

A Review of Cerebral Autoregulation: Assessment and Measurements

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Principles of Cerebral Autoregulation Testing

Cerebral Autoregulation (CA) is the intrinsic ability of the brain to maintain stable cerebral blood flow (CBF) while mean arterial blood pressure (MAP) and cerebral perfusion pressure (CPP) are changing.¹ It constitutes a regulatory mechanism to provide metabolic substrates under physiological and pathological conditions, for instance after neuro-trauma or spontaneous intra-cranial haemorrhage. Constant CBF is regulated by changing arteriolar diameter, which will alter cerebral blood volume (CBV) and, ultimately, intra-cranial pressure (ICP). On the other hand, ICP is the sum of the partial pressures of brain tissue, cerebrospinal fluid (CSF) and CBV.^{2, 3}

CA has two components: (a) Metabolic Autoregulation, which is the cerebrovascular response to changes in paCO_2 , and (b) Pressure Autoregulation, which is the cerebrovascular response to changes in transmural vascular pressure resulting from changes in CPP or MAP. Moreover, Pressure Autoregulation has a slow component, referred to as “static CA” and a fast component, namely “dynamic CA”. CA testing is a process which requires two parameters, a stimulus and a dependent variable. In clinical practice, two stimuli are used for metabolic CA testing: (a) induced hyper- or hypo-ventilation, and (b) administration of acetazolamide, a carbonic anhydrase inhibitor.

CA pressure can be challenged by external mechanical or pharmacologic blood pressure changes. Alternatively, intrinsic slow MAP fluctuations can also be used as a physiological constant which provides a consistent, and continuously available, stimulus generator.

CBF, ICP and, more recently, partial pressure of cerebral oxygen (pbt O_2) are assigned as the dependent variables. Monitoring ICP and pbt O_2 requires placement of intracranial probes, which restricts its use largely to the ICU. Monitoring the volume of CBF requires sophisticated scanning equipment, such as Xenon or SPECT techniques. Monitoring cerebral blood flow velocity (CBFV), which is the first mathematical approximation to the volume of blood flow, is readily available using trans-cranial Doppler ultrasound (TCD), which has become widely accepted and is now considered a valid tool for CA assessment.^{4,5} Grading CA requires an index, which is usually derived as a ratio of the magnitude of absolute (or relative) changes in the derived parameter relative to the stimulus parameter. Table 1 provides a summary of pressure CA testing techniques, the indices used and their references.

Metabolic Autoregulation (MA)

MA regulates CBF according to the metabolic needs of the tissue, primarily in response to changes in brain tissue pH.^{6,7,8} Coupling cerebral metabolism with CBF creates a link for increasing CBF in response to local or global ischaemia. MA produces vasodilatation in an attempt to increase CBF when tissue pH drops during ischaemic, hypoxic or hypercarbic events.^{9,10} In contrast, profound respiratory alkalosis achieved with hyperventilation results in cerebral vasoconstriction, which not only increases cerebrovascular resistance but also decreases the cerebral blood volume.

This secondary effect on CBV is the mechanism whereby hyperventilation is useful in treating acute intracranial hypertension. Hyperventilation represents external manipulation of the most basic homeostatic mechanism. However, there is an accompanying risk of iatrogenic ischaemia, if severe hyperventilation results in relative or absolute decrease in cerebral blood flow.

MA can be measured via the CBF response (ml/g/min) to changes in paCO₂ (mmHg), and has been found to be approximately 3-4% during normocapnic ventilation.^{11,12,13} However, during hyperventilation, the relative global CBF change per mmHg paCO₂ has been found to be closer to 2%¹¹ and this becomes even less as CBF is further decreased. On a global basis, MA is robust and is usually preserved after severe Traumatic Brain Injury (TBI). About 75% of patients with preserved MA will manifest significant ICP responsiveness to hyperventilation.¹⁴ However, significant regional inhomogeneities in cerebrovascular responsiveness to CO₂, ranging from complete loss of auto-regulation to hyper-responsiveness^{13,15,16,17} have been demonstrated in patients with severe TBI.

Therefore, in addition to iatrogenically inducing ischaemia, hyperventilation can result in paradoxical shunting of blood flow from areas of the brain with intact or partially preserved metabolic autoregulation, to areas where this response is blunted or lost (e.g. partially or totally destroyed brain tissue).¹⁸ Therefore, in patients with severe TBI or aneurysmal subarachnoid haemorrhage, the cautious and judicious use of hyperventilation is necessary.

