Basic science review

Quantifying Cerebral Autoregulation in Health and Disease

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ABSTRACT

Objective: *To review methods of quantifying human cerebral autoregulation in health and disease.*

Data sources: *Articles and published abstracts on methods to quantify cerebral autoregulation in health and disease.*

Summary of review: *Cerebral autoregulation is defined as the relationship between cerebral blood flow and cerebral perfusion pressure. Complex neurohumoral processes are involved in myogenic and metabolic mechanisms to maintain cerebral blood flow at a constant level in the presence of fluctuating systemic and cerebral perfusion pressures. Despite advances in physiological measurement, there is no standard measurement of cerebral blood flow and quantifying cerebral autoregulation remains problematic. Clinical monitors such as transcranial Doppler and jugular bulb oximetry have high levels of error with poor specificity and sensitivity. Cerebral autoregulation is impaired in traumatic brain injury and subarachnoid haemorrhage, so that cerebral blood flow becomes pressure-passive. Hypotension is associated with significant secondary neuronal damage following traumatic brain injury. Hypertensive emergencies represent failure of the upper autoregulatory threshold, often with devastating neurological consequences. The monitoring and treatment of autoregulatory failure remains limited and is essentially directed at maintaining an appropriate systemic blood pressure. Consequently, the use of strategies to manipulate cerebral perfusion requires care and circumspection.*

Conclusions: *Cerebral autoregulation is impaired with brain injury with cerebral blood flow often becoming pressure-passive. The monitoring and treatment of autoregulatory failure is limited and usually directed at maintaining systemic blood pressure with the effectiveness of this strategy often being unknown.*
(**Critical Care and Resuscitation 2004; 6: 59-67**)

Key words: Cerebral blood flow, autoregulation, cerebral perfusion pressure, brain injury

In 1783, the "Monro-Kelly doctrine" defined the asymptotic relationship between intracranial pressure and volume.[1,2] The doctrine states that due to the non-compliant skull and dura, small increases in intracranial volume result in sharp increases in intracranial pressure. Fifty years ago, pioneering work by Guillaume and Janny identified intracranial hypertension as the prime pathophysiological entity in traumatic head injury.[3] In 1960, Lundberg described continuous measurement of intracranial pressure and ventricular drainage of cerebrospinal fluid in patients with head injury.[4]

The unique anatomical relationship of the skull and brain are important when determining the effects of changes in cerebral blood flow. The elastant reserve of the brain to accommodate increases in intracranial volume is limited. Cerebral blood flow is maintained at a constant rate in the presence of changing systemic blood pressures. Under physiological conditions,

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increases in cerebral blood flow are minimised by these autoregulatory processes. Physiological increases in cerebral blood flow that are usually associated with transient rises in sympathetic activity are accommodated by decreases in intracranial volume by recirculation of cerebrospinal fluid and venoconstriction. Regulation of cerebrovascular volume is under intense neurohumoral control.[5]

Pathological increases in cerebral blood flow or interstitial/cellular oedema will rapidly exhaust elastant reserve if it continues unabated. In pathological conditions such as traumatic brain injury or subarachnoid haemorrhage, increases in intracranial volume are multifactorial and involve vascular and non-vascular mechanisms.

Cerebral autoregulation

The brain is an efficient autoregulator. Normally, cerebral blood flow is maintained at a constant rate over a range of systemic pressures.[6] Autoregulatory systems are complex and involve a number of myogenic (pressure) and metabolic systems.[5,7]

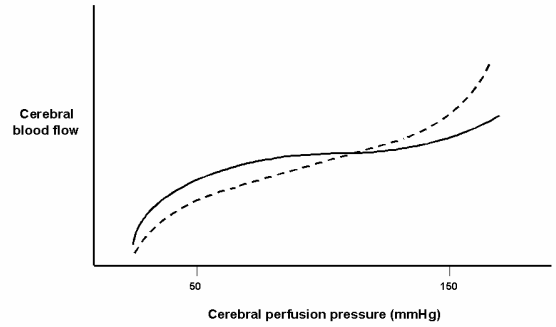

Figure 1. Idealised autoregulatory relationship between cerebral blood flow and cerebral perfusion pressure showing range of constant flow under physiological conditions (solid line) and following traumatic brain injury (dashed line)

