Driving Cerebral Perfusion Pressure with Pressors: How, Which, When?

J. A. MYBURGH
Department of Intensive Care Medicine, The St George Hospital, Sydney, NEW SOUTH WALES

ABSTRACT

In traumatic brain injury, cerebral hypoperfusion is associated with adverse outcome, particularly in the early phases of management. This has resulted in the increased use of drugs such as adrenaline, noradrenaline, dopamine and phenylephrine to augment or maintain systemic blood pressures at near normal levels. This is now part of standard practice and is endorsed by the Brain Trauma Foundation guidelines. It probably matters little which agent is used, provided appropriate monitoring is in place and those reversible causes of hypotension are promptly excluded and treated.

However, blindly applying management guidelines to all patients may negate these early benefits. The time has come move away from artificially separated concepts of "intracranial pressure" versus "cerebral perfusion pressure" based strategies. These should be considered in parallel and applied to an individual patient, rather than making the patient fit into an all-encompassing treatment algorithm. . A paradigm shift from a "set and forget" philosophy to one of "titration against time" to achieve appropriate therapeutic targets is now required.

In this context the rational use of vasoactive agents to optimise cerebral perfusion pressure may be employed. On the basis of limited animal and human evidence, noradrenaline appears to be the most appropriate catecholamine for traumatic brain injury, although definitive, targeted trials are required. (**Critical Care and Resuscitation 2005; 7: 200-205**)

Key words: Cerebral perfusion, inotropic agents, resuscitation, head injury, review

The recognition of the importance of defending cerebral perfusion pressure in acute brain syndromes such as traumatic brain injury and aneurysmal subarachnoid haemorrhage has resulted in a marked increase in the use of vasoactive agents in these patients. This has developed in the absence of definitive outcome based studies of the use of these drugs in these conditions. There are no studies that have demonstrated the benefit of one inotrope over another or combination of inotrope(s). Consequently, there is marked variation in the selection, use, and role of vasoactive agents in acute brain syndromes.

Cerebrovascular effects of vasoactive agents

Regarding the cerebral circulation, two factors make the application of a reductionist view, i.e. "keep the blood pressure up and the brain will perfuse" somewhat simplistic.

Firstly, the brain is an efficient autoregulator. Cerebral blood flow is maintained at a constant rate over a range of changing perfusion pressures. Auto-regulatory systems are complex and involve a number of myogenic (pressure) and metabolic systems.[1] Cerebral vasoregulation is under the influence of complex neurohumoral systems. Secondly, the blood-brain barrier forms an anatomical and metabolic barrier to systemic drugs. The access of vasoactive agents to the cerebral vasculature is regulated by factors such as lipid solubility and exposure to metabolic enzyme systems within the blood-brain barrier.[2,3]

Under physiological conditions, catecholamines do not normally cross the blood brain barrier. This is an integral mechanism in maintaining cerebral autoregulation. However, this effect may be altered by

Correspondence to: Assoc. Professor J. A. Myburgh, Department of Intensive Care Medicine, The St George Hospital, Gray Street, Kogarah, Sydney, NEW SOUTH WALES 2217 (e-mail: j.myburgh@unsw.edu.au)

changes in blood-brain barrier permeability, induced either by systemic physiological perturbations or by associated pathophysiological or pathological conditions. The direct effect of catecholamines on the cerebral circulation under physiological and pathophysiological conditions remains contentious, due to variability of experimental models and methods of measurement of cerebrovascular mechanics.

Physiological studies

In animal models, catecholamine-induced hypertension with adrenaline,[4] dopamine[5] and phenylephrine[6] has been demonstrated to alter the morphology of the blood-brain barrier. This has been attributed to changes induced by the associated induced hypertension the upper autoregulatory threshold exceeded and by alterations in blood-brain barrier permeability.

There are few studies quantifying and comparing the effects of catecholamines on cerebrovascular mechanics. In an early study, King *et al* compared the effects of adrenaline (using doses of 6-22 μg/min) and noradrenaline (19 - 73 μg/min) on cerebral blood flow, measured using the nitrous oxide method, in awake, human volunteers.[7] Induced hypertension with adrenaline was associated with increased cerebral blood flow that was attributed to increased cerebral metabolism. Noradrenaline was associated with decreased cerebral blood flow that was attributed to increased cerebrovascular resistance in the absence of demonstrable changes in metabolism.

