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Predicting the response of intracranial pressure to moderate hyperventilation

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Summary

Background. Hyperventilation may cause brain ischaemia after traumatic brain injury. However, moderate reductions in $PaCO_2$ are still an option in the management of raised intracranial pressure (ICP) under some circumstances. Being able to predict the ICP-response to such an intervention would be advantageous. We investigated the ability of pre-hyperventilation ICP and cerebrospinal compensatory reserve to predict the reduction in ICP achievable with moderate hyperventilation in head injured patients.

Methods. Thirty head injured patients requiring sedation and mechanical ventilation were investigated. ICP was monitored via an intraparenchymal probe and intracranial cerebrospinal compensatory reserve was assessed using an index (R_{ap}) based on the relationship between mean ICP and its pulse amplitude. Measurements were made at a constant level of $PaCO_2$ during a 20-minute baseline period. The patients were then subjected to an acute decrease in $PaCO_2$ of approximately 1 kPa and, after an equilibration period of 10 minutes, measurements were again made at a constant level of $PaCO_2$ for a further 20 minutes. A multiple linear regression model, incorporating baseline $PaCO_2$, ICP, and R_{ap} was used to identify the relevant predictors of ICP reduction.

Findings. Baseline ICP and R_{ap} were both significant predictors of ICP-reduction ($p = 0.02$ and 0.001 respectively) with R_{ap} being the more powerful parameter.

Conclusions. A model based on cerebrospinal compensatory reserve and ICP can predict the achievable ICP-reduction and may potentially be used to optimise patient selection and intensity of hyperventilation.

Keywords: Traumatic brain injury; hyperventilation; intracranial compliance; intracranial pressure.

Introduction

Raised intracranial pressure (ICP) is associated with unfavourable outcome after traumatic brain injury [8, 16]. Based on the available evidence, the most recent Guidelines for the Management and Prognosis of Severe Traumatic Brain Injury [2] recommend a threshold of 20–25 mmHg above which raised ICP should be treated. Once mass lesions are evacuated drainage of cerebrospinal fluid (CSF) via an external ventricular drain is the preferred method to treat raised ICP [2], this may not always be possible with diffuse brain swelling since the ventricles may be difficult to cannulate, or the drainage may become blocked, especially when the ventricles are small or collapsed. In such patients manipulation of the arterial partial pressure of CO_2 ($PaCO_2$) is one of the options to lower ICP suggested by the guidelines, initially to a $PaCO_2$ of not lower than 4.0 kPa. However, if this and other medical therapies such as mannitol fail to control ICP, second tier therapies such as high dose barbiturate therapy, or hyperventilation to a $PaCO_2$ <4.0 kPa are an option [2].

The reluctance to use hyperventilation is based on the well documented potential of this intervention to cause cerebral ischaemia [3, 12]. To avoid ischaemia, jugular bulb oxygen saturation (SJO_2) or arterio-jugular oxygen content difference monitoring are recommended [2]. Although it has been shown that it is possible to optimise hyperventilation based on such monitoring [5], SJO_2 monitoring may miss relevant ischaemic episodes due to its low sensitivity to regional ischaemia [4]. In view of this shortcoming of monitoring technology, and the relevant side effects of all second tier therapies it would be useful to be able to predict the ICP-reduction that can be achieved per kPa of reduction in $PaCO_2$, based on pre-hyperventilation physiology. This would allow the

clinician to prospectively weigh the risk and benefit of hyperventilation and thus optimise patient selection and intensity of $PaCO_2$ manipulations.

The beneficial effects of hyperventilation are due to a reduction in cerebral blood volume (CBV) with the ICP-reduction equalling the change in CBV divided by intracranial compliance. The relationship between ICP and intracranial volume is described by the pressure-volume curve [14, 22]. During hyperventilation, the patient's 'working point', defined by the co-ordinates mean ICP and global intracerebral volume, can be expected to move downwards along his or her individual intracranial pressure-volume curve. We have previously developed an index (R_{ap}) based on the ICP waveform data that estimates cerebrospinal compensatory reserve and hypothetically gives information on the patients' position on the pressure-volume curve [6]. It is therefore likely that pre-hyperventilation R_{ap} can be used as a predictor of the achievable ICP reduction.

