Changes in Cerebral Compartmental Compliances during Mild Hypocapnia in Patients with Traumatic Brain Injury

Emmanuel Carrera,¹ Luzius A. Steiner,³ Gianluca Castellani,¹ Peter Smielewski,¹ Christian Zweifel,¹ Christina Haubrich,¹ John D. Pickard,¹ David K. Menon,² and Marek Czosnyka¹

Abstract

The benefit of induced hyperventilation for intracranial pressure (ICP) control after severe traumatic brain injury (TBI) is controversial. In this study, we investigated the impact of early and sustained hyperventilation on compliances of the cerebral arteries and of the cerebrospinal (CSF) compartment during mild hyperventilation in severe TBI patients. We included 27 severe TBI patients (mean 39.5 ± 3.4 years, 6 women) in whom an increase in ventilation (20% increase in respiratory minute volume) was performed during 50 min as part of a standard clinical CO₂ reactivity test. Using a new mathematical model, cerebral arterial compliance (Ca) and CSF compartment compliance (Ci) were calculated based on the analysis of ICP, arterial blood pressure, and cerebral blood flow velocity waveforms. Hyperventilation initially induced a reduction in ICP (17.5 ± 6.6 vs. 13.9 ± 6.2 mmHg; $p < 0.001$), which correlated with an increase in Ci ($r^2 = 0.213$; $p = 0.015$). Concomitantly, the reduction in cerebral blood flow velocities (CBFV, 74.6 ± 27.0 vs. 62.9 ± 22.9 cm/sec; $p < 0.001$) marginally correlated with the reduction in Ca ($r^2 = 0.209$; $p = 0.017$). During sustained hyperventilation, ICP increased (13.9 ± 6.2 vs. 15.3 ± 6.4 mmHg; $p < 0.001$), which correlated with a reduction in Ci ($r^2 = 0.297$; $p = 0.003$), but no significant changes in Ca were found during that period. The early reduction in Ca persisted irrespective of the duration of hyperventilation, which may contribute to the lack of clinical benefit of hyperventilation after TBI. Further studies are needed to determine whether monitoring of arterial and CSF compartment compliances may detect and prevent an adverse ischemic event during hyperventilation.

Keywords: blood flow; brain trauma; cerebrospinal fluid; CBF autoregulation

Introduction

ACCORDING TO THE MONRO-KELLIE DOCTRINE, the skull and vertebral column define a rigid and incompressible space. Within this compartment, three distinct components may be identified: the brain and spinal cord tissue (approximately 70% of the total volume), the cerebrospinal fluid (CSF, 15%), and blood and extracellular fluid (15%). An increase in one volume must be compensated by a decrease in the volume of one or both of the other compartments (Mokri, 2001). The modern concept of relationship between volume and pressure within and between these different compartments has been established by Marmarou and colleagues (1975, 1978), and used to defined the intracerebral and cerebral arterial compliances as, respectively, the ability of the intracerebral and

arterial compartment to accommodate an increase in cerebrospinal fluid (CSF) volume or cerebral arterial blood volume (CaBV) without a significant increase in intracranial pressure (ICP) or arterial blood pressure (ABP). The compliance of the CSF compartment is traditionally presented as its ability to distend following increase in ICP, a relationship that is visualized by the slope of the pressure-volume curve (Marmarou et al., 1975). In clinical practice, because volume loading of the craniospinal system is usually required to assess the volume pressure relationship, continuous monitoring of cerebral compartmental compliances is not easily performed at the bedside. To address this issue, Avezaat and Van Eijndhoven (1984) have established, in animals, a continuous estimation of cerebral compliances using changes in amplitude of cerebral blood volume and arterial blood pressure.

¹Academic Neurosurgery Unit, Department of Clinical Neurosciences, ²Department of Anaesthesia, Addenbrooke's Hospital, University of Cambridge, Cambridge, United Kingdom.

³Department of Anaesthesia, University Hospital, Lausanne, Switzerland.

More recently, this model has been adapted in humans using waveform analysis of ICP, ABP, and cerebral blood flow velocities (CBFV) (Carrera et al., 2010a; Kim et al., 2009). Based on this model, the cerebral arterial compliance (Ca) was shown to be significantly reduced during hypocapnia in healthy volunteers (Carrera et al., 2010b). During plateau waves of ICP in traumatic brain injury patients (TBI), a reduction of the compliance of the CSF compartment (Ci) and an increase in Ca due to intrinsic vasodilatation were observed (Kim et al., 2009). Schematically, a decrease in arterial compliance corresponded to a reduced ability of the arterial bed to compensate for added cerebral arterial blood volume and an increased CSF compartment compliance corresponded to an increased ability to compensate for added volume.