Pressure Autoregulation (PA)

PA is the intrinsic ability of the brain to maintain a stable CBF over a wide range of perfusion pressures by varying the degree of vasoconstriction or vasodilatation. (Figure 1). The vascular mechanisms responsible for maintaining stable CBF occur mainly in the distal arterial and arteriolar systems.⁹ In the normal situation, where PA is intact, CBF is kept constant at 40-50 ml/100g/min over the range of Arterial Blood Pressure

Table 1
Stimuli, Dependant Parameters, and Indices in Cerebral Pressure Autoregulation Testing

Stimulus	Dependant variable	Index	Author(s) (ref#)
Pharmacologic MAP elevation	ICP, PVI	magnitude and direction of changes	Bouma ³⁴
Pharmacologic MAP elevation (Noradrenaline)	CBFV	static rate of regulation (sRoR)	Strebel, ³² Lang ³⁵
Pharmacologic MAP elevation	ICP	n/a, visual inspection of correlation	Lang ³⁵
Pharmacologic MAP elevation	ICP	Mx: moving correlation coefficient MAP-CBFV	Lang ³⁶
Pharmacologic MAP elevation	ptiO ₂	RCptiO ₂ : rate of change in ptiO ₂	Lang ³⁶
Pharmacologic MAP reduction (Na-Nitroprusside)	ICP, MAP	Transfer function analysis of ICP and MAP- FFT spectra	Nichols ³³
Mechanical MAP reduction (Tilt Table)	CBFV	TCD-based Pulsatility Index	Daffertshofer, ³⁸ Heckmann ⁴⁰
Mechanical MAP variations (carotid artery compression)	CBFV	transient hyperaemic response test (THR)	Giller ⁶⁵
Mechanical MAP variations (thigh cuff release)	CBFV	restoration of CBFV over time (rate of regulation- RoR)	Aaslid ²⁹
Mechanical MAP variations (6-per-minute ventilation)	CBFV	Phase Shift between MAP and CBFV	Diehl, ³⁰ Lang ³⁰
Spontaneous MAP variations	CBFV	Mx: moving correlation coefficient MAP-CBFV	Czosnyka ³⁹
Spontaneous MAP variations	ICP	PRx: moving correlation coefficient MAP-ICP	Czosnyka ⁶¹
Spontaneous MAP variations	CBFV/ICP	cross-correlation analysis	Steinmeier ⁴⁴
Spontaneous MAP variations	CBFV, peripheral vasomotion	choerence and covariance analysis	Lang ⁶⁶

MAP=mean arterial blood pressure, ICP=intracranial pressure, ptiO₂=partial pressure of cerebral oxygen, CBFV=Cerebral blood flow velocity, FFT=fast Fourier transformation.

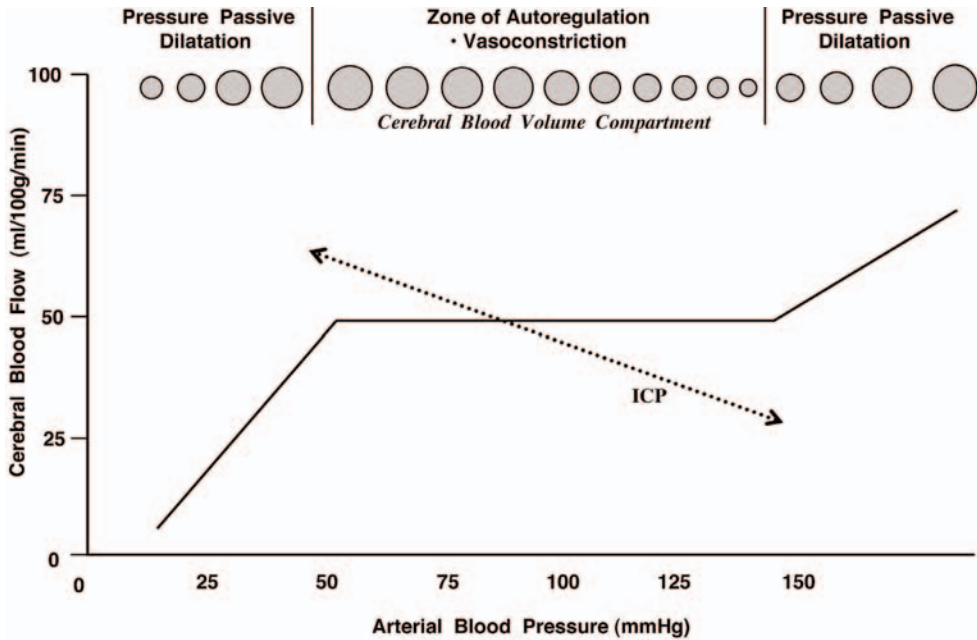


Figure 1. Shows intact cerebral autoregulation where, within the autoregulatory range between 50 and 150 mmHg ABP (x-axis), cerebral blood flow (y-axis) remains stable. There is no correlation between pressure and flow. The M_x is less than 0.3.