Using a multiple linear regression approach we developed a model, based on baseline $PaCO_2$, ICP, and R_{ap}, to predict the reduction in ICP that can be achieved per kPa of reduction in $PaCO_2$.

Methods

All adult head injured patients (age >16 years) admitted to our Neurosciences Critical Care Unit (NCCU) from April 2001 to April 2002 were eligible for entry into this study. The study protocol was presented prospectively to the multidisciplinary NCCU user committee, to address ethical issues concerning publication of these data, which were routinely collected as a part of standard clinical management. Since data are fully anonymised, there were no data protection issues involved, it was agreed that formal informed consent was not required for this report. Exclusion criteria were respiratory failure, which would have interfered with the reduction of $PaCO_2$, and $PaCO_2$ <4.30 kPa, to avoid exceeding the Unit's lower $PaCO_2$ limit of 3.5 kPa. Patients were treated according to a cerebral perfusion pressure orientated protocol, which aimed to keep cerebral perfusion pressure above 70 mmHg and ICP below 25 mmHg [19]. All patients were sedated with propofol, artificially ventilated, and when necessary, paralysed with atracurium. Where appropriate, surgical removal of space occupying lesions, osmotic agents, and moderate hypothermia were used.

Study protocol

ICP monitoring was performed using an intraparenchymal probe (Codman MicroSensors ICP Transducer, Codman & Shurtleff, Raynham, MA, USA). Mainstream end-tidal CO_2 monitoring was used (Marquette Solar 8000M, GE Medical Systems, UK) and mean arterial blood pressure was monitored from the radial artery using a standard kit (Edwards Lifesciences, Irvine, CA, USA). Furthermore, SJO_2 and flow velocity in the middle cerebral artery were monitored. Data were collected during routine determination of CO_2-reactivity, which is part of standard clinical practice on this Unit. After recording baseline data for 20 minutes and obtaining a baseline value for $PaCO_2$ (AVL Omni, Roche Diagnostics GmbH, Graz, Austria) the minute volume of the ventilator was increased by 15 to 20%. If due to this intervention the Unit's standard treatment guidelines ($PaCO_2$ >3.5 kPa and or SJO_2 >55%) were exceeded, the protocol was abandoned. After an initial stabilisation period of 10 minutes, end-tidal CO_2 was kept stable and data were again recorded for 20 minutes. $PaCO_2$ was measured at the middle of this stable phase. Infusion rates of vasoactive drugs were not changed and body temperature was kept stable throughout the study period. After CO_2-reactivity testing had been completed, $PaCO_2$ was slowly adjusted to the level that the responsible physician deemed appropriate.

Assessment of cerebrospinal compensatory reserve

Classically, three parts of the intracranial pressure-volume curve are described [14]: a flat part at lower intracerebral volumes, where good compensatory reserve is found, i.e. ICP remains low and stable despite changes in intracranial volume. The curve then bends rapidly upwards, acquiring an exponentially rising shape. This part of the curve represents low compensatory reserve, i.e. ICP increases considerably even with relatively small increases in intracerebral volume. Finally, at high levels of ICP, the curve bends to the right, denoting terminal disturbance in cerebrovascular responses, when cerebral perfusion pressures are too low. The cerebral arterial bed cannot dilate any more and starts to collapse due to the further increase in ICP, therefore the system 'gains' some extra buffering capacity previously occupied by arterial blood volume. This third part of the pressure-volume curve has been confirmed experimentally [10, 14] and also observed clinically, although only indirectly by observations of changes in amplitude of the ICP pulse waveform [6, 20] (Fig. 1). The three parts of the pressure-volume curve can be identified by determining cerebrospinal compensatory reserve using an index, R_{ap}, calculated as the moving correlation coefficient between the amplitude of the fundamental harmonic of the ICP pulse wave and mean ICP [6]. Possible values of R_{ap} range from -1 to $+1$. This index makes use of the fact that the amplitude of the ICP waveform increases with mean ICP, at first slowly and, as compensatory reserve decreases, more rapidly towards 1. In the flat part of the pressure-volume curve R_{ap} is approximately 0. In the exponentially rising part of the curve R_{ap} increases and eventually reaches a value of 1. With very high ICP values (>25 mmHg) R_{ap} may become negative, representing the third part of the pressure-volume curve. This indicates completely exhausted cerebrospinal compensatory reserve with deranged cerebrovascular responses, i.e. blood vessels are maximally dilated. Here values near -1 may be found. Within the range of ICP found in the described group of patients, decreasing values of R_{ap} represent increasing intracranial cerebrospinal compensatory reserve i.e. a shift of a patients 'working point' downwards along the intracranial pressure-volume curve. In our previous studies we demonstrated that coincidence of high ICP (>25 mmHg) and low R_{ap} (<0.6) was a strong predictor of fatal outcome [6] and R_{ap} showed loss of further vasodilatatory capacity on top of plateau waves [7].

