Cerebral haemodynamics during experimental intracranial hypertension

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Abstract

Intracranial hypertension is a common final pathway in many acute neurological conditions. However, the cerebral haemodynamic response to acute intracranial hypertension is poorly understood.

We assessed cerebral haemodynamics (arterial blood pressure-ABP, intracranial pressure-ICP, Laser doppler flowmetry-LDF, basilar artery Doppler flow velocity-Fv and vascular wall tension-WT) in 27 basilar artery-dependent rabbits during experimental (artificial CSF infusion) intracranial hypertension.

From baseline (~9 mmHg; SE 1.5) to moderate ICP (~41 mmHg; SE 2.2), mean Fv remained unchanged (47 to 45 cm/s; P = 0.38), ABP increased (88.8 to 94.2 mmHg; p<0.01), whereas LDF and WT decreased (LDF 100 to 39.1% p <0.001; WT 19.3 to 9.8 mmHg, p <0.001). From moderate to high ICP (~75 mmHg; SE 3.7), both mean Fv and LDF decreased (45 to 31.3 cm/s p < 0.001, LDF 39.1 to 13.3%, p <0.001), ABP increased still further (94.2 to 114.5 mmHg; p<0.001) while WT was unchanged (9.7 to 9.6 mmHg; p=0.35).

This animal model of acute intracranial hypertension demonstrated two ICP dependent cerebroprotective mechanisms: with moderate increases in ICP, WT decreased and ABP increased, while with severe increases ICP, an ABP increase predominated. Clinical monitoring of such phenomena could help individualize the management of neurocritical patients.

Introduction

Acutely raised intracranial pressure (ICP) or intracranial hypertension is a final pathophysiologic feature common to many neurological conditions including intracranial hemorrhage, traumatic brain injury or acute shunt blockage in hydrocephalus [1]. Such an intracranial hypertension is universally detrimental; it impairs cerebral blood flow (CBF) [2], electrical activity [3] and metabolism [4,5]. Given these pathophysiological sequelae of intracranial hypertension, it is not surprising that active control of intracranial pressure plays a pivotal role in the management of neurological disorders including traumatic brain injury [6].

The haemodynamic response to raised ICP is, however, incompletely described. Sudden increases in ICP decrease cerebral perfusion pressure (CPP; calculated as ABP- ICP) and thus can limit perfusion to the brain [7]. However, depending on the nature of the pathology, this decrease in CPP can be somewhat compensated for by an active cerebral vasodilation such that CBF can be maintained despite decreases in CPP – a process known as cerebral autoregulation [8–11]. Recent studies indicate that the CBF response to a sustained decrease in CPP caused by a decrease in ABP, or an increase in ICP have key physiological differences [12–14]. For example, Bragin and colleagues measured the cerebral haemodynamic response to sustained decrements of CPP (30 minutes at each level of ICP) and found when the decrease in CPP was brought about by an increased ICP, the lower limit of autoregulation was around 30 mm Hg, whereas with decreases in CPP brought about by a decreased ABP, the lower limit of autoregulation was around 50 mm Hg [12,13].

In addition, the haemodynamic response to increased ICP is complicated by the presence of the "Cushing response" – a triad of arterial hypertension, changes in heart rate, and breathing abnormalities [15]. This particular combination of physiologic responses suggests involvement of vital centres within the brainstem and indeed rendering certain areas of the brainstem hypoxic (the nucleus tractus solitarii, for

example) results in significant increases in ABP and changes in heart rate [16]. The physiologic relevance of the Cushing response to cerebral haemodynamics, however, remains unclear.

In this study we revisited the question of haemodynamic responses to graded and extreme elevations in ICP. Utilizing recent advances in mathematical modelling of cerebral haemodynamics, combined with complementary global and local assessments of cerebral perfusion, we aimed to describe cerebral haemodynamics in a rabbit model of intracranial hypertension. Specifically, we hypothesized that with moderate increases in ICP, cerebral vascular wall tension would decrease in attempt to maintain brain perfusion and that only with severe increases in ICP, would ABP increase.

Methods

Animals and ethics

These experiments were carried out in accordance with the standards provided by the UK Animals Scientific Procedures act of 1986 under a UK home office license and with permission from the institutional animal care and use committee at Cambridge University.