According to the guidelines of the Brain Trauma Foundation, moderate hyperventilation targeting an arterial partial pressure of CO₂ (PaCO₂) between 28 and 32 mmHg is one of the therapeutic strategies to manage elevated ICP in patients with TBI (Bratton et al., 2007). However, the physiological and clinical benefits of moderate hypocapnia remain controversial, limiting its use in clinical practice (Marion and Spiegel, 2000). Various physiological parameters have been studied to determine the hemodynamic changes following hyperventilation and to investigate the lack of clinical benefit despite a reduction in ICP. These hyperventilation-induced ICP reductions are the consequence of reductions in CBV. However, the reductions in vessel caliber that reduce CBV also consistently produce a significant reduction in cerebral blood flow, leading to tissue ischemia (Kety and Schmidt, 1948; Petruk et al., 1974; Reivich, 1964). Focusing on the study of intracranial compliances, we hypothesized that hyperventilation induces a reduction in Ca during hypocapnia, which is related to an increase in arterial vascular tone and an increase in Ci related to the decrease in CBV.

In the present study, we sought to investigate the course of compartmental compliances during mild hyperventilation in severe TBI. For this purpose, changes in Ca and Ci were determined using continuous monitoring of ABP, ICP, and CBFV waveforms and compared with changes in ICP and CBFV during hyperventilation obtained as part of routine CO₂ reactivity testing.

Methods

Patients

We prospectively collected data in 27 patients (39.5 ± 3.4 years; 6 women) with severe TBI (Glasgow coma score ≤ 8) admitted to the Addenbrooke's Neurosciences Critical Care Unit who benefited from routine CO₂ reactivity testing to aid prognostic stratification. Exclusion criteria included respiratory failure, baseline CO₂ < 33 mmHg, and failure to obtain transcranial Doppler signals. This population has been previously described while focusing on different topics (Steiner et al., 2004, 2005). The study was approved by the local ethics committee.

Management and monitoring

During the study, all patients were intubated, sedated with propofol (2–5 mg/kg/h iv) and fentanyl (1–2 μ g/kg/h iv), and paralyzed with iv atracurium. All patients were treated according to a cerebral perfusion pressure–orientated protocol to maintain cerebral perfusion pressure above 70 mmHg

and ICP below 25 mmHg. There was no change in therapeutic strategy throughout the study period. ABP was measured invasively with a 21 SWG catheter inserted in the radial artery. ICP was monitored using an intraparenchymal probe (Codman MicroSensors ICP Transducer, Codman & Shurtleff, Raynham, MA). CBFV of the middle cerebral artery (MCA) was measured using transcranial Doppler (Multi Dop X4, DWL Elektronische Systeme, Sipplingen, Germany). The two 2-MHz probes were held in place with a Lam head rack. CBFV from both hemispheres were averaged. End-tidal CO₂ (EtCO₂) was monitored using mainstream capnography (Marquette solar 8000 M; Medelco, Boynton Beach, FL). Data were monitored and recorded continuously using the analogue output of the monitor, analog-to-digital conversion, and waveform time integration. Data were then analyzed using the ICM+ software (Smielewski et al., 2005).

Intervention

After recording baseline data for 20 min and determining baseline physiological variables, the minute volume of the ventilator was increased by 15–20%. If this intervention induced a PaCO₂ < 26 mmHg and/or a jugular bulb saturation $< 55\%$, hyperventilation was immediately stopped. After an initial “stabilization period” of 10 min, the EtCO₂ was maintained for at least 50 min at this level (“stable hyperventilation period”). EtCO₂ values were validated by comparison with PaCO₂ values determined by arterial blood gas analysis at the beginning and at the end of the stable hyperventilation period.

Data analysis

Definition and calculation of the compartmental compliances. We defined the *CSF compartmental compliance* (Ci) as the ratio between the pulsatile amplitudes of CaBV (as described below) and ICP; and the *cerebral arterial compliance* (Ca) as the ratio between the pulsatile amplitudes of CaBV and ABP.