Data processing and statistical analysis

Data were recorded continuously as averaged 6-second values using the analogue output of the monitors, analogue-digital conversion, and waveform time integration [28]. After digitisation, data were stored on a portable computer for off-line data analysis. For the final analysis all values were averaged for the 20-minute baseline and the 20-minute hyperventilation phase. Flow velocity data for both hemispheres were averaged. CO_2-reactivity was calculated as the relative (%) change in flow velocity per kPa change in $PaCO_2$, whereas ICP reductions were calculated as absolute change (mmHg) per kPa change in $PaCO_2$. All data are presented as mean $\pm$ standard deviation. Data were analysed using paired T-tests and multiple linear regression methods. P values

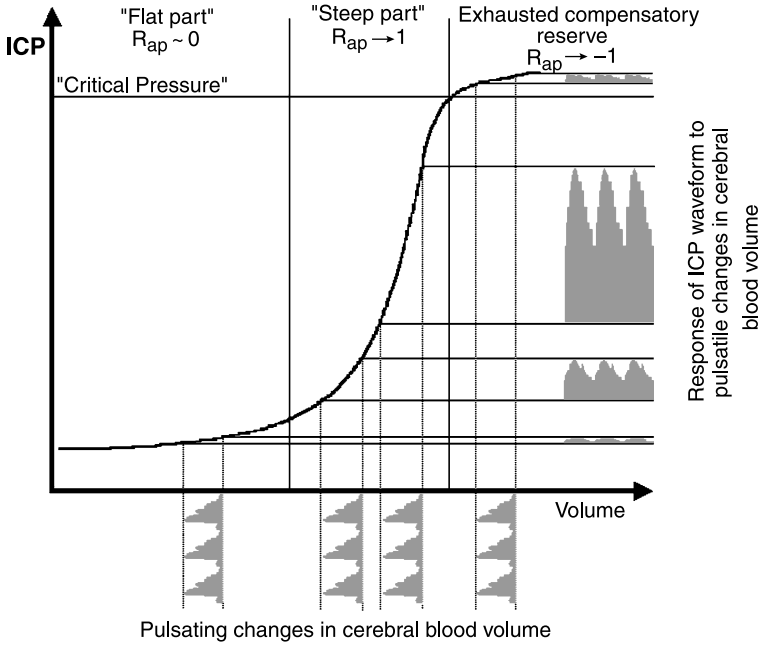

Fig. 1. Intracranial pressure-volume curve. *ICP* Intracranial pressure. R_{ap} Index of cerebrospinal compensatory reserve. Illustration of the intracranial pressure-volume curve and the relationship between pulsating changes in cerebral blood volume and the ICP waveform. Adapted from [1, 14]

<0.05 were considered to represent statistical significance. Calculations were performed using SPSS 11 for Windows (SPSS Inc, Chicago, IL, USA).

Results

We investigated 30 head injured patients (age: 38 ± 15 years, 5 women, 25 men, median admission GCS 5.5, range 3–12), 1 to 12 days after injury (median: day 3). The CT scans showed diffuse injury I, II and III in 4, 11, and 3 patients respectively. Non-evacuated mass lesions were present in 2 and evacuated mass lesions in 10 patients [17]. In one patient the study had to be abandoned because SJO_2 fell below 55% at a $PaCO_2$ of 4.2 kPa, however on a second attempt one day later the physiological parameters stayed within the limits of the treatment guidelines and data from this study was included. Hyperventilation reduced $PaCO_2$ from 5.1 ± 0.36 to 4.4 ± 0.35 kPa ($p < 0.0001$). Only four patients were hyperventilated to a $PaCO_2$ <4.0 kPa, the lowest $PaCO_2$ reached was 3.67 kPa. CO_2-reactivity was $28.7 \pm 18.0\% \cdot kPa^{-1}$. An overview of hyperventilation-induced changes in the measured variables is presented in Table 1.