Physiological recordings from lumbar CSF infusions in 28 NZ white rabbits (7 female, 21 male; weight 2.7-3.7 kg) were retrospectively analysed [17]. General anesthesia was induced using intravenous alphaxalone/alphadalone (Saffan, Pitman-Moore, Uxbridge, UK, 0.2 mL/kg) and maintained using 1-3% halothane in 3:1 nitrous oxide/oxygen. Rabbits had their common carotid artery ligated so that blood flow to the brain was basilar artery dependent. This made a doppler assessment of global blood flow possible through the insonation of only the basilar artery.

Two weeks after common carotid artery ligation, anaesthesia was repeated as above. The jugular vein was cannulated and a tracheostomy was performed. ABP was measured through in the dorsal aorta after catheter insertion in the femoral artery (GaelTec, Dunvegan, UK). Cerebral blood velocity was measured

using an 8 MHz Doppler ultrasound probe (PCDop 842, SciMed, Bristol, UK) positioned over the basilar artery (accessed through a 7mm burr-hole at the bregma as described in [18]. ICP was monitored using an intraparenchymal microsensor (Codman and Shurtleff, Raynham, MA, USA) inserted through a right frontal burr-hole and a laser Doppler flowmetry probe was placed epidurally through a further right frontal burr-hole (Moor Instruments, Axbridge, Devon, UK).

A lumbar laminectomy was performed to allow the positioning of a permanent catheter (sealed with cyanoacrylate after introduction) into the lumbar subarachnoid space. This facilitated the controlled infusion of artificial cerebrospinal fluid during the experimental protocol. Rectal temperature was monitored and the animals were placed on a padded warming blanket. The rabbits were given an intravenous infusion of pancuronium (pavulon, 0.5 mg/kg/hour) and ventilation was controlled according to arterial PCO_2 via periodic arterial blood gas analyses. The animals were supported in the Sphinx position using a purpose-built head frame with three-point skull fixation. All experiments were performed in an animal laboratory at the same time of day. Experiments are reported in compliance with the ARRIVE guidelines for the reporting of animal experiments [19].

Protocol

Following 20 minutes of rest, a 5 minutes of baseline data were recorded. Thereafter, ICP was artificially increased by infusion of Hartmanns solution into the lumbar CSF space. Infusion rates were initially 0.1 mL/min. ICP increased to reach a plateau of around 40 mm Hg after approximately 10 minutes, thereafter the infusion rate was increased to rates between 0.2 and 2 ml/min to produce severe intracranial hypertension. ICP was increased until the point where diastolic flow velocity approached zero, which corresponded to an ICP of between 60 and 100 mm Hg (mean 75 mm Hg) at the termination of the experiment. Rabbits were euthanized with thiopental at the conclusion of the test.

Data acquisition and analysis

ABP, ICP, basilar artery flow velocity (Fv) and expired CO_2 signals were recorded digitally at a sampling frequency of 50 Hz. Data were subsequently analysed off-line using custom-built, commercially available data analysis software (ICM+; http://www.neurosurg.cam.ac.uk/icmplus). Heart rate (HR) was calculated by estimating the fundamental frequency of the ABP spectra in a moving 10 second window. Diastolic and systolic values of blood pressure and flow velocity were calculated by estimating the minimum and maximum values over a 0.5 second window, shifted each 0.25 second. Mean values were then calculated over 10 second period. LDF was expressed as a.u. minus the 'biological zero' as measured in the asystolic rabbit at the conclusion of the experiment. Mean values of ABP, ICP, LDF, and Fv were calculated every 10 seconds. Fundamental amplitudes of ICP, ABP, and Fv were calculated using spectral analysis within the range of the rabbits HR (100-400 bpm). End-tidal CO_2 values were corrected using the arterial PCO_2 concentration from the blood gas analysis to account for any end-tidal to arterial PCO_2 gradients.

Cerebral vascular resistance (CVR) was calculated as the cerebral perfusion pressure divided by the basilar artery flow velocity. Cerebral arterial compliance was calculated as the derived cerebral arterial volume pulse amplitude divided by the arterial blood pressure pulse amplitude as described previously [20].