The calculation of the amplitude of ICP, ABP, and CaBV was performed using the fundamental harmonic of the Fourier transformation. For comparison among patients, the normalized values of Ca (CaN) and Ci (CiN) were also determined by comparison with baseline values.

Calculation of the cerebral arterial blood volume. The cerebral arterial blood volume was calculated using a model recently reported (Carrera et al., 2010a, 2010b; Kim et al., 2009) and fully described in the Appendix. In summary, this model is based on the assumption that the change in intravascular volume over one cardiac cycle corresponds to the difference between arterial inflow and venous outflow (Avezaat et al., 1979). Then, assuming that the cross-sectional area of the insonated artery remains constant and that since the venous outflow has a low pulsatility compared to arterial inflow (Aaslid et al., 1991), the time integral of the difference between the pulsatile CBFV and the time-averaged mean CBFV produces a new pulsatile signal of CaBV.

Statistical analysis

Time course of the physiological parameters and compartmental compliances. We first determined ABP, ICP, CBFV, and compartmental compliances (Ci, Ca) at four time-

TABLE 1. BASELINE CHARACTERISTICS OF PATIENTS ($n = 27$)

Age (yr)	39.5 $\pm$ 3.4
Gender (women)	6 (16%)
Glasgow Coma Scale	5 [3–8]
<i>Physiological variables</i>	
ICP (mmHg)	17.5 $\pm$ 6.6
ABP (mmHg)	96.6 $\pm$ 9.4
CPP (mmHg)	79.2 $\pm$ 7.7
PaCO ₂ (mmHg)	38.4 $\pm$ 0.5

Values are expressed as mean $\pm$ standard deviation, n (%), and median [interquartile range].

points: at baseline (T1), after early hyperventilation (T2), after 20 min (T3), and 50 min (T4) of sustained hyperventilation. To evaluate the effect of early and sustained hyperventilation, we respectively compared physiological parameters and indices between T2 and T1 (early hyperventilation vs. baseline) and between T4 and T2 (late vs. early hyperventilation) using the Wilcoxon sign-rank test. Additionally, we compared physiological parameters and indices between T4 and T1 (late hyperventilation vs. baseline) to determine the effect of sustained hyperventilation using the Wilcoxon sign-rank test.

Correlation between ICP, CBFV, and compartmental compliances. The relationship between changes in ICP and CBFV (as a surrogate of cerebral blood flow) and changes in CiN and CaN were determined during the phase of early hyperventilation (T2 vs. T1) and during the phase of sustained hyperventilation T4 vs. T2. An inverse correlation was considered based on the shape of the pressure volume previously described (Marmarou et al., 1975). To test the relationship between the different parameters, we built a linear regression model with changes in mean ICP as the dependent variable and changes in Ca and in Ci as the independent variables. This analysis was performed for changes in these parameters between T2 and T1 and repeated for changes between T4 and T2. All calculations were performed using SPSS 15.0 for Window (SPSS, Chicago, IL). The significance level was set at 0.05 (two-tailed).

Results

Patients

The baseline characteristics of the 27 severe traumatic brain injury patients included in this study are summarized in Table 1. An example of the evolution of physiological parameters and compartmental compliances is presented in Figure 1. The evolution of the different physiological measures and compartmental compliances at baseline and at the three time-points during hyperventilation are presented in Figure 2 and compared in Table 2.

Early hyperventilation

During early hyperventilation (time-points T1 vs. T2), there was a significant reduction in ICP (17.5 $\pm$ 6.6 vs. 13.9 $\pm$ 6.2 mmHg; $p < 0.001$) and CBFV (74.6 $\pm$ 27.0 vs. 62.9 $\pm$ 22.9 cm/sec; $p < 0.001$). The study of compartmental compliances showed an increase in CiN (+25.4 $\pm$ 29.2%; $p < 0.001$) during early hyperventilation, whereas CaN decreased significantly (-14.0 $\pm$ 12.4%; $p < 0.001$). Furthermore, during early hyper-

ventilation, the reduction in ICP was inversely correlated with the changes in CiN ($r^2 = 0.213$; $p = 0.015$; Fig. 3A) but not with the changes in CaN ($r^2 = 0.082$; $p = 0.15$). On the contrary, the reduction in CBFV was only marginally and inversely correlated with the changes in CaN ($r^2 = 0.209$; $p = 0.017$; Fig. 3B) but not with the changes in CiN ($r^2 = 0.010$; $p = 0.6$). The result of the linear regression analysis showed that between T2 and T1 (baseline) changes in ICP were significantly associated with changes in Ci ($p < 0.001$) and in Ca ($p = 0.027$).