(ABP) from 50 mmHg to 150 mmHg,^{1, 20, 21} As CPP rises within this pressure-active range, progressive vasoconstriction serves to maintain CBF at a constant level, and this results in a concomitant decrease in CBV. Under conditions of intracranial hypertension, this often causes ICP to decrease, which in turn improves compliance^{22, 23} Since CBV is an important contributor to ICP, lowering the CBV can be useful in controlling intracranial hypertension.^{24, 25, 26}

Below and above the ABP range of 50-150 mmHg, PA is no longer maintained and CBF approximates to a linear relationship as a pressure-passive system.^{20, 27, 28} Raising or lowering the CPP produces a corresponding increase or decrease in CBF (as well as CBV), resulting in a scenario where ICP parallels CPP (see Figure 2). Of particular note, below the lower breakpoint of Pressure Autoregulation (50 mmHg), ICP will decrease as CPP is lowered and CBF will fall in parallel. Therefore, although the transient decrease in ICP will appear beneficial, hypoperfusion may result. This may cause cellular injury and, eventually, refractory intracranial hypertension resulting from the development of cytotoxic cerebral oedema due to the effects of cell damage and death.

Finding The Best Stimulus

Given the above considerations, CA testing in clinical practice, and especially in an ICU setting, should be performed safely and quickly. Ideally it should be done non-invasively without patient positional changes or even the need to transport the patient to a SPECT scanner. This testing should not include the risk of raising ICP or result in cerebral ischaemia. Historically, CA testing in clinical practice started with measuring

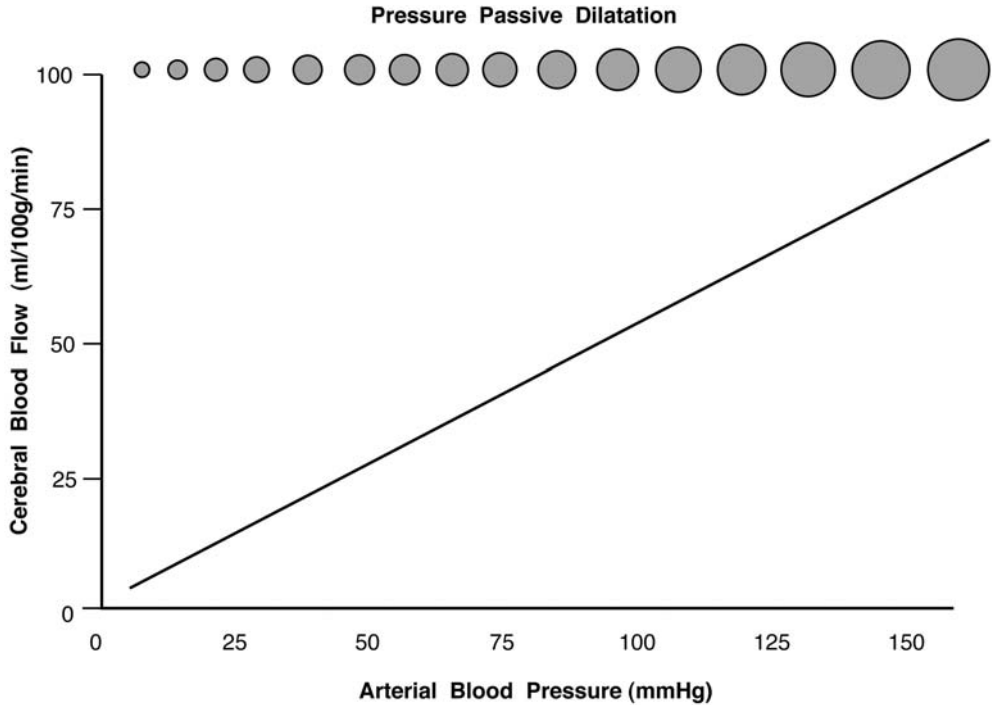


Figure 2. Demonstrates impaired cerebral autoregulation where flow (Y-axis) is entirely dependent on pressure (x-axis). There is a positive correlation between pressure and flow. The M_x is greater than 0.3.

the graded response to hyperventilation (metabolic CA), or pharmacologically induced blood pressure change (static CA). Such measurements involved transporting the patient to a scanner and/or using radioactive tracers.