Table 1. *Haemodynamic variables*

	Baseline	Hyperventilation	p
$PaCO_2$ (kPa)	5.07 ± 0.37	4.38 ± 0.36	<0.0001
ABP (mmHg)	97 ± 9	100 ± 12	0.08
ICP (mmHg)	17 ± 7	14 ± 7	<0.0001
CPP (mmHg)	80 ± 9	86 ± 12	0.0004
FVm ($cm \cdot sec^{-1}$)	77.7 ± 29.3	61.6 ± 28.8	<0.0001
R_{ap}	0.38 ± 0.35	0.22 ± 0.32	0.002

Data are presented as mean ± SD. Comparisons were performed with paired T-Tests. *$PaCO_2$* Arterial partial pressure of CO_2; *ABP* arterial blood pressure; *ICP* intracranial pressure; *CPP* cerebral perfusion pressure; R_{ap} index of cerebrospinal compensatory reserve.

Baseline ICP ranged from 6 to 33 mmHg, R_{ap} from −0.34 to 0.95. There were no patients with evidence of exhausted cerebrospinal compensatory reserve (ICP >25 mmHg and R_{ap} near −1). ICP reductions ranged from 0.3 to 23.3 $mmHg \cdot kPa^{-1}$ (6.0 ± 5.5 $mmHg \cdot kPa^{-1}$). Hyperventilation significantly reduced R_{ap} (0.38 ± 0.35 vs. 0.23 ± 0.32 $p < 0.002$), indicating the expected increase in cerebrospinal compensatory reserve and downwards shift of the patient along the pressure-volume curve (Fig. 2). The hyperventilation-induced reduction in ICP ($mmHg \cdot kPa^{-1}$) showed a significant correlation with baseline ICP and baseline R_{ap} (Fig. 3). There was no significant correlation with admission GCS, baseline $PaCO_2$, baseline CPP or baseline flow velocity. The CT class had no effect on the observed response of ICP. A multiple linear regression model, incorporating baseline $PaCO_2$, ICP, and R_{ap}, identified baseline R_{ap} as the strongest predictor of the achievable ICP reduction:

$$\text{ICP} - \text{reduction} = 2.9 - \text{PaCO}_2 + (0.3 \cdot \text{ICP}) + (8.2 \cdot \text{R}_{ap})$$

(All parameters measured at baseline; for ICP: $t = 2.6$, $p = 0.02$ and for R_{ap}: $t = 3.7$, $p = 0.001$). Interestingly our data suggest that the time-point at which the measurements were made may influence the predictive power of ICP and R_{ap}. When only data acquired during the first two days after injury ($n = 14$) were considered there was no significant correlation between ICP and the