Myogenic autoregulation

Myogenic autoregulation is the term used to describe changes in cerebrovascular transmural pressure in response to fluctuations in mean arterial pressure. This is mediated through adrenergic stimulation of vascular smooth muscle and microfluxes of endogenous vasodilators (e.g. nitric oxide) and vasoconstrictors (e.g. endothelin). In cerebrovascular terms, myogenic autoregulation is regarded as the relationship between cerebral blood flow and cerebral perfusion pressure (or mean arterial pressure in the absence of intracranial hypertension). Under physiological conditions, cerebral blood flow is maintained at a constant rate until autoregulatory thresholds (both upper and lower) are exceeded and cerebral blood flow becomes "pressure passive". The "break points" where this occurs vary considerably between individuals, but is traditionally recorded in standard physiology textbooks as 60 and 160 mmHg, although these commonly accepted values have never been validated.

Metabolic autoregulation

Metabolic autoregulation is the term used to define non-myogenic mechanisms of cerebral vasoregulation. Of these, reactivity of the cerebral vasculature to systemic and local changes in arterial carbon dioxide tensions ($PaCO_2$) is regarded as the basis of metabolic autoregulation. Under physiological conditions, cerebral blood flow and $PaCO_2$ have a pseudo-linear relationship: hypercapnia causes cerebral vasodilation, whilst hypocapnia causes vasoconstriction. This mechanism is due to carbon dioxide induced changes in cerebral perivascular pH resulting in changes in cerebrovascular tone.[8] Although cerebrovascular carbon dioxide reactivity is frequently used as a surrogate index of metabolic autoregulation, several mechanisms are involved. These include fluxes in cerebral tissue oxygenation,[9] calcium and potassium concentrations, nitric oxide, endothelin, eicosanoids, vasopressin, endogenous neuropeptides[5] and drugs such as volatile[10,11] and intravenous anaesthetics.[12,13]

In clinical terms, cerebral autoregulation primarily relates to the cerebral blood flow/cerebral perfusion pressure relationship. Studies analysing the effects of drugs, physiological and pathological processes on cerebral autoregulation are directed at this relationship. There are numerous methods of measurement and quantification of this relationship. The extents to which the various components of autoregulation are impaired or altered by physiological perturbations or pathological processes vary considerably.

Measurement of cerebrovascular function

The validity and interpretation of studies of cerebrovascular function is dependent on the accuracy of physiological measurement. Of these, the measurement of cerebral blood flow and quantification of cerebral autoregulatory relationships are most critical.

Cerebral blood flow

An accurate, real-time measurement of cerebral blood flow is required for studies of cerebrovascular function. To date, no ideal measurement system exists, either in the basic science research or in clinical medicine.

Measurement has proven difficult due, in part, to the relative inaccessibility of the brain and the complexity of the cerebrovascular anatomy. The recognition that global changes in cerebral blood flow may not represent

regional or cellular changes is another confounding variable. Diverse ranges of methods to measure cerebral blood flow have been devised, each with particular advantages and limitations.

Indicator methods. Indicator methods may be defined as methods in which the rate of delivery or removal of a substance to or from the brain by the circulation is measured, and utilise the Fick principle. These substances may be categorised into those that readily diffuse in and out of the brain and those that remain confined to the cerebral vasculature. The measurement interval is dependent on the rate of uptake and elution of the indicator and requires a constant flow rate during the measurement period. Ideally, the indicator should be neither metabolised nor pharmacologically active, should have a short half-life and equilibrate rapidly between blood and brain tissue.

Examples of a diffusible indicator method include the Kety method that used nitrous oxide as one of the first indicators and is often regarded as the benchmark for indicator methodology.[14] Hydrogen clearance is performed by the implantation of platinum polargraphic electrodes.[15,16] Whilst this has the advantage of obtaining an index of local flow around the implanted electrodes, multiple sites are required to determine global blood flow. Implantation haematoma may cause false negatives and if large enough, may result in post-traumatic changes in regional and global cerebral blood flow.[17] Xenon is an inert, freely diffusible gas and cerebral blood flow may be measured using either the radiolabelled isotope (Xe^{133}) or with the non-radioactive form in conjunction with computerised tomography.[18,19] These techniques provide reproducible, repeated intermittent measurements and are useful in mapping cerebral blood flow changes.[20,21] Of these techniques, both nitrous oxide and xenon[22] may have direct cerebrovascular effects.

Cerebral blood flow may be measured by injecting a known quantity of an indicator that remains intravascular and measuring the time-course of its appearance in the cerebral venous blood. This is the principle that is commonly used in dye or thermodilution measurement of cardiac output. These measurements are made intermittently and are subject to errors associated with incomplete indicator mixing, variability in rate of injection and recirculation.