CrCP was calculated using both measured (HR, ABP, HR, CPP) and modelled variables (Ca - cerebral arterial compliance) as described in [21] and shown below:

$$CrCP = ABP - \frac{CPP}{\sqrt{(CVRi \cdot Ca \cdot HR \cdot 2\pi)^2 + 1}}$$

Where CrCP – critical closing pressure, ABP- arterial blood pressure, CPP- cerebral perfusion pressure, CVRi- cerebrovascular resistance (invasive, i.e. calculated as CPP divided by mean blood flow velocity), Ca- cerebral arterial compliance, HR- heart rate.

Arterial wall tension (WT) was calculated as CrCP- ICP.

Although data across the whole recording period are presented, three points of interest were identified to allow statistical comparison of intracranial haemodynamics: baseline before any infusion ("baseline ICP", during a plateau ICP immediately prior to the final steep rise in intracranial pressure ("moderate ICP"), and in the period after the final rise in ICP ("high ICP").

The relationships between the changes in CPP and cerebral perfusion were analysed by first referencing each rabbits CPP to their CPP at baseline. To compare cerebral perfusion as measured by LDF and Doppler ultrasound, both LDF and Fv were expressed as a percentage of their baseline value. For each rabbit, the average LDF (% of baseline) and Fv (% of baseline) was calculated in 5 mm Hg wide intervals of decreasing CPP or increasing ICP using Microsoft excel (Microsoft Corp., Redmond, USA) and ICM + tools (Monash University, Melbourne, Australia).

Statistical analyses

Data are presented as mean and associated standard error of the mean. Pairwise comparisons of haemodynamic parameters between the three different ICP conditions ("low", "moderate", and "high") were performed using Student's T-Test. The alpha-value was set at 0.05 and no corrections were made for multiple comparisons. Of the available 28 experiments, one was excluded from analysis due to an inability to increase ICP above 30 mm Hg with CSF infusion, leaving 27 rabbits for the final analysis. As the nature of this study was retrospective and the analytical techniques applied were not available at the time the experiments were designed, no formal sample size calculations were carried out, rather, all available valid data were used. Statistical analysis was performed using IBM SPSS version 21.0 software (IBM Corp., Armonk, USA).

Results:

No adverse effects of the common carotid artery ligation were apparent. The mean length of the protocol was 28.2 minutes (SD 8.4). Monitored variables during a typical CSF infusion experiment are depicted in figure 1. ICP increased due to incremental increases in the rate of CSF infusion. In this example, cortical perfusion, as indicated by LDF, showed a monotonic decrease with increasing ICP, whereas global perfusion, as assessed by basilar artery flow velocity, was well maintained until ICP reached values greater than 40 mm Hg. Mean ABP in this case remained stable until ICP increased above 30 mm Hg, at which point it increased and eventually reached values of 200 mm Hg.

Figure 2 shows selected derived haemodynamic parameters in the same rabbit during the final segment of the experiment (ICP increasing above 40 mm Hg). As a result of this raised ICP, calculated CrCP increased and eventually reached values equivalent to the diastolic ABP. At this point, the diastolic closing margin (diastolic ABP minus CrCP) is equal to zero or negative indicating that the forces acting to close the microvasculature are greater than the forces keeping the vessels open. This time point coincided with a cessation of diastolic flow velocity in this case. The pulse amplitude of ICP (AMP) increased with increasing mean ICP with the exception of at very high levels of mean ICP at which point AMP appeared to decrease with increasing ICP in this rabbit. This phenomenon was observed in 11 of the 27 rabbits. The relationship between AMP and mean ICP in these 11 rabbits is presented in figure 3, which depicts an 'upper breakpoint' at a mean ICP=78 mm Hg (range 55 to 118 mm Hg equivalent to CPP=39 mm Hg; range 28 to 63 mm Hg). The diastolic closing margin at this 'upper break point' was close to zero (9.5 mm Hg) and diastolic flow velocity was low (12.6 cm/s or 30.5% of baseline).