Sustained hyperventilation

During sustained hyperventilation (time-points T2 vs. T4), there was a significant increase in ICP (13.9 $\pm$ 6.2 vs. 15.3 $\pm$ 6.4 mmHg; $p < 0.001$) without a significant change in CBFV (62.9 $\pm$ 22.9 vs. 61.7 $\pm$ 27.6 cm/sec; $p = 0.3$). The study of compartmental compliances showed changes neither in CiN (1.4 $\pm$ 18.8%; $p = 0.6$) nor in CaN (+2.8 $\pm$ 13.8%; $p = 1.0$). However, during sustained hyperventilation, the increase in ICP was inversely correlated with the changes in CiN ($r^2 = 0.297$; $p = 0.003$; Fig. 4) but not with the changes in CaN ($r^2 = 0.034$; $p = 0.4$). Compared to baseline (T4 vs. T1), the study of compartmental compliances showed an increase in CiN (+26.8 $\pm$ 3.2; $p < 0.001$) and a reduction in CaN (-11.3 $\pm$ 19.6%; $p < 0.001$). The result of the linear regression analysis showed that between T4 and T2 changes in ICP were significantly associated with changes in Ci ($p = 0.005$) but not in Ca ($p = 0.44$).

Discussion

In this study, we showed, using a new mathematical model, that even a mild decrease in PaCO₂ induces a reduction in cerebral arterial compliance and an increase in CSF compliance. The decrease in ICP induced by hypocapnia was correlated with the changes in CSF compliance during all stages of hyperventilation, whereas changes in CBFV used as a surrogate marker of cerebral blood flow were correlated with cerebral arterial compliance changes only during the first stage of hyperventilation.

In the current study focusing on intracerebral compliances, we investigated the relationship between pressures and volumes during hyperventilation. The statistically significant correlation between changes in ICP and Ci suggest that the reduction in ICP during the early stage of hyperventilation is the consequence of the decrease in cerebral arterial blood volume leading to an increase in the compliance of the CSF compartment. At the arterial level, the hypocapnia-induced vasoconstriction (Valdúez et al., 1997) may be responsible for the increase in arterial vascular tone and for the significant reduction in cerebral arterial compliance. However, we were not able to find a link between the arterial and CSF compartment as no significant correlation was found between changes in ICP and changes in Ca nor between Ci and changes in CBFV, used as a surrogate of cerebral blood flow.

Our results may help to understand the lack of clinical benefit of hyperventilation. In the early phase, the reduction of ICP and the increase in CSF compliance are counterbalanced by the decrease in CBF and cerebral arterial compliance. When acute hyperventilation is induced, brain alkalosis is responsible for a rapid arterial vasoconstriction affecting mostly the resistance vessels—distal arterioles and capillaries (Atkinson et al., 1990) leading to reduction in

FIG. 1. Example of Ca and Ci changes during hyperventilation in an 18-year-old woman with severe traumatic brain injury (GCS 7).

cerebral blood flow, cerebral blood volume, and intracranial pressure (Ainslie and Duffin, 2009). The physiological mechanisms involved in the effects of hypocapnia are not fully understood. However, a constant finding is the direct relationship between the increase in cerebrovascular tone and the increase in cerebrovascular smooth muscle calcium levels, which are modulated by different mechanisms including changes in the activity of potassium channels (Kitazono et al., 1995), nitric oxide (Faraci and Brian, 1994), cyclic nucleotides, and prostaglandins (Eriksson et al., 1983). Recent studies have emphasized on the role of ATP-dependent K⁺ and voltage-gated K channels, which may be regulated by changes in pH, leading to endothelial cell hypopolarization and in turn to an opening of voltage-gated Ca²⁺ channels and a increase in intracellular Ca²⁺ (Kitazono et al., 1995). During sustained hyperventilation, brain extracellular pH recovers almost at baseline due to a reduction of the bicarbonate level. However, the persistent low Ca, despite a reincrease in ICP in our study, may suggest that both cerebral compartmental compliances, however linked mathematically, describe separate phenomena related to intravascular and parenchymal buffering capacities. Whereas Ca may reflect changes in CBF in the arterial compartment, changes in Ci may reflect changes in compli-