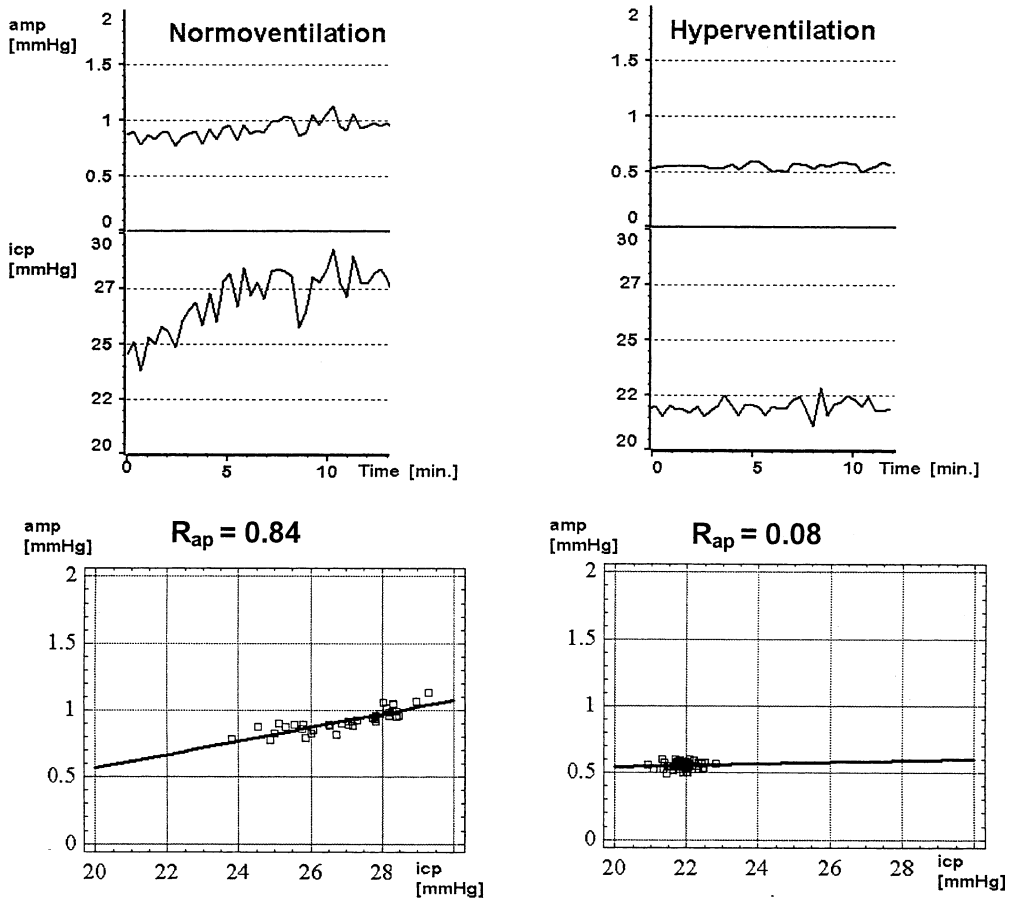

Fig. 2. Determination of cerebrospinal compensatory reserve (R_{ap}). *amp* Amplitude of the fundamental harmonic of the ICP pressure wave; *icp* intracranial pressure. Data shown from one patient: R_{ap} is calculated as the linear correlation coefficient between mean ICP and ICP amplitude. Low values represent good cerebrospinal compensatory reserve whereas values rising towards +1 indicate reduced reserve. Hyperventilation results in an improvement of cerebrospinal compensatory reserve

achievable ICP-reduction yet the correlation between R_{ap} and ICP-reduction remained significant ($p = 0.01$, $r^2 = 0.40$). In contrast when data for the days 3–12 ($n = 16$) were analysed the correlations were significant for both parameters (ICP: $p = 0.001$, $r^2 = 0.57$, R_{ap}: $p = 0.01$, $r^2 = 0.37$).

Discussion

We describe a model for the prediction of hyperventilation-induced reductions in ICP and have found that the best predictor is the patients' cerebrospinal compensatory reserve calculated by ICP waveform analysis. However, our model is limited to patients on the first and second part of the pressure-volume curve. We have included patients from the complete clinical range of ICP including normal ICP in order to validate the model also for values of R_{ap} in the range of zero, which can not only be found with low ICP but also after craniectomy or after CSF drainage. Because there were no patients with exhausted cerebrospinal compensatory reserve and terminal disturbance in cerebrovascular responses (third part of the pressure-volume curve) in the studied group of patients we cannot make any prediction on ICP reductions in patients with exhausted cerebrospinal compensatory reserve. Further prospective testing of the proposed model will be necessary, specifically targeting patients with exhausted possibilities of medical ICP therapy where a $PaCO_2$ reduction must be weighed against therapies such as barbiturates or craniectomy. It is possible to speculate that the fact that ICP is not a predictor of ICP-reduction early after trauma is due to effects of ''secondary intracranial hypertension'' [23] although ICP in the two groups is not significantly different. However, our data do not allow drawing any conclusions. It is important to remember that the number of investigated patients in each subgroup is small and the probability of type 1 and type 2 errors