Table 1 outlines all recorded and derived parameters at baseline, moderate, and high ICP. The Cushing response is reflected by the marked increase in ABP, and decrease in HR between moderate and high ICP. However, increases in ABP were also observed between baseline and moderate increases in ICP. The

Cushing vasopressor response occurred in 25 out of 27 experiments and was initiated at an average ICP of 26.2 mm Hg (range 10 to 45 mm Hg). As a result of the Cushing vasopressor response, despite an increase in ICP by 35 mm Hg between the 'moderate' and 'high' ICP conditions, CPP only decreased by 14 mm Hg (Table 1).

Mean flow velocity of the basilar artery was not significantly changed from baseline to moderate ICP, whereas cortical LDF and diastolic flow velocity decreased. Cerebral vascular resistance and wall tension decreased from baseline to moderate ICP, and arterial compliance increased from low, to moderate to high ICP conditions. Consistent with the increased ICP, CrCP increased throughout the infusion. End-tidal CO_2 did not change significantly during the experiment.

The comparison of cortical LDF and basilar artery Fv in response to raised ICP is shown in figure 4a. This demonstrates that cortical LDF was most sensitive to increases in ICP followed by diastolic velocity and then systolic velocity. When expressed as a function of CPP, a similar response was observed; LDF was most sensitive, systolic velocity least sensitive, and diastolic velocity moderately sensitive to decreases in CPP (figure 4b).

The inter-relationships between changes in ICP, CBF, vascular wall tension, ABP, CPP and HR in all 27 rabbits are shown in figure 5. CBF appears well maintained with up to 60 mm Hg increases in ICP. This maintenance of CBF was contributed by both decreases in wall tension and increases in ABP. Wall tension progressively decreased with increasing ICP particularly during early increases in ICP. At the highest levels of ICP, WT started to increase.

Discussion:

We detail three novel insights into the cerebrovascular response to raised ICP. First, two intrinsic and mechanistically distinct compensatory adaptations to raised ICP were observed: 1) with moderate increases in ICP, CBF is maintained by decreases in vascular wall tension; and 2) at higher levels of ICP, cerebral perfusion is protected by the Cushing vasopressor response that maintains CPP and keeps cerebral vessels open. Second, regional differences in the control of cerebral perfusion seem to exist with cortical blood flow being more sensitive to an increase in ICP than global blood flow. Third, at dramatically high ICP (and low CPP) decreases in the amplitude of ICP pulsations can be observed. Herein we discuss the possible physiologic underpinnings and clinical implications of these observed phenomena.

ICP-dependent cerebroprotection; vascular wall tension and the Cushing response.

During increases in ICP, global CBF was maintained until ICP had increased by 55 mm Hg above baseline ICP (Fig.4 and 5). CBF was maintained by two mechanisms; a decrease in vascular wall tension (at more moderate levels of ICP) and increases in ABP. During moderate increases in ICP, estimated wall tension progressively decreased (Fig.5, table 1). This decrease in wall tension represents a decrease in cerebral vasomotor tone and thus an autoregulatory response that acts to maintain CBF in the face of a decreased CPP. Similar decreases in calculated wall tension have also been described in response to hypercapnia, arterial hypotension, and plateau waves of ICP [21,22]. During the increase in ICP, estimated wall tension decreased and reached a plateau during ICP increases between 30 and 60 mm Hg. (Fig. 5, Table 1). This plateau of vascular wall tension (at around 6-8 mm Hg) may represent a condition of maximum vasodilation biologically fixed by the rigid collagen fibres in the tunica adventitia [23].

Further increases in ICP caused a vigorous Cushing response as reflected by reductions in HR and increases in ABP (mean ABP increasing by > 30 mm Hg in 13 out of 27 rabbits). However, in contrast to our hypothesis, this hypertensive response was also present with moderate ICP increases (in 12 out of 27

individuals the hypertensive response was observed with increases of ICP of less than 25 mm Hg). This relatively 'early' increase in ICP may indicate that the ICP induced increases in ABP play a protective role in maintaining perfusion rather than merely signifying irreversible neurologic damage. In support of this finding, a similar increase ABP in humans has been observed at even moderate ICP during lumbar CSF infusion studies [24,25].