ance in vascular compartment inaccessible to TCD monitoring, possibly the venous circulation and CSF compartment jointly (Bradac et al., 1976). New imaging techniques have recently been developed and may be useful in the future to assess the compliance of this intracranial compartment (Alperin et al., 2005). Clinically, the consequence of a persistent low cerebral arterial compliance during sustained hyperventilation may be potentially harmful, since hyperventilation may decrease the hemodynamic reserve and potentially aggravate ischemia, for instance, clinical reduction in CPP and potential clinical deterioration, even with a decrease in ICP value and increased CSF compliance.

Several physiological parameters and indices have been evaluated to measure hemodynamic changes during hyperventilation and hypocapnia in healthy volunteers and in traumatic brain injury (Cold et al., 1981; Czosnyka et al., 2008; Newell et al., 1996; Piechnik et al., 1999; Steiner et al., 2005). However, compared with these previously described parameters, the new mathematical model used in the present study allows continuous monitoring of the compliance of the arterial and CSF compartments. Using waveform analysis of the different physiological signals opens new perspectives in the understanding of brain physiology. Further studies are

FIG. 2. Evolution of physiological parameters during hyperventilation in 27 patients. MABP, mean arterial blood pressure; ICP, intracranial pressure; CBFV, cerebral blood flow velocity; CiN, compliance of the CSF compartment (normalized data); CaN, compliance of the arterial compartment (normalized data). *T1 (baseline) and T2 values are significantly different ($p < 0.05$). #T4 (sustained hyperventilation) and T2 values (early hyperventilation) are significantly different ($p < 0.05$).

needed to determine whether continuous monitoring of compartmental compliances may be helpful to monitor hyperventilation in the treatment of elevated ICP.

Several limitations deserve attention. Firstly, regarding the methodology used to calculate CBV: we postulate that the diameter of the MCA was constant during changes in PaCO_2 . Our assumption is based on ultrasound (Poulin and Robbins, 1996), angiographic (Huber and Handa, 1967), and MRI (Valdúez et al., 1997) studies showing that changes in MCA

diameter are limited and not significantly affected by changes in PaCO_2 . A potential decrease in MCA diameter would even increase the impact of hypocapnia on Ca since the calculation of CaBV is based on the measure of CBFV and not CBF. In the model, we used the measure of the CBFV in the MCA, since this artery is responsible for the blood supply of most of the hemisphere parenchyma. Simultaneous evaluation of other arteries (e.g., the anterior and posterior cerebral arteries) may provide a better estimation of cerebral compliances of the

TABLE 2. EFFECT OF HYPERVENTILATION ON PHYSIOLOGICAL VARIABLES AND INDICES

	<i>Baseline (T1)</i>		<i>Early hyperventilation (T2)</i>		<i>Sustained hyperventilation (T4)</i>		<i>P value T2 vs. T1</i>	<i>P value T4 vs. T2</i>	<i>P value T4 vs. T1</i>
Mean values									
ABP (mmHg)	96.6	±9.4	98.5	±10.9	99.7	±12.7	0.1	0.6	0.09
ICP (mmHg)	17.5	±6.6	13.9	±6.2	15.3	±6.4	<0.001	<0.001	<0.001
CBFV (cm/sec)	74.6	±27.0	62.9	±22.9	61.7	±21.6	<0.001	0.3	<0.001
Amplitudes									
AMP _{ABP} (mmHg)	22.0	±5.8	21.6	±5.7	21.7	±6.1	0.7	0.6	0.7
AMP _{ICP} (mmHg)	2.0	±1.7	1.5	±1.6	1.5	±1.7	<0.001	0.9	<0.001
AMP _{CaBV}	3.0	±1.3	2.5	±1.2	2.5	±1.2	<0.001	0.1	<0.001
Compliances									
Ca	0.14	±0.04	0.12	±0.04	0.12	±0.04	<0.001	0.4	0.002
CaN (%)	100	–	86.1	±12.4	88.8	±19.6	<0.001	0.6	<0.001
Ci	2.2	±1.5	2.8	±2.2	2.9	±2.1	<0.001	0.9	<0.001
CiN (%)	100	–	125.4	±29.2	126.8	±30.2	<0.001	1.0	<0.001

ABP, arterial blood pressure; ICP, intracranial pressure; CaBV, cerebral arterial blood volume; CBFV, cerebral blood flow velocity; AMP, amplitude; Ca, arterial compliance; CaN, arterial compliance (normalized values); Ci, CSF compartment compliance; CiN, CSF compartment compliance (normalized values). Values are presented as mean ± SD.