Radiolabelled microspheres of appropriate diameter may be injected that become trapped in capillary beds. Scintillography over the region is performed and the degree of radioactivity is compared to another region for which the blood flow is known. These techniques have been validated extensively.[23-25] Limitations with this method include the intermittent nature of measurement, species-specific selection of microsphere size, expense, and limitation by the number of available isotopes and potential inaccuracy under pathophysiological states. These techniques have limited clinical utility where rapid or dynamic measurements are required.

Flow meter methods Most of these techniques utilise the Doppler principle which states that sound reflected from a moving target will be shifted in frequency by an amount proportional to the target velocity.[26] Electromagnetic and ultrasonic Doppler flow meters may be directly implanted on cerebral arteries or veins to measure blood velocity. This is used an index of flow and is dependent on vessel diameter. Doppler methods have the advantage of providing a continuous and accurate measurement of velocities. The functional anatomy of the arteries supplying the brain varies between individuals; the proportion of total flow in any single vessel may not be constant, and flow redistribution between major cerebral vessels may occur.[27] Therefore, accurate measurement of global cerebral blood flow cannot be assured unless simultaneous flow in all major vessels is measured.

Transcranial Doppler ultrasonography with a 2 MHz pulsed Doppler probe allows non-invasive, intermittent or continuous assessment of the velocity of blood flow through large cerebral vessels. Insonation through a naturally occurring acoustic window such as the trans-temporal approach allows assessment of flow through the anterior, middle and posterior cerebral arteries, terminal internal carotid artery and anterior and posterior communicating arteries.[28] This technique is now widely used as a clinical, qualitative assessment of cerebral blood flow velocity. Despite widespread use, transcranial Doppler has the same limitations as implantable arterial Doppler transducers with respect to the difference between blood velocity and flow. The technique is highly operator dependent and marked inter-individual differences have been described. An operator error rate of 15 - 30% has been described, although this may be reduced by continuous transcranial Doppler measurement techniques.[29,30] Measured indices of flow include systolic, mean and diastolic flow velocities.

Distinct patterns associated with normal, hyperaemic, vasospastic and absent flow are recognised. Derived indices such as the Gosling pulsatility index (systolic/diastolic difference divided by the mean velocity) and Lindegaard ratio (between middle cerebral and extracranial internal carotid artery velocities) may assist in differentiating these flow patterns.[31,32] These derived indices are used to indirectly assess the state of cerebrovascular resistance and to improve the accuracy of the recorded signal. However, the relationship between velocity and flow will always be subject to

considerable error without a real-time assessment of vessel diameter.

Laser Doppler flowmetry is used to examine the flow through the microcirculation. Coherent light at wavelengths of 600 - 800 nm is delivered to the underlying tissues via a fibre optic cable. The magnitude and frequency shifts of the reflected light relate to the number and velocity of tissue red blood cells.[33,34] This method measures frequency shifts due to red cell movement in a small region of tissue (e.g. cerebral). This diameter may be as small as 1 mm. Although measurement is continuous, there is an assumption that flow in this region is representative of that in the rest of the brain. Unlike hydrogen clearance, this technique is relatively non-invasive with no effect on cerebral blood flow. Further developments of this technique include scanning laser Doppler flowmetry, where regional cerebral blood flow maps are recorded.[35] Evaluation of this method in a variety of tissue types has demonstrated acceptable agreement with flow measured by other techniques such as hydrogen clearance.[36-38] As with other Doppler techniques, alterations in vessel calibre will affect measurement. Local concentrations of vasoreactive substances may influence measurements.

Cerebral perfusion pressure measurement

Cerebral perfusion pressure is defined as the difference between mean arterial pressure and intracranial pressure. In this relationship, mean arterial pressure is the predominant factor and accuracy of this measurement is imperative. Ideally, this should be performed by cannulation of a major artery (e.g. femoral or brachial) using a calibrated, high-resonance transducer, referenced to the level of the aortic root. For the estimation of cerebral perfusion pressure, both measurements should be referenced to the level of the circle of Willis, usually at the external auditory meatus.

Intracranial pressure monitoring has an established place in clinical neurosurgical and neurointensive care practice and is primarily an index of intracranial elastant reserve. Despite being used for more than 60 years and the promulgation of evidence-based guidelines, there are wide variations in the usage, interpretation and treatment thresholds. Many of these variations are due to practical, logistic and commercial reasons. The relationship between cerebral blood flow and intracranial pressure is highly regulated under physiological conditions but variable under pathological states.