Although it has been over 100 years since Harvey Cushing described this response [15], whether it is beneficial or detrimental is still debated [26]. The current data indicate two possible mechanisms by which the vasopressor response may be beneficial. First by increasing the ABP, the driving pressure for CBF - the CPP - is maintained. Second, by increasing the intravascular pressure, the vessels are more resistant to the collapsing force of ICP (i.e. the difference between the ABP and the CrCP is maintained).

The Cushing vasopressor response keeps vessels open by maintaining ABP above the CrCP. CrCP is the ABP at which cerebral blood flow approaches zero[27] and reflects closing forces acting on the vessel, namely ICP and wall tension [23]. Therefore CrCP is an important parameter during any conditions where wall tension or ICP may change (such as syncope[28], the Valsalva maneuver[29], or plateau waves of ICP[22]). The difference between the 'opening' force ABP and 'closing' force of CrCP is the force that keeps vessels open and has been denoted the 'closing margin' [30]. If this closing margin is reduced to zero, vessels will collapse resulting in cessation of flow. By increasing ABP, the Cushing vasopressor response acts to maintain this closing margin.

In cases where, despite the Cushing response, closing margin during diastole is equal to zero we observed a complete cessation of cerebral diastolic flow (Fig.2). The abolition of the diastolic closing margin seems to have two consequences observable with haemodynamic monitoring; vessels collapse during diastole giving zero flow velocity and the amplitude of the ICP pressure pulse (itself determined by the pulsatile addition of blood volume) decreases (Fig.2).

Thus, it seems that the brain has two intrinsic mechanisms to protect itself from hypoperfusion during intracranial hypertension; decreases of cerebral arterial wall tension at low to moderate ICP and a Cushing vasopressor response that predominates at high ICP. A practical application of these findings is that these intrinsic mechanisms are the main therapeutic measures that can be used to adjust CBF; decreasing vascular wall tension (using pharmacological or ventilator intervention), or increasing ABP (using vasopressors). However, inspection of figure 5 indicates that the efficacy of each intervention may depend on the prevailing cerebrovascular factors that are only appreciated through multimodality monitoring; if wall tension is already close to zero, further attempts at vasodilation are unlikely to improve perfusion as the vessels may already be maximally dilated. In these situations, increasing ABP may be the only viable way to increase CBF.

Differential control of cortical compared to global blood flow

Using in-vivo global and cortical CBF measurement during dynamic changes in ICP, we demonstrated that cortical blood flow decreased almost linearly with increasing ICP whereas global flow (basilar artery flow velocity) was well maintained until a very high ICP (~60 mm Hg). A similar phenomenon is observed when CBF was expressed as a function of CPP. In addition, global cerebrovascular resistance decreased with increasing ICP, while cortical vascular resistance increased consistent with differential autoregulatory control of cortical and global blood flow (table 1).

A potential explanation for the vulnerability of cortical compared to global CBF could lie in a differential vascular reactivity of cortical compared with non-cortical brain. Such a discrepancy could theoretically result in a 'vascular steal' phenomena whereby, during periods of reduced cerebral perfusion pressure, vessels within actively autoregulating sub-cortical areas dilate, while those in the cortex do not change caliber. This topographic difference in resistance would result in CBF being diverted away from the cortex. Such a vascular steal phenomena has been previously described in the context of cerebrovascular CO_2

reactivity [31]. In support of a topographic differences in autoregulatory capacity, Horsefield et al

demonstrated an intrinsic difference in the autoregulatory efficiency of the grey matter compared to

white matter of healthy humans [32]. They demonstrated that in response to a transient decrease in CPP

induced by leg cuff release, CBF recovered more quickly in the white matter compared to the grey

matter.

Further support for a differential autoregulatory capacity of the cortical compared to non-cortical areas

comes from clinical monitoring studies. In a group of severe TBI patients with monitored ABP, ICP, LDF

and middle cerebral artery Fv, Zweifel et al., assessed the correlation between slow changes in CPP and

slow changes in CBF [33]. In this situation, there was a higher correlation between CPP and LDF than

between CPP and middle cerebral artery Fv. Moreover, investigations combining near infrared

spectroscopy derived cortical oxygenation and transcranial Doppler derived middle cerebral artery Fv also

indicate a cortical vulnerability. Budohoski and colleagues found that the correlation between ABP and Fv

seem to be lower than the correlation between ABP and NIRS oxygenation[34], while Kuriyama and

colleagues demonstrated that prior to the onset of syncope, cortical oxygenation decreases while middle

cerebral artery Fv remains constant[35]. From a teleological point of view, such cortical sensitivity to high

ICP could be a mechanism for diverting blood flow to areas of the brain most crucial for survival; the

brainstem cardiorespiratory nuclei.