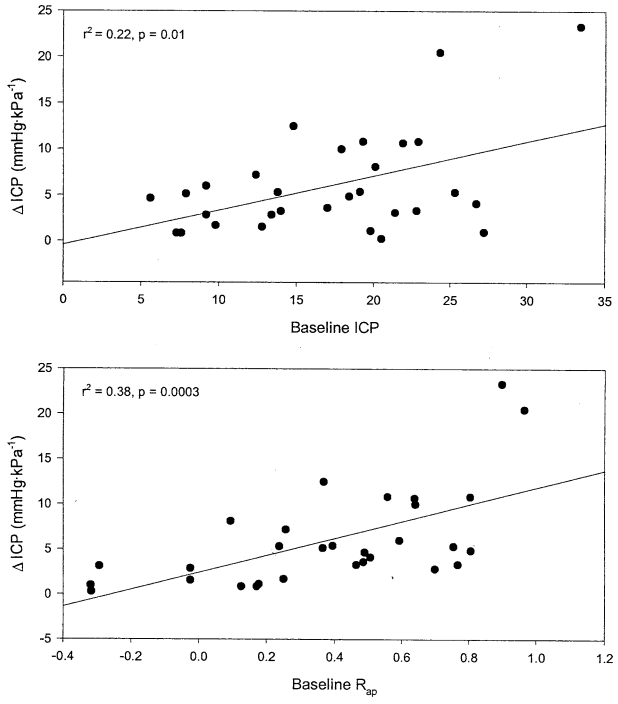

Fig. 3. Predicting the ICP-response to hyperventilation. *ICP* Intracranial pressure, R_{ap} index of cerebrospinal compensatory reserve. ICP and R_{ap} are both significantly associated with ICP reduction. Multiple linear regression confirms R_{ap} to be the better predictor than ICP

increases. Further prospective studies are needed to confirm this observation.

Our model is based on measurements made with intraparenchymal strain-gauge ICP monitors. This is not the gold-standard of ICP measurement [2] and the limitations of our approach must be addressed. The main drawback of the ICP monitor we used is the potential for zero drift, which would possibly affect the model because baseline ICP may be incorrect. While we cannot exclude this, the used device has been compared clinically against intraventricular catheters by several independent investigators [9, 11] and was found to be accurate and stable and was rated as a reliable alternative to a ventriculostomy for monitoring ICP [9]. The drift that may have affected our baseline ICP is likely to have been small ($0.3\,\mathrm{mmHg}\cdot\mathrm{day}^{-1}$ [11]) and as our studies were performed 3.6 ± 2.6 days after injury unlikely to have significantly influenced the validity of our model. In contrast, the intraparenchymal sensor has been shown to produce a less damped waveform than the intraventricular catheter [11], which may be an advantage when an index derived from the amplitude of the ICP signal is calculated. However, we cannot exclude that our data might have been more reliable if it had been based on intraventricular ICP values.

A further limitation is that R_{ap} depends on a closed intracranial space for accurate calculation. It is unclear how R_{ap} would be affected by an open intraventricular drain. A closed or blocked catheter is acceptable, provided there is no excessive damping of the ICP waveform as R_{ap} depends on a reasonable fidelity of the transmitted ICP curve. The model we propose should still be valid after CSF has been drained to control ICP. Removal of (incompressible) CSF will reduce ICP and shift the patient to a lower working-point on his or her pressure-volume curve leading to a decrease in R_{ap}, which is in agreement with our model. However, this will need to be tested prospectively. Finally, R_{ap} is a global parameter, and despite the fact that in most head injured patients there are no relevant regional differences in ICP, interhemispherical pressure gradients have been reported [21] and in these cases, it is unknown how R_{ap} will be affected.

In theory, the reduction in ICP equals the change in CBV divided by intracranial compliance. But as compliance is dependent on ICP, in fact, a full analysis of the pressure-volume curve, or use of formulas developed by Marmarou *et al.* [15] are necessary to assess the denominator of this equation. Moreover, measurement of the hyperventilation-induced change in CBV is not possible at the bedside. Prediction or indirect estimation of the change in CBV [27] is also difficult as it will depend not only on the magnitude of the change in $PaCO_2$ but also on CO_2-reactivity, which is disturbed to varying degrees after head injury. On the other hand, it is possible to measure intracerebral compliance by injecting small boluses of saline into the cerebrospinal fluid space or by withdrawing small amounts of cerebrospinal fluid [18]. Alternatively, the recently introduced Spiegelberg Compliance Monitor (Spiegelberg GmbH & Co KG, Hamburg, Germany) could be used, but there are some limitations to these methods. Bolus injections into the cerebrospinal fluid space necessitate direct access to the cerebral ventricles. With contemporary intraparenchymal ICP monitors intraventricular drainage is not always used, particularly in patients with small or effaced ventricles. Similarly, the original Spiegelberg Compliance Monitor can only be used if the ventricles are accessible. An intraparenchymal version of this compliance monitor has been developed; however, preliminary results showed a poor correlation with values obtained from intraventricular readings [26]. Finally, intracranial compliance seems to be influenced by cerebral perfusion pressure and the status of autoregulation [10]. Because of these limitations we have decided to use an index

based on readily available data that can be extracted from the ICP waveform, rather than absolute values of intracranial compliance. R_{ap} is not identical with intracranial compliance or the pressure volume index but rather describes the position of the intracranial systems' 'working point' on the patients' pressure-volume curve and further work is needed to compare R_{ap} against the Spiegelberg compliance monitor.