Measurement of intracranial pressure[39] with an intraventricular catheter is the most accurate and clinically useful method. It has the advantages of zero calibration, cerebrospinal fluid drainage and may allow dynamic testing of intracranial pressure-volume relationships. Disadvantages include technical difficulty with insertion, particularly in patients with cerebral oedema and compression of the lateral ventricles, and an increased incidence of infection. These systems allow the measurement of absolute values.

Solid-state systems such as fiberoptic (e.g. Camino®) or strain-gauge tipped catheters (e.g. Codman®) may be placed subdurally, intraparenchymally or intraventricularly.[40-42] These systems transduce intracranial pressure to provide high-fidelity waveforms. They have the advantage of being of small calibre. Insertion is relatively atraumatically performed through a small craniotomy. Disadvantages include inability to perform zero calibration after insertion and baseline drift that may be clinically significant after 5 days.[43] Variable degrees of implantation trauma has been observed, especially when the cable entered through a sulcus. This appears to resolve over time (to a total of 30 days), but suggests that catheter-associated trauma may result in local damage and potential increases in intracranial pressure.

Cerebrovascular resistance

As flow and pressure are readily measured variables in clinical and research practice, vascular resistance is extrapolated from Ohm's Law and used as an index of vascular reactivity. For the cerebral circulation, cerebrovascular resistance is represented as the ratio between cerebral perfusion pressure and cerebral blood flow. However, this derivation is extrapolated from a non-biological system that assumes linear flow through a uniform conductor down a pressure gradient. This does not apply to non-Newtonian, biological systems. Given the difficulties in measuring cerebral blood flow and the non-specificity of a derived index, calculated cerebrovascular resistance has limited clinical validity. Despite this, it continues to be used as a surrogate index of cerebrovascular reactivity and for determination of autoregulatory function in a number of clinical studies of subarachnoid haemorrhage, pre-eclampsia, stroke and traumatic brain injury.[44-47]

The potential for error and limitation of interpretation increases if techniques of cerebral blood flow measurement are themselves limited, such as using velocity changes with transcranial Doppler as an index. Consequently, interpretation of studies using cerebrovascular resistance as a primary endpoint demands considerable circumspection.

Myogenic autoregulation As outlined above, the assessment and quantification of cerebral autoregulation depends on the accuracy of cerebral blood flow measurement. Ideally, continuous real-time measurements are required to determine dynamic changes of cerebral blood flow over a range of cerebral perfusion pressures.

There is no standard method to characterise myogenic autoregulation. Due to the variability of measurements and perturbations, both in clinical and non-clinical studies, there are differing, and often conflicting results in studies of autoregulatory function.

Assessing changes in cerebral blood flow in response to changes in cerebral perfusion pressure may be conducted by inducing a hypertensive (using vasoactive agents, such as phenylephrine,[48] noradrenaline, dopamine, adrenaline[49] or angiotensin II[50]) or a hypotensive perturbation (using β blockers or ganglionic blockers). Mechanical methods for inducing changes in systemic blood pressure include inflation and deflation of intravascular (arterial or venous) balloons,[51] pneumatic cuffs (mainly used in clinical research)[48] and controlled haemorrhage.[52] Reduction in cerebral perfusion pressure may also be induced by elevation in cerebrospinal fluid pressure by cisternal infusion of water.[29,52]

Patterns of autoregulatory responses have been proposed. Static autoregulatory responses are defined as relative blood flow changes in response to steady-state changes in the blood pressure. Dynamic methods assess the response to a rapid change in blood pressure. These two methods have been compared with both intact and impaired autoregulatory capacity.[53]

The relationship between cerebral blood flow and cerebral perfusion pressure may be determined by a number of methods. These relationships have most commonly been determined by regression analysis between mean arterial pressure and cerebral blood flow.[54,55] This provides a statistically appropriate method of determining the response of the dependent variable (i.e. cerebral blood flow) on the abscissa (pressure). The slope of the regression line is primarily used as the index of autoregulatory function. An example of this relationship is shown in Figure 2. In this animal study, the effects of ramped infusions of adrenaline, noradrenaline and dopamine on cerebral blood flow (measured by an implanted Doppler flow probe on the sagittal sinus) and mean arterial pressure in awake sheep and under propofol anaesthesia were determined.[56]

Other methods of measurements have used derived cerebrovascular resistance[57] from changes in flow and pressure. For the reasons outlined above, this is not an accurate representation of vascular reactivity.