In a physiological ovine preparation, the effects of infusions of ramped infusions of adrenaline and noradrenaline (0 - 60 μg/min) and dopamine (0 - 60 μg/kg/min) on cerebral blood flow, intracranial pressure and cerebral perfusion pressure were determined.[8] Dopamine significantly increased cerebral blood flow and intracranial pressure in a dose-dependent manner without demonstrable changes in calculated cerebrovascular resistance or $CMRO_2$. The effects of dopamine on cerebral blood flow and intracranial pressure was significantly greater than adrenaline, which increased cerebral blood flow albeit to a lesser extent and noradrenaline, which did not. Of the three catecholamines, noradrenaline had the least effect on cerebrovascular mechanics, despite inducing an equivalent systemic effect to dopamine and noradrenaline, suggesting little or no direct effect on the cerebral circulation. This study demonstrated that in a directly comparative model, catecholamine-induced hypertension was associated with changes in cerebrovascular mechanics that were independent of calculated cerebral metabolic rate for oxygen. The variance between this study and King *et al's* earlier study may be explained by the difference in doses used – a standardised infusion over a dose range using a continuous method of cerebral blood flow measurement compared to disparate doses in different individuals. Cerebrovascular resistance is a derived index that is prone to cumulative measurement errors and should be interpreted with circumspection when assessing cerebrovascular changes.

Dopamine exerted a more pronounced effect on cerebral blood flow and intracranial pressure once upper autoregulatory thresholds were exceeded. This implies that dopamine was either able to cross the blood-brain barrier at lower concentrations or that there may be a direct effect of dopamine on the cerebral circulation. Selective transmission of dopamine may occur across the natural defects in the blood-brain barrier such as the posterior pituitary gland or pineal gland that have specific dopaminergic receptors, or via non-adrenergic central neural mechanisms.[9,10] This may be compounded by high circulating concentrations of catecholamines (either endogenous or exogenous) which may also open the morphological barrier, by inducing an acute rise in systemic blood pressure[2,11] This phenomenon has been implicated in the pathogenesis of hypertensive encephalopathy.[12]

Pathological studies

There is therefore a sound physiological basis for the direct cerebrovascular effects of vasoactive agents under certain conditions. Induced hypertension with catecholamines is a relatively uncommon clinical situation, although these drugs are increasingly being used in acute brain syndromes to augment cerebral perfusion pressure.

Pathological changes in cerebral autoregulation and blood-brain barrier permeability induced by conditions such as traumatic brain injury and subarachnoid haemorrhage, render the cerebral circulation more vulnerable to vasoactive agents than the associated induced hypertension.

There are few human studies comparing vasoactive agents in pathological condition. Catecholamines and vasoconstrictors have been used for years as first line drugs to increase cerebral perfusion pressure. Rosner *et al*, described his practice of using phenylephrine and or noradrenaline to aggressively augment cerebral perfusion pressure in a longitudinal series of 93 patients in whom CPP was maintained > 90 mmHg.[13] These patients were compared with a historical cohort of similar patients. Lower mean intracranial pressures (determined by quadratic logarithm analysis) and improved Glasgow Outcome Scores in the CPP group were demonstrated. However, these results should be interpreted with some caution due to the intervention bias and weak comparative methodology. Nevertheless, this non-randomised, retrospective study indicated a

potential role for cerebral perfusion pressure based treatment in traumatic brain injury without demonstrably adverse effects on intracranial pressure.

A small study by Biestro *et al*, compared the effects of dopamine, noradrenaline, methoxamine and dopamine+methoxamine on cerebral perfusion pressure and intracranial pressure in a series of head injured patients.[14] Noradrenaline and dopamine+methoxamine were equally effective in increasing cerebral perfusion pressure without demonstrable increases in intracranial pressure.