Clinical implications

Baseline ICP was identified as a relevant predictor of the decrease in ICP following induction of hyperventilation; however, as can be seen in Fig. 3, there is a group of patients with ICP >20 mmHg that shows only a very limited ICP reduction. This is not surprising as, despite the fact that in head injured patients ICP and intracranial compliance have been shown to be related by an inverse relationship [25], there are exceptions to this rule. For example, a recent study found that episodes of raised ICP >20 mmHg were only associated with reduced compliance in 40%, whereas episodes of low compliance were associated with ICP >20 mmHg in 44% [13]. The relationship between intracranial compliance and ICP is further influenced by the age of the patient. It has been shown that, for a given ICP, children have a higher compliance than patients in their thirties who again have a higher compliance than patients in their seventies [13].

In patients with high ICP and a R_{ap} close to 1, hyperventilation will efficiently lower ICP, whereas patients with high ICP and low R_{ap} are unlikely to show a considerable decrease in ICP. Therefore, using R_{ap}, it is possible to identify patients who will need large reductions in $PaCO_2$ to achieve the desired ICP-reduction and, depending on baseline $PaCO_2$, patients that would need a $PaCO_2$ below recommended thresholds to achieve the desired ICP reduction. In these patients, other treatment strategies should be considered to treat raised ICP. The fact that baseline $PaCO_2$ has no predictive value was expected as the effects of CO_2 on the vessels are independent of baseline $PaCO_2$ in the investigated range of partial pressures [24]. Further possible applications of the predictive value of R_{ap} are situations where ICP is still normal but R_{ap} is rising indicating developing brain swelling. Here $PaCO_2$ could perhaps be reduced to prevent a rise in ICP. Alternatively, it may be possible to predict which patients will tolerate an increase in $PaCO_2$ in order to minimise periods of low $PaCO_2$ or to decide whether a patient will tolerate the increase in $PaCO_2$ that occurs when weaning from mechanical ventilation is started. However, these scenarios need to be tested in prospective studies.

In summary, R_{ap} may be a useful index of cerebrospinal compensatory reserve to improve patient selection and intensity of manipulations of $PaCO_2$ to control raised ICP in head injured patients. Further prospective testing of our model will be necessary, targeting patients with exhausted possibilities of medical ICP therapy where the risk of hyperventilation-induced ischaemia must be weighed against therapies such as barbiturates or craniectomy.

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Comment

This manuscript describes efforts by the investigators to develop a model of intracranial physiology which would predict the response of intracranial hypertension to the treatment with moderate hyperventilaton. In one sense, hyperventilation is one of the simplest treatments that we have for management of intracranial hypertension. The response depends on the ability of the brain's vessels to respond to change in pCO_2. Since this reactivity to pCO_2 can be impaired after injury, the actual change in flow and volume induced by the change in pCO_2 can vary significantly. Another factor that can alter the response to hyperventilation is the compliance of the brain, which can also be altered by injury. When the brain is stiff, even small changes in intracranial volume can dramatically change ICP.

The final model developed by the investigators, based on baseline pCO_2 and ICP and on R_{ap}, then would seem consistent with what might be expected from the physiology involved in the process. The study described in the manuscript is carefully done, and documented in detail. The authors appropriately discuss the major limitations of the study.

The ultimate question of how useful this model will be in guiding treatments will need additional study. It might be argued that hyperventilation is such a simple treatment to apply that a trial of hyperventilation might be worthwhile in all patients who need treatment of intracranial hypertension. But perhaps the knowledge of the likelihood that hyperventilation would be successful might alter the priority that hyperventilation might play in the treatment of an individual patient.

One final characteristic of hyperventilation as a treatment of intracranial hypertension which was not addressed by this model is the rather transient nature of the effect of hyperventilation on the brain's circulation. I am not sure that hyperventilation is important to the way that we currently manage intracranial hypertension.

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