Metabolic autoregulation Carbon dioxide reactivity is frequently used as an index of "metabolic" cerebral autoregulation. Estimation of carbon dioxide reactivity requires validated measurements of cerebral blood flow and arterial carbon dioxide tension. Some studies have used end-tidal carbon dioxide concentrations as an index of arterial carbon dioxide tensions. However, arterial to end-tidal gradients may exist in conditions of altered systemic perfusion and mechanical ventilation, which may over- or under- estimate $PaCO_2$. Accordingly, arterial measurements are preferable.

Alterations in cerebral blood flow have been produced by manipulations of $PaCO_2$.[58] Hypocapnia causes cerebral vasoconstriction and hypercapnia cerebral vasodilation. However, under physiological conditions, carbon dioxide induced changes in cerebral blood flow will be maintained within autoregulatory limits by metabolic mechanisms. An example of changes in cerebral blood flow in response to changes in $PaCO_2$ is shown in Figure 3.[59]

Recent advances in intraparenchymally placed electrodes allow highly localised measurements of brain tissue carbon dioxide, pH and oxygen. These direct measurements have the advantage of producing tissue-based measurements that are independent of arterial concentrations and provide information about regional or local metabolic activity. However, they do not reflect global cerebral metabolic function.[9,60]

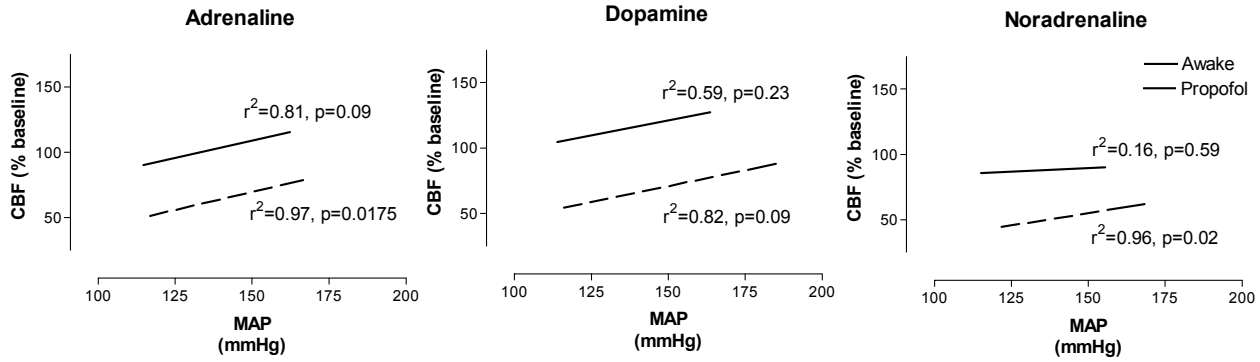

Figure 2. Autoregulation expressed as linear regression lines for normalised cerebral blood flow (CBF: % baseline) and mean arterial pressure (MAP: mmHg) in awake sheep (solid lines), and under steady-state propofol (15.mg/min) (dashed lines) anaesthesia during infusions of adrenaline, noradrenaline and dopamine[56]

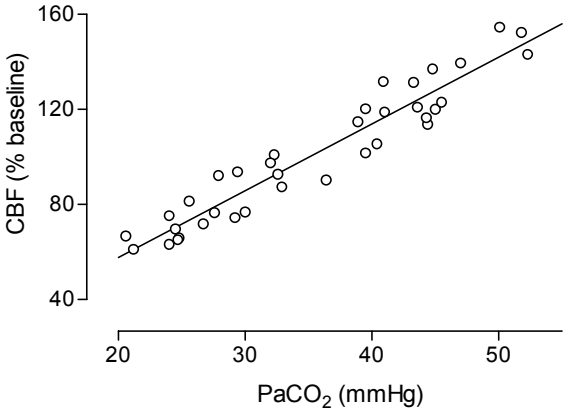

Figure 3. Reactivity of cerebral blood flow (CBF) to changes in arterial carbon dioxide tension (PaCO2: mmHg) expressed as a regression analysis (r2=0.87, p<0.0001)[59]

Clinical implications

Despite some advances in physiological measurement of cerebral blood flow and perfusion pressure, the ability to quantify cerebral autoregulation in health and disease remains limited. Indeed, there is no standardised method of determining cerebral blood flow at the bedside, and such a monitor will probably remain elusive for some time. Clinicians are left with essentially inaccurate tools such as transcranial Doppler or jugular venous, oximetry that despite having widespread acceptance, have poor specificity and sensitivity. The application of potent therapies directed at derived measurements from these is potentially hazardous and clinicians should be cognisant of such limitations.