Ract and Vigue compared the effects of dopamine and noradrenaline, using a cross-over design, in nineteen head injured patients.[15] For the same mean arterial pressure, intracranial pressure was significantly greater with dopamine than with noradrenaline. This was not associated with changes in indirect measurements of cerebral blood flow with jugular venous saturation or transcranial Doppler. This small human study is in accordance with the physiological studies outlined, suggesting that, in traumatic brain injury that is associated with altered cerebral autoregulation and blood-brain barrier permeability, dopamine has more pronounced effects on the cerebral circulation.

Clinical implications

"Cerebral perfusion pressure (CPP)" based treatments focus on maintaining an appropriate cerebral perfusion pressure at all stages from injury to discharge. Cerebral perfusion pressure may be maintained equally by augmenting mean arterial pressure whilst reducing or controlling intracranial pressure. However, most CPP based algorithms are directed at augmentation of mean arterial pressure. This includes the early and liberal use of inotropes (such as adrenaline, noradrenaline and dopamine), vasopressors (such as phenylephrine or metaraminol), induced normo- or hypervolaemia, normocapnia, and nursing the patient flat.[16]

Importantly, a targeted CPP threshold of 60 - 70 mmHg may artefactually increase intracranial pressure. Consequently, thresholds for "acceptable" intracranial pressures using CPP-based therapies have increased to 20 - 30 mmHg.[17] However, the distinction between actual intracranial hypertension due to cerebral oedema and raised intracranial pressure due to medical therapies remains difficult.

An attempt to determine whether there was a true difference in outcome between CPP and ICP based treatment strategies was attempted by Robertson *et al*.[18] In this study, two groups of patients (n = 189) with severe head injury (defined as a motor component of the Glasgow Coma Score < 5 within 48 hours) were randomised (in a block randomisation fashion) to receive either "CPP" or "ICP" based treatment. The principle difference between the two groups related to prescribed targets of mean arterial pressure (> 90 vs. > 70 mmHg), cerebral perfusion pressure (> 70 vs. > 50 mmHg), arterial carbon dioxide tension (35 - 40 vs. 25 - 30 mmHg) and pulmonary artery occlusion pressure (15 vs. 10 mmHg).

The study was underpowered to determine differences in outcome (defined by Glasgow Outcome Score), and primary endpoints were adjusted to determine the incidence of secondary insults (defined as episodes of sustained jugular venous desaturation < 50%). Cerebral perfusion pressure was maintained at significantly higher levels in the CPP group. There was no statistically significant difference in mean intracranial pressure; nor was there a difference in the incidence of refractory intracranial hypertension between the groups. The frequency and duration of episodes of jugular venous desaturation was significantly lower in the CPP group. Whilst there was no difference in the incidence of delayed intracranial haematomas between the groups, there was a higher incidence of pulmonary oedema (attributed to the Acute Respiratory Distress Syndrome -ARDS) in the CPP group. No differences in six-month Glasgow Outcome Scores were demonstrated. This study concluded that secondary ischaemic insults caused by systemic factors after severe head injury were prevented with a targeted CPP based management protocol.

Although no benefit in outcome was demonstrated, potential adverse effects of this management strategy, i.e. "ARDS," may offset these beneficial effects. Although this study had major methodological flaws, the conclusions were interesting in drawing attention to the potential adverse effects. Whilst the cause of "ARDS" was probably due to fluid overload caused by aggressive fluid loading to achieve a target pulmonary artery occlusion pressure, this highlights one of the pitfalls of protocol-driven treatment strategies. Indeed, this conclusion is concordant with anecdotal reports of patients receiving very large doses of inotropes to achieve prescribed cerebral perfusion pressures. This is particularly alarming if this occurs in patients with underlying cardiac or renal disease.

Astonishingly, given the limitations of the Robertson *et al* study, these results prompted a revision of the Brain Trauma Foundation Guidelines recommendations for cerebral perfusion pressure in 2001, which now recommend a CPP > 60 mmHg due to the increased risk of developing ARDS with higher CPP-based treatments.

Clearly, it is difficult to prove whether there is any difference between cerebral perfusion pressure and intracranial pressure based treatment strategies. In fact,

attempting to show such a difference is focussing on the wrong priority. It appears that although the current emphasis on cerebral perfusion pressure is valid and stems from the best (albeit limited) published evidence to date, reduction of intracranial pressure is an equally important factor.

