation may be less effective in the early days after ICH.
- Oeinck et al.²⁷ and Aries et al.²⁸ evaluated dynamic cerebral autoregulation (Doppler) in

26 patients with SICH on Days 1, 3, and 5 post-neurological stroke, and showed that cerebral autoregulation is usually preserved, but its impairment is associated with large haematoma volumes, arterial hypotension, and poor functional prognosis.

- Jaeger et al.²⁹ evaluated optimal CPP in 38 patients after head injury, observing that below the level of optimal CPP, brain tissue oxygen decreased in parallel to CPP, whereas brain tissue oxygen reached a plateau above optimal CPP. Optimal CPP correlated significantly with the CPP level, where brain tissue oxygen reached its plateau.
- Andrade et al.³⁰ described a new experimental porcine model designed to simulate expansive brain haematoma causing intracranial hypertension (IH). Under anaesthesia, IH was simulated with a balloon insufflation. The IH variables were measured with ICP parenchymal monitoring, epidural, cerebral oximetry, and transcranial Doppler. The ICP epidural showed a slower rise compared with parenchymal ICP. A correlation between ICP and cerebral oximetry was observed. The model described here seems useful to understand some of the pathophysiological characteristics of acute IH.

The impairment of the cerebrovascular reactivity index infers on vasomotor component (myogenic control) of cerebral autoregulation. However, the neural and biochemical components may be preserved. The variation of CPP is one of the variables that most influence the cerebrovascular reactivity index without intervening with mean cerebral autoregulation. Optimal CPP is associated with the lowest PRx possible. From this point, increasing CPP does not improve the oxygen supply because it remains constant.²⁹ Maintaining an optimised cerebrovascular reactivity index is important in order to maintain an adequate oxygen supply without the need for extreme variations of cerebral perfusion.

In this case report there was a later impairment of PRx and cerebral autoregulation, with the need for a decompressive craniectomy in order to control intracranial hypertension. Therefore, this report supports regular autoregulation assessment in ICH.

CONCLUSION

Advances in multiparametric neuromonitoring allow a better understanding of cerebral

autoregulation in SICH and a better analysis of previously considered theoretical concepts. Changes in practice based on autoregulation impairment will become a reality when we include these autoregulation monitoring methodologies in bedside assessment.³¹

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