The measurement of intracranial pressure and use of therapies directed at lowering it are well established. In many clinical situations, intracranial pressure is used, often inadvertently, as a surrogate measure of cerebral blood flow. This relationship is not established, as significant alterations in cerebral blood flow may occur without demonstrable changes in intracranial pressure.[61] If intracranial hypertension develops, the mechanism may be due to vascular (such as post-ischaemic hyperaemia) or non-vascular (such as interstitial cerebral oedema) causes. The treatments of the causes are intrinsically different and it remains difficult to distinguish the two.

Whilst new developments in cerebrovascular pressure-waveform Fourier analysis may assist in distinguishing vascular from non-vascular mechanisms,[62] this application of intracranial pressure monitoring is not routine practice. Equally, changes in intracranial pressure consequent to changes in cerebral blood flow do not refect autoregulatory function, the detection of which remains elusive.

Despite the difficulties and limitations of assessing cerebral autoregulation, intensive care physicians are intimately aware of the clinical consequences of autoregulatory failure. At the lower end of the spectrum, cerebral hypoperfusion is directly attributed to adverse outcomes in traumatic brain injury[63-65] aneurysmal subarachnoid haemorrhage[66] and following cardiac arrest. Failure of upper autoregulatory function usually presents as hypertensive emergencies such as intracranial haemorrhage or eclampsia. In these contexts, restoration of normal systemic mean arterial pressure is the priority, without causing cerebral hypoperfusion or other vital organ ischaemia or cerebral hyperaemia. Determining whether a patient is maintaining adequate cerebral perfusion is difficult to assess, particularly if there is decreased consciousness. In many aspects, the calibrated arterial line remains the most important neurological monitor.

Hypotension is regarded as the most potent secondary insult following traumatic brain injury. Strategies are directed at maintaining normotension to a level consistent with pre-morbid function, and the early use vasoactive agents such as catecholamines are increasingly used. Measurement of jugular venous saturation may provides an indirect assessment of cerebral perfusion.[67] Changes in jugular venous saturation usually occur independently of changes in intracranial pressure. Low jugular venous saturations (<55%) are suggestive of cerebral hypoperfusion, the frequency and duration of which are associated with an adverse outcome.[68] Conversely, high levels of jugular venous saturation (> 85%) may be indicative of cerebral hyperaemia or inadequate neuronal metabolism; prolonged episodes of high jugular venous saturations are also associated with adverse outcomes.[69] Although there is insufficient data to provide evidence-based indications for the routine use of jugular bulb oximetry, these monitors may be regarded as cerebral "pulse oximeter" and provide some information about the relationship between cerebral blood flow and metabolism.

Augmentation of cerebral blood flow by induced hypertension, hypervolaemia and haemodilution ("HHH" therapy) to treat cerebral vasospasm associated with aneurysmal subarachnoid haemorrhage is a strategy that has been advocated for 25 years. However, there is little evidence that "HHH" therapy either reverses vasospasm or improves outcome for aneurysmal subarachnoid haemorrhage.[70] Indeed, the use of vasoactive agents to increase cerebral blood flow in these patients may be associated with adverse outcomes due to cerebral hyperaemia and ischaemia.[71] Furthermore, "HHH" therapy is associated with an increased rate of medical complications that may be due, in part, to the

injudicious use of vasoactive agents in these patients.[72] Part of the concern about the morbidity associated with "HHH" therapy is the use of (often arbitrarily) prescribed target endpoints such systolic blood pressure. There are little data to support the agreement between a nominated systolic blood pressure and resultant cerebral blood flow, let alone the associated errors in measurement of both variables, neither of which provide information about cerebral autoregulatory function.

In conclusion, cerebral autoregulation is a principle physiological function that is essential for normal brain function. Loss of autoregulatory function is associated with devastating neurological consequences. Despite advances in physiological measurement and monitoring, the ability of clinicians and researchers to quantify and manipulate autoregulation remains limited, and circumspection about the utility of current monitors and treatment is required.

Received: 12 February 2004
Accepted: 27 February 2004

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