With the availability of non-invasive TCD monitoring, several less invasive testing protocols, which do not involve patient transport, have been developed. Aaslid and co-workers described a TCD-based CA index, calculated from a sudden drop in blood pressure induced by rapidly deflating thigh blood pressure cuffs following a two minute inflation above systolic blood pressure.²⁹ The index is calculated from the time course of cerebral blood flow restoration to pre-test levels. Since this technique induces a 20 mmHg pressure drop, it can significantly affect ICP and its use is limited to testing outside the ICU. Diehl and co-workers developed an index which uses a high-pass filter model of CA.³⁰ CA is "... quantified as phase shift angle ($\Delta \phi$ °) between oscillations in CBFV and MAP at a frequency of 6/min. A phase shift angle of 0 degrees indicates total absence of autoregulation, while 90 degrees can be gauged as optimal autoregulation". This index is suitable for ICU patients.³¹ However, this test involves changing ventilator settings to enforced 6 breaths/min ventilation. Strelbel and co-workers described a modified TCD-based index also called "Rate of Regulation" (RoR) which quantifies both dynamic (dRoR) and static (sRoR) CA.³² sRoR was calculated by, "... observing the Velocity in the middle cerebral artery (V_{mca}) in response to a phenylephrine-induced increase in MAP".

Pharmacologic blood pressure lowering and/or elevation has been used in many

studies^{21,23,25,32,33,34,35,36,37} and it is widely accepted as a safe testing algorithm, because vasoactive agents are commonly used in an ICU setting. However it is not suitable for CA testing outside the ICU. In addition to the enforced 6 breaths/min ventilation test, the so called "Tilt Table Test" (TTT) for systemic and TCD-based cerebral autoregulation testing is commonly used outside the ICU.^{21,38,39,40} Table 1 provides a comprehensive summary of CA testing studies.

Physiology of CA Testing

The most attractive testing protocol would, ideally, not use any external manipulations such as changing the ventilator settings or the administration of vasoactive substances, whilst at the same time maintaining the normal supine body position. Moreover, the protocol should be non-invasive, time-efficient and easy to institute. Spontaneous, intrinsic and rhythmic fluctuations of Arterial Blood Pressure (ABP) and other monitored variables provide an opportunity for such CA testing. Such oscillations are found in ICP, as well as in cerebral and peripheral blood flow, and they occur within distinct frequencies. These oscillations are called B-waves, when they occur at 0.5-3/min (0.008-0.05 Hz). B-waves were first described by Lundberg as spontaneous oscillations of ICP.⁴¹ Auer and Droste showed that these oscillations are caused by spontaneous changes of pial artery diameter.^{42,43} Steinmeier suggested that B-waves are linked to spontaneous fluctuations of CPP.⁴⁴ Einhüpl discovered that systemic cardiovascular parameters such as ABP and heart rate also demonstrate typical B-wave patterns⁴⁵ and, finally, Zunker described them from recordings using cutaneous finger-tip Laser Doppler Flowmetry (LDF).⁴⁶

Mayer-Waves (M-Waves), which are recorded as spontaneous fluctuations of ABP independent of respiration, were first described in 1876.⁴⁷ These waves occur at 3-9/min (0.05-0.15 Hz). Using different monitoring techniques such as TCD,⁴⁶ cutaneous LDF⁴⁸ and cerebral microcirculatory LDF,⁴⁹ M-waves have been recorded in many different organs.

Multiple generators and neuronal pathways are involved in the regulation of cerebral, muscle and cutaneous blood flow. The generators of M- and B-waves are thought to be located in the brain stem, in particular in the rostral-ventro-lateral-medulla (rVLM). Main modifying inputs come from baro-afferents, via the nucleus of the tractus solitarius (nTS) and the caudal ventro-lateral medulla (cVLM).⁵⁰ The pre-sympathetic outflow from the rVLM is mediated via monosynaptic projections to the preganglionic neurons in the intermedio-lateral nucleus (IL) of the spinal cord.⁵¹ These fibres project to post-ganglionic sympathetic vasoconstrictor fibres of the final pathways to the different end-organ systems via the peripheral sympathetic ganglia.⁵² The cerebral vasculature appears to have different and/or alternative pathways coming from the dorsal raphe nucleus or locus coeruleus via the facial and/or the trigeminal nerves to the cerebral arteries.^{53,54,55,56,57,58}