FIG. 3. Correlation between CiN and ICP changes ($r^2 = 0.213$; $p = 0.015$) (A) and between CaN and CBFV changes ($r^2 = 0.209$; $p = 0.017$) (B) during early hyperventilation.

whole brain. We made the second assumption of our model (low pulsatility of the venous of CBFV) based on previous studies, which demonstrated that the pulsatility of the venous CBFV is very low compared to the arterial CBFV, especially when the pulsatility is estimated at the level of the venous sinus. Residual pulsation of the venous system may be mainly consequent of concomitant arterial pulsations (Schaller, 2004). Second, we did not validate our model with other established techniques. Recent developments in imaging techniques may be used in future studies to compare our continuous and dynamic measure of compliance with the anatomic dimension provided by MRI (Alperin et al., 2005; Tain and Alperin, 2009). Validation of the methods using an experimental model may also be of value. Third, the value of ABP recorded at the level of the radial artery is only an estimation of cerebral ABP; however, it is currently the gold standard for monitoring of

FIG. 4. Correlation between CiN and ICP changes during sustained hyperventilation ($r^2 = 0.297$; $p = 0.003$).

systemic arterial blood pressure. Finally, we cannot exclude that the effect of vasopressors (noradrenaline), used in some of our patients, may have modified the ABP, ICP, and CBFV signal waveforms as previously described (Wilkinson et al., 2001; Yura et al., 1995). However, when used, the dose and type of vasopressors were never modified during the hypocapnia reactivity testing, limiting their impact on the calculation of the changes in compliances.

In this study, we showed that sustained moderate hyperventilation induced a reincrease in ICP but also a persistent decrease in Ca, suggesting that sustained hyperventilation may potentially aggravate ischemia. Further studies are needed to study the role of Ca and Ci in the monitoring and prevention of ischemic events during hyperventilation for treatment of elevated ICP. In particular, comparison with imaging techniques assessing regional hemodynamics such as 15O-Positron Emission Tomography or Xenon CT may help understand the role of the compartmental compliances measured using our new mathematical model during the acute phase after traumatic brain injury.

Acknowledgment

This work was supported by the Swiss National Science Foundation (PASSMP3-124262 to E.C., and PBBSP3-125550 to C.Z.) and the National Institute of Health Research, United Kingdom.

Author Disclosure Statement

The software for brain monitoring ICM+ (www.neurosurg.cam.ac.uk/icmplplus) is licensed by the University of Cambridge (Cambridge Enterprise). We (P.S. and M.C.) have a financial interest in a part of the licensing fee.

APPENDIX. CALCULATIONS OF CEREBRAL ARTERIAL BLOOD VOLUME—MATHEMATICAL METHODS

Cerebral arterial blood volume (CaBV) was calculated from CBFV according to the method first described by Avezaat and Eijndhoven (1984) with respect to the carotid artery magnetoflowmetry signal.

The change in cerebral blood volume over one cardiac cycle corresponds to the difference between arterial inflow and venous outflow. This can be calculated using the following equation:

$$CBV(\tau) = \int_{\tau=0}^{\tau} (CBFa(t) - CBFv(t))dt \quad (1)$$

where CBV(t) is cerebral blood volume, CBFa(t) is cerebral arterial blood flow, CBFv(t) is cerebral venous blood outflow, and all are expressed as functions of time.

Assuming that the cross-sectional area of the insonated artery remains constant, the above equation can be rewritten as a discrete time difference equation in terms of flow velocity CBFV:

$$(n) = \sum_{i=m}^n [CBFVa(i) \cdot S_a - CBFVv(i)] \Delta t(i) \quad (2)$$

where Δt is the sampling interval, CBFVa(t) is cerebral arterial blood flow velocity, CBFVv(t) is cerebral venous blood flow velocity, and S_a and S_v are the cross-sectional areas of arteries and veins, respectively, at the flow measurement points.