The mechanisms underlying this differential response of cortical and global perfusion to increased ICP are

unclear. It could reflect intrinsic differences in vascular biology such as increased vascularity in the white

matter compared with the grey matter or reflect regional differences in the hydrodynamic response to

CSF infusion. For example, an increase in ICP via a CSF infusion could cause a greater increase in ICP in

regions closer to the CSF space, including the cortex. Regional impairment of CBF has been demonstrated

in the periventricular spaces during CSF infusion in normal pressure hydrocephalus patients [36]. In this

latter study, infusion of artificial CSF into the subarachnoid space resulted in a decrease in CBF that was

most prominent in the watershed areas close to the ventricles. Whether such autoregulatory gradients to CSF infusion also exist in relation to distance from the subarachnoid spaces is unknown.

Relationship between ICP pulsatility and mean ICP

The linear relationship between pulse amplitude and mean ICP has been described many years ago [37] and is one of most specific landmarks of ICP signal. It has been classically interpreted by loss of cerebrospinal compensatory reserve with increasing mean ICP, elegantly interpreted by the exponential pressure-volume relationship. Avezaat and van Eijndhoven observed a right side deflection point of the volume-pressure response at very high levels of ICP, experimentally studied with an inflated epidural balloon [38]. The same phenomenon can be observed as the upper breakpoint of the amplitude- mean ICP relationship, and has been observed clinically in rare cases of patients after TBI who died of refractory intracranial hypertension [39] or in the paediatric neurosurgical population [40]. It is an uncommon appearance, counterbalanced by the Cushing increase of ABP, and its etiology is unclear. It could be related to terminal closing of the cerebral arterial bed when the CrCP approaches ABP. In support of this the observed upper breakpoint was associated with a low diastolic closing margin and diastolic flow velocity.

Perspectives

ICP monitoring has become a standard of care after severe traumatic brain injury, however we do not yet have any class 1 evidence that ICP or more extensive haemodynamic monitoring improves patient outcome [41]. Typically, fixed thresholds of ICP or CPP are used as a guide for therapy [42], despite it being unlikely that a single threshold of either ICP or CPP is optimal for every patient. Unfortunately, highly individual haemodynamic and metabolic physiology hamper the use of 'one size fits all' ICP or CPP thresholds. The current study highlights that modest (+/- 10 mm Hg) alterations in ICP decrease cortical perfusion and result in decreases in vascular wall tension. Thus, even in the controlled experimental

condition, just knowing the ICP or CPP is unlikely to indicate if the CBF is adequate. Probably only by integrating global (ICP, CPP, pressure reactivity, Doppler derived wall tension, CrCP and Fv) and local (microdialysis, brain oxygen pressure) physiologic markers will we be able to clearly understand the state of the patients cerebral circulation and how it may be optimized.

Limitations

The current results reflect the cerebral haemodynamic response to raising ICP through the addition of CSF volume. Although a practical model for interrogating the cerebral haemodynamic response to raised ICP, the observed haemodynamic response may differ somewhat to those observed clinically in the injured, oedematous brain where changes in volume of the intracranial blood, CSF, or parenchymal compartments are all common. Clinical observational studies in TBI patients may help to confirm the current results. Application of cortical LDF during an infusion of fluid into the subarachnoid space raises the possibility of LDF probe displacement by the infusion. Although gross displacement of the LDF probe could easily be ruled out visually, subtle changes in orientation of the LDF probe would be more difficult to detect and could result in decreases in flux.