From Invasive to Non-Invasive CA Monitoring

Czosnyka and colleagues developed an index (Mx — mean index of autoregulation) which can quantify CA, based on spontaneous fluctuations.⁵⁹ The Mx represents a mathematical approach to quantify the relationship of spontaneous fluctuations between CPP and CBFV, and can be used as an index to express the stability of cerebral blood flow during CPP changes. Based on previous studies, values less than

0.3 indicate intact CA, (implying an increase in CPP should have little or no effect on CBFV), whilst values >0.3 indicate failure of CA. Our group has recently examined the advantages of using MAP (instead of CPP) for Mx calculations and has reported that the ABP derived index of Mx (Mx-ABP) produces similar results to the original Mx index.³⁷ In a prospective analysis of data from 37 patients after TBI, we also validated Mx-CPP expression, examined its prognostic relevance and assessed its relationship with MAP, CPP, ICP, and CBFV.

Mx-CPP >0.3 indicates impaired CA and patients in this group following TBI had a significant positive correlation of CPP with CBFV, confirming failure of CA. In those with Mx <0.3 , CPP was not correlated with CBFV, indicating intact CA. These findings were also confirmed for Mx-ABP. Moreover, we found a significant correlation between impaired CA, indicated by Mx-CPP and Mx-ABP, and poor outcome in patients with TBI.

Our data confirm that dynamic CA disturbances during the first five days after TBI are associated with an unfavorable outcome. This observation is supported by previous work from the Cambridge group, who reported that the Mx correlated with outcome in patients with TBI ($r=0.41$, $p<0.0002$), and that CA was severely disturbed during the first two days in patients who died.⁵⁹ Further evidence to support the prognostic value of CA failure is provided in a study of 31 comatose patients with TBI in whom CA was assessed by measuring CPP and cortical CBF, measured with laser Doppler flowmetry.⁶⁷ In their study, 9 of 11 patients with persistent loss of autoregulation died; but transient loss of dynamic CA "did not always indicate poor outcome, provided the impaired autoregulation responded to treatment." ABP, CPP, ICP and CBFV were not correlated with CA, but it must be noted that our average CPP was considerably higher than in other studies. Our study has validated this new index of preserved or failed CA in patients with TBI. The index is also valid if ABP is used instead of CPP, which eliminates the need for invasive ICP measurements for CA assessment.

The Link Between Pressure And Flow

Czosnyka and colleagues have suggested that a moving correlation index between MAP and ICP, called PRx (Pressure Reactivity Index), can be used to monitor and quantify Cerebral vasomotor Reactivity (CR) in patients with TBI.⁶¹ In an attempt to examine further the validity of using spontaneous pressure fluctuations for CA testing, our group evaluated the PRx.⁶⁰ We studied its relationship with CBFV and CA, and identified variables associated with impairment or preservation of CR in a study in 40 patients with TBI. Our study found that a PRx value less than 0.3 indicates intact CR and a PRx more than 0.3 impaired CR.

MAP, ICP, mean CPP, and CBFV, measured bilaterally with TCD were recorded. Dynamic CA was measured using the Mx for each cerebral hemisphere. All variables were compared in patients with intact versus patients with impaired CR. We were able to demonstrate no correlation between MAP/ CPP and CBFV in 19 patients with intact CR. In contrast, there was a statistically significant correlation between ABP or CPP and CBFV in 21 patients with impaired CR, whose CA was significantly reduced. There was no correlation with ICP, ABP, CPP and inter-hemispheric CA differences, but these variables were largely within normal limits. In this study, we were able to show that the PRx is a valid measurement to monitor and quantify CR in patients with TBI. This ICP-based index reflects changes in cerebral blood flow and CA capacity, suggesting a close link between blood flow and ICP in patients with TBI. This explains

why ABP/CPP elevation may be useful for reducing ICP, especially in those TBI patients with intact CR.

Hemispheric Asymmetry and Temporal Profiles of Cerebral Pressure Autoregulation in TBI

Two issues readily cause problems in CA testing, Hemispheric Asymmetry (HA) and Temporal Profiles (TP). Our group has examined both and has further studied the HA and TP relationships with ABP and CBFV, and their prognostic relevance.⁶²

Mx was calculated from non-invasively obtained, second daily continuous MAP measurements, for each hemisphere in 25 TBI patients for as long as they were receiving sedation and analgesia. Forty-nine recordings (range one to six per patient) were obtained, Four Temporal Profile time periods were defined: (a) immediate post-injury days (PID) 0 and 1, (b) early — PID 2 and 3, (C) intermediate — PID 4 and 5, and (d) late — PID 6. GOS was estimated at discharge. GOS 4 and 5 were considered as favorable (15 patients) and GOS 1-3 unfavorable outcomes (10 patients).