Targeted therapy revisited

As outlined above, the absence of evidence-based strategies reduces the treatment options available to clinicians to an intentional treatment approach. Clearly aspects of "intracranial pressure" based treatments are required and are appropriate as is the maintenance of cerebral perfusion pressure.

Despite inadequacies and limitations of routine, bedside clinical measurement of cerebral blood flow, changes in cerebral blood flow following traumatic brain injury are increasingly recognised as important determinants the pathophysiological process.

Over a range of systemic blood pressures, cerebral blood flow is linearly dependent. Although cerebral hypoperfusion associated with systemic hypotension is well recognised, cerebral hyperaemia associated with increased systemic blood pressures probably occurs equally as often These theoretical zones of hypoperfusion and hyperaemia are the clinically relevant zones where secondary brain injury may potentially occur.[19,20]

Cerebral blood flow/perfusion pressure relationships change over time. These may be due to absolute changes in cerebral blood flow induced by the head injury and due to recovery of cerebral autoregulatory function.

Abnormal patterns of abnormal cerebral blood flow occur at various time intervals following injury. In a seminal article, Bouma *et al* describe changes in cerebral blood flow in the first forty-eight hours following traumatic brain injury in a cohort of 186 patients.[22] Cerebral blood flow, measured using Xe^{133}, was significantly reduced in the initial twelve hours following injury and associated with cerebral ischaemia, measured by transcranial Doppler. This phenomenon was independent of systemic hypotension and attributed to the primary injury.

The concept of mapping cerebral blood flow over time following injury was explored further by Martin *et al*.[20] Using a similar technique to Bouma *et al*, phases in cerebral blood flow and associated degree of ischaemia were determined from time of injury to 15 days post injury in a series of 313 patients. Three distinct phases of cerebral blood flow were identified.

An initial period of hypoperfusion, essentially similar to the patterns identified by Bouma *et al*, was detected in the majority of patients in the first 24 hours. A subset of patients developed a consequent phase of cerebral hyperaemia up to 5 days post injury, with a nadir of hyperaemia occurring at 72 hours. Thereafter, a syndrome of normal to low cerebral blood flow associated vasospastic transcranial Doppler patterns was identified in a further subset, suggestive of prolonged cerebral vasospasm.

A pathological basis exists for each of these phases, which may explain associated changes in intracranial pressure and may provide a platform upon which to target appropriate therapies.

"Time-based" targeted therapy

Applying the principles outlined by Bouma *et al* and Martin *et al* and integrating the physiological basis of "ICP" and "CPP" based therapies, a novel approach based on evolution of the injury may be developed, in particular, the use of vasoactive agents to optimise cerebral perfusion.

The hypoperfusion phase (0 - 72 hours)

Cerebral blood flow is reduced in the first 72 hours following injury, with resultant global and regional ischaemia. Intrinsic mechanisms for this process include neurohumoral vasoconstriction, intravascular thrombosis, extrinsic microvascular compression due to glial swelling, mass lesion and traumatic subarachnoid haemorrhage.[20,22] Extrinsic mechanisms include extracranial injuries, associated hypovolaemia, and iatrogenic factors such as the injudicious use of mannitol or hyperventilation. During this phase, myogenic autoregulation is markedly impaired and cerebral blood flow is essentially directly dependent on systemic blood pressure. Resultant neuronal ischaemia may result in "cytotoxic" cerebral oedema with associated increased intracranial pressure.

The principles outlined in the Brain Trauma Foundation guidelines essentially apply to this phase. Treatment is focussed around the maintenance of adequate systemic blood pressure. This includes prompt resuscitation, accurate measurement of systemic blood pressure and where indicated intracranial pressure. Once intracranial pressure monitoring is in place, systemic blood pressure must be assiduously maintained during this phase so that cerebral perfusion pressure is maintained $\geq$ 70 mmHg.

Control of intracranial pressure is directed at maintaining adequate cerebral perfusion pressure, with the assumption that restoration of cerebral perfusion to the ischaemic brain will result in improvement in cytotoxic oedema. Drainage of cerebrospinal fluid and prompt evacuation of mass lesions are the most effective methods of reducing intracranial pressure during this period.