The experimental paradigm involved bilateral ligation of the common carotid artery prior to experimentation – this could affect cerebral haemodynamics *per se*. Indeed, recent investigations have indicated that common carotid artery ligation in NZ rabbits can lead to nascent aneurysm formation at the basilar terminus after 12 weeks[43] with subtle changes in structure of the basilar terminus detectable as early as 5 days after ligation[44]. While an important consideration, the current investigation analysed within individual cerebral haemodynamic changes and no neurological deficit was observed in these rabbits before testing. Moreover, rendering the rabbits basilar artery dependent ensured that flow velocity measured at the basilar artery represented a global cerebral perfusion and provided a well-controlled model to address our proposed questions.

Halothane was used for the induction and maintenance of anaesthesia, which could be relevant to the interpretation of cerebral haemodynamic data as halothane has the dose dependent potential to cause cerebral vasodilation, intracranial hypertension and systemic hypotension [45–47]. However, after induction, the dose of anaesthesia was titrated as low as possible while maintaining adequate anaesthesia. Moreover, intracranial pressure and ABP were both monitored intensively during this study and were both normal during baseline recording (Table 1).

Finally, the current analysis is derived from the digital recordings of experiments performed (by SH HR and MC) and published in the past [17,48]. The first analysis investigated the relationship between CO_2 reactivity and cerebral autoregulation [17], while the second analysis compared the accuracy of three non-invasive estimates of ICP [48]. Although this is potentially a limitation, it can also be argued that the multiple use of experimental material to conduct separate mathematical modeling studies is scientifically and ethically sound because it takes full advantage of recent advances in physiologic mathematical modeling while limiting the number of animals that need to be sacrificed in accordance with the 3 R principles for animal research (replacement, reduction and refinement-http://www.nc3rs.org.uk/.

Conclusion

The brain attempts to compensate for an increased ICP by both reducing cerebrovascular wall tension and increasing ABP, but the relative importance of these mechanisms depends on the prevailing ICP. In addition, cortical perfusion appears to be exquisitely sensitive to increases in ICP and this may not be detected by global measures of perfusion. Multimodal monitoring including derived haemodynamic indices may better help personalise clinical management in neurocritical disease.

Disclosure:

ICM+ software (Cambridge Enterprise, Cambridge, UK, http://www.neurosurg.cam.ac.uk/icmplus/) is a multimodal data acquisition and analysis software licensed by the University of Cambridge, Cambridge

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Figure legends

Figure 1 Measured haemodynamic response to lumbar CSF infusion in the rabbit

ICP was increased over the period of 30 minutes from baseline levels (10 mm Hg) to high levels (>100 mm

Hg). Cortical LDF (top panel) decreased with this increasing ICP, whereas Fv in the basilar artery remained

stable until ICP was above 50 mm Hg. Mean arterial blood pressure increased when ICP increased above 30 mm Hg as part of the Cushing reflex.

LDF – Laser Doppler flowmetry; Fv – flow velocity in the basilar artery; ABP – Arterial blood pressure; CPP – Cerebral perfusion pressure; ICP – Intracranial pressure.

Figure 2 Derived haemodynamic parameters in response to lumbar CSF infusion in the rabbit

In the same rabbit as figure 1, progressive increases in ICP caused an increase in CrCP, and ABP diastolic, as well as a corresponding decrease in the difference between them – the diastolic closing margin (second panel). At very high ICP, CrCP approached ABPd, which was associated with a drop of diastolic flow velocity to zero (top panel). AMP of ICP increased along with mean ICP until very high ICP, at which point AMP began to decrease (third panel).

CrCP – Critical closing pressure; ABPd – Diastolic arterial blood pressure; Fvs – Systolic flow velocity in the basilar artery; Fvd – Diastolic flow velocity in the basilar artery; AMP – Pulse amplitude of ICP; ICP – Intracranial pressure.