A Mx difference >0.2 was arbitrarily classified as Hemispheric Asymmetry (HA). HA was observed at least once in 12 of the 25 patients (48%) and in 18 of 49 recordings (37%). HA was observed during all Temporal Profile time periods: 35%, 43%, 25%, 43% respectively. It also was unrelated to outcome. There was no difference in mean CBFV or ABP between patients with and without HA. HA was not related to inter-hemispheric CBFV differences. A significant improvement in Mx was seen over time.

We concluded that hemispheric CA asymmetry is common after TBI. It does not bear significant clinical or predictive relevance and is unrelated to CBFV or ABP. CA is most profoundly disturbed during the immediate post-injury phase and improves gradually during the ICU course.

Aging and CA

Changes in CA have been reported by several groups in patients with TBI. Despite growing interest in biological research, the exact mechanism of control in healthy control subjects remains obscure. Investigating the effects of aging on CA may provide further insights into these mechanisms, but at present there is a paucity of studies investigating this. However, one study⁶³ suggests that age does have an influence on CA. Our own study⁶⁴ into the effects of aging found conflicting results. We used the Mx-ABP index of dynamic CA to investigate CA in patients across a wide spectrum of ages (23-68 years) and did not find any correlation between age and CA. The healthy control subjects tested in our study all had intact CA. We separated the subjects into a “young” and an “old” group and looked for any differences in the Mx-ABP index, but did not find any statistically significant differences, implying that age did not affect CA. Clearly, more research is required in the area of aging and CA in order to provide a greater understanding of the underlying mechanisms involved over time.

Summary and Outlook

Invasive and non-invasive CA testing has become clinically possible and offers the opportunity to study a “capacity-index”, in addition to the static monitored parameters such as ICP, CBFV, or pbtO_2 . Historically, CA testing represented an academic

exercise, which did not translate into therapy. Now, pathologic thresholds are available and CA has been confirmed to bear prognostic value.

In keeping with the “clinical” history of measuring ICP and pbtO_2 , the question now becomes whether therapeutic manoeuvres aimed at improving CA will have a relevant effect on outcome and long-term prognosis in ICU patients with either TBI or spontaneous subarachnoid haemorrhage. It would be necessary to study the effect of changing MAP on CA in an attempt to optimize CA, similar to what might be called a CA-oriented CPP therapy.²⁵

We have shown that CA and cerebrovascular reactivity (CR) are closely linked.⁶⁰ The utility of CR-directed therapy rather than CA-directed therapy in TBI seems logical because CR is derived from ICP, which is the main treatment target, rather than from CBFV which is used for CA assessment. Steiner from the Cambridge Group has demonstrated that monitoring the CR can identify an optimal cerebral perfusion pressure (CPP-OPT) in 60% of a large series of patients with TBI. The authors stressed that at least 24 hours of continuous monitoring were required to determine CPP-OPT.⁶⁸ This period is needed for accurate assessment of CR over a sufficiently wide range of spontaneous fluctuations of MAP. They did, however, not manipulate CPP but looked at spontaneous changes.

The next clinically logical step would be to formulate a study protocol in which CPP is varied, whilst comparing CA and CR along with a “blood pressure challenge”, ideally with a bedside-based-real time CA/CR monitor. In addition, new real-time software (Navigator) is available to continuously follow and manipulate cardio vascular haemodynamics within preset physiological ranges (Prof. G. Parkin — personal communication and collaboration).

It is also conceivable that CA testing might offer an opportunity to define the optimum level of hyperventilation. Would it be possible to restore pressure CA by increasing vasomotor tone by mild to moderate hyperventilation? What are the effects of various drugs on CA?

The ICU offers an ideal environment to safely test different therapeutic options while physiologic variables such as ICP, pbtO_2 , CBF or CBFV are carefully monitored. Using a non-invasive protocol, studies can be performed during the ICU period with follow-up studies of CA during in-hospital rehabilitation and later convalescent periods being evaluated. With the growing number of publications, CA assessment appears to be gaining wider acceptance and interest in research to evaluate and understand the immediate and long-term effects of neuro-intensive care therapies and interventions.

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