During this phase, medical therapies directed at raised intracranial pressure such as osmotherapy or hyperventilation should only be used if cerebral perfusion pressure is maintained at an appropriate level and the patient is adequately monitored. Jugular bulb oximetry may have a limited role in this phase. Jugular venous desaturations (< 50 - 55%) most probably represent cerebral oligaemia, and the prevention of these episodes is associated with improved outcomes.[18,23]

Extracranial surgery should be limited to life or limb threatening injuries only. This includes fixation of closed long bone fractures until the patient is stabilised. Patients undergoing prolonged early surgery should have intracranial pressure or jugular bulb oximetry in situ.

Assessment of adequacy of the response to augmentation of cerebral perfusion pressure is made by intracranial pressure trends, CT scan appearance and where possible, neurological assessment.

The hyperaemic phase (3 - 7 days)

The development of cerebral hyperaemia represents two processes. Firstly, this may be clinical expression of an ischaemia-reperfusion injury mediated through inflammatory mediators. This is associated with cellular hyperglycolysis, vasoplegia and absolute increases in cerebral blood flow(> 55mL/100g/minute). This has been described in 20 - 32% patients.[20]

Secondly, autoregulatory recovery begins during this period and the effects of associated therapies directed at augmenting cerebral blood flow / perfusion pressure may result in an "iatrogenic" hyperaemia. These include catecholamines (adrenaline, noradrenaline and dopamine), mannitol and post hypocapnoeic vasodilation (in patients receiving hyperventilation). Hyperaemia may result in raised intracranial pressure due to vasogenic cerebral oedema.

The diagnosis of cerebral hyperaemia is difficult. These patients are characterised by those who develop progressive intracranial hypertension after 3 days. Initial strategy is directed at ensuring accurate measurement of intracranial pressure and quantifying parenchymal changes on CT appearance.

Catecholamine-induced hyperaemia should be suspected in patients who require progressively increasing doses of catecholamines (e.g. > 40 μg/min of adrenaline or noradrenaline) to attain a prescribed cerebral perfusion pressure of 70 mmHg. This phenomenon is due to tachyphylaxis to prolonged catecholamine infusions and may be responsible for iatrogenically increasing intracranial pressure. If CT appearance is unchanged, cerebral perfusion pressure targets may be lowered (50 - 60mmHg) in order to use lower doses of inotropes. This exercise may be facilitated by jugular venous saturation monitoring or transcranial Doppler to provide an index of adequate cerebral blood flow for the lower cerebral perfusion pressure. Whilst the incidence and frequency of jugular venous desaturation is associated with adverse outcomes, so too have high jugular venous saturations. These data suggest that hyperaemia is a potentially preventable secondary insult.[24]

If patients continue to have raised intracranial pressure, strategies directed at reducing intracranial pressure should be considered. In this context, "anti-hyperaemic" strategies such as cerebral volume regulation ("Lund" therapy), early decompressive craniectomy, low dose barbiturates and possibly "optimised" hyperventilation or hypothermia may have potential, effective roles.

Conclusion

In traumatic brain injury, cerebral hypoperfusion is associated with adverse outcome, particularly in the early phases of management. This has resulted in the increased use of drugs such as adrenaline, noradrenaline, dopamine and phenylephrine to augment or maintain systemic blood pressures at near normal levels. This is now part of standard practice and is endorsed by the Brain Trauma Foundation guidelines. It probably matters little which agent is used, provided appropriate monitoring is in place and those reversible causes of hypotension are promptly excluded and treated.

However, blindly applying management guidelines to all patients may negate these early benefits. The time has come move away from artificially separated concepts of "intracranial pressure" versus "cerebral perfusion pressure" based strategies. These should be considered in parallel and applied to an individual patient, rather than making the patient fit into an all-encompassing treatment algorithm. A paradigm shift from a "set and forget" philosophy to one of "titration against time" to achieve appropriate therapeutic targets is now required. In this context the rational use of vasoactive agents to optimise cerebral perfusion pressure may be employed. On the basis of limited animal and human evidence, noradrenaline appears to be the most appropriate catecholamine for traumatic brain injury, although definitive, targeted trials are required.

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