Figure 3 Upper breakpoint of intracranial mean pressure-amplitude relationship (n=27; mean +/- SE)

In 11 rabbits, an upper breakpoint of the intracranial mean pressure-amplitude relationship was observed whereby further increases in mean ICP resulted in decreases in the pulse amplitude of ICP. This upper breakpoint was associated with low diastolic closing margins (9.5 mm Hg) and diastolic flow velocities (12.6 cm/s – 30.5 % of baseline)

ICP – Intracranial pressure; AMP- pulse amplitude of intracranial pressure

Figure 4a and 4b Cerebral blood flow during lumbar artificial CSF infusion in rabbits (n=27 mean +/- SE)

In 4a, global (as assessed by basilar artery Fv) and cortical (as assessed by LDF) CBF are normalized to baseline CBF and then expressed relative to changes in ICP produced by the lumbar CSF infusion. LDF appears most sensitive to increases in ICP, followed by diastolic flow velocity and then systolic flow velocity. When CBF is plotted against changes in CPP (4b), again, cortical LDF appears most sensitive to decreases in CPP, followed by diastolic flow velocity and then systolic flow velocity.

CBF –cerebral blood flow; Fv- Flow velocity; Fvs – Systolic flow velocity in the basilar artery; Fvd – Diastolic flow velocity in basilar artery; LDF – Laser doppler flowmetry

Figure 5 Cerebral haemodynamic response to increasing ICP (n=27 mean +/- SE)

In this study group averaged global Fv was well maintained until an ICP 55 mm Hg above baseline (top panel). This maintained Fv was achieved by both a decrease in wall tension and an increase in ABP (panel 2 and 3). HR did not show major changes until relatively large increases in ICP (60-75 mm Hg above baseline; panel 4). As a consequence of the vasopressor response, CPP was relatively buffered especially during relatively large increases in ICP. From baseline ICP to ICP increases of 15-20 mm Hg, CPP decreased from a mean of 78 to 58 mm Hg whereas from ICP increases of 25 to 30 mm Hg to ICP increases of 35-40 mm Hg CPP only decreased from 54 to 45 mm Hg.

Table 1 Haemodynamic parameters during experimental intracranial hypertension in rabbits (n=27).

	Baseline		Moderate ICP			High ICP			
	Mean	SE	Mean	SE	Significance compared to baseline	Mean	SE	Significance compared to baseline	Significance compared to moderate ICP
ABP mean (mm Hg)	88.84	3.29	94.15	3.21	*	114.54	3.67	**	**
ABP systolic (mm Hg)	116.07	3.90	121.81	3.77		143.78	4.32	**	**
ABP diastolic (mm Hg)	72.77	3.25	77.84	3.04	*	96.27	3.36	**	**
HR (BPM)	273.27	6.96	262.73	7.64	*	227.21	11.13	**	**
ICP mean (mm Hg)	9.00	1.51	40.75	2.17	**	75.05	3.65	**	**
AMP (mm Hg)	0.40	0.10	1.81	0.17	**	3.59	0.33	**	**
CPP (mm Hg)	79.71	3.46	53.08	2.77	**	39.64	2.16	**	**
$P_{ET}CO_2$ (mm Hg)	32.29	0.56	31.74	0.69		31.49	0.77		
Fv mean (cm/s)	47.04	2.99	44.99	2.82		31.33	2.45	**	**
Fv diastolic (cm/s)	34.17	2.76	30.49	2.58	*	15.59	1.67	**	**
Fv systolic (cms/s)	66.93	3.64	65.51	3.33		50.97	2.66	**	**

Ca (%)	100.00	0.00	130.81	14.87	*	166.90	20.46	*	*
CVR (%)	100.00	0.00	72.70	3.05	**	89.41	8.67		*
WT (mm Hg)	19.27	1.84	9.75	1.27	**	9.58	1.36	**	
CrCP (mm Hg)	28.42	2.05	50.61	2.12	**	85.09	3.99	**	**
LDF (%)	100.00	0.00	39.10	29.82	**	13.27	5.19	**	**
Cortical CVR (%)	100.00	0.00	157.10	85.01	*	231.35	37.56	*	*

*P value = <0.05, ** P value < 0.001

ABP – Arterial blood pressure; HR – Heart rate; ICP – Intracranial pressure; AMP – Pulse amplitude of ICP; CPP – Cerebral perfusion pressure; Fv – flow velocity in the basilar artery; Ca – Cerebral arterial compliance; CVR – Cerebral vascular resistance; WT – Wall tension; CrCP – Critical closing pressure; LDF – Laser Doppler flowmetry; $P_{ET}CO_2$ – pressure of end tidal CO_2