We further assume that since the venous outflow (CBFVv) has a low pulsatility compared with arterial inflow (Aaslid et al., 1991) with negligible changes over the cardiac cycle, it may be approximated by a constant flow equal to averaged arterial inflow (CBFVa):

$$S_v \cdot CBFVv(n) = \text{mean}(CBVa) \cdot S_a \quad (3)$$

where $\text{mean}(CBVa)$ is a time-averaging function of cerebral arterial blood flow velocity.

Thus, the pulsatile cerebral arterial blood volume (CaBV) can be expressed as:

$$CaBV(n) = \sum_{i=m}^n [CBFVa(i) - \text{mean}(CBVa)] \quad (4)$$

A Fourier transformation of CaBV allows calculation of the amplitude of the CaBV (AMP_{CaBV}) as an amplitude of the fundamental harmonic.

References

- Aaslid, R., Newell, D.W., Stooss, R., Sorteberg, W., and Lindgaard, K.F. (1991). Assessment of cerebral autoregulation dynamics from simultaneous arterial and venous transcranial Doppler recordings in humans. *Stroke* 22, 1148–1154.
- Ainslie, P.N., and Duffin, J. (2009). Integration of cerebrovascular CO₂ reactivity and chemoreflex control of breathing: mechanisms of regulation, measurement, and interpretation. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 296, R1473–1495.
- Alperin, N., Lee, S.H., Sivaramakrishnan, A., and Hushek, S.G. (2005). Quantifying the effect of posture on intracranial physiology in humans by MRI flow studies. *J. Magn. Reson. Imaging* 22, 591–596.
- Atkinson, J.L., Anderson, R.E., and Sundt, T.M., Jr. (1990). The effect of carbon dioxide on the diameter of brain capillaries. *Brain Res.* 517, 333–340.
- Avezaat, C.J., and van Eijndhoven, J.H. (1984). Cerebrospinal fluid pulse pressure, in: *Cerebrospinal Fluid Pulse Pressure and Craniospinal Dynamics*. C.J. Avezaat and J.H. van Eijndhoven (eds), Decor Davids: Amsterdam, pps. 57–69.
- Avezaat, C.J., van Eijndhoven, J.H., and Wyper, D.J. (1979). Cerebrospinal fluid pulse pressure and intracranial volume-pressure relationships. *J. Neurol. Neurosurg. Psychiatry* 42, 687–700.
- Bradac, G.B., Simon, R.S., and Heidsieck, C.H. (1976). Angiographically verified transient alteration of the intracranial arteries and veins in dependence of different CO₂ tensions. *Neuroradiology* 10, 257–262.
- Bratton, S.L., Chestnut, R.M., Ghajar, J., McConnell Hammond, F.F., Harris, O.A., Hartl, R., Manley, G.T., Nemecek, A., Newell, D.W., Rosenthal, G., Schouten, J., Shutter, L., Timmons, S.D., Ullman, J.S., Videtta, W., Wilberger, J.E., and Wright, D.W. (2007). Guidelines for the management of severe traumatic brain injury. XIV. Hyperventilation. *J. Neurotrauma* 24, Suppl. 1, S87–90.
- Carrera, E., Kim, D.J., Castellani, G., Zweifel, C., Czosnyka, Z., Kasparowicz, M., Smielewski, P., Pickard, J.D., and Czosnyka,

- M. (2010a). What shapes pulse amplitude of intracranial pressure? *J. Neurotrauma* 27, 317–324.
- Carrera, E., Kim, D.J., Castellani, G., Zweifel, C., Smielewski, P., Pickard, J.D., and Czosnyka, M. (2010b). Effect of hyper and hypocapnia on cerebral arterial compliance in normal subjects. *J. Neuroimaging* (In press)
- Cold, G.E., Christensen, M.S., and Schmidt, K. (1981). Effect of two levels of induced hypocapnia on cerebral autoregulation in the acute phase of head injury coma. *Acta Anaesthesiol. Scand.* 25, 397–401.
- Czosnyka, M., Smielewski, P., Lavinio, A., Pickard, J.D., and Panerai, R. (2008). An assessment of dynamic autoregulation from spontaneous fluctuations of cerebral blood flow velocity: a comparison of two models, index of autoregulation and mean flow index. *Anesth. Analg.* 106, 234–239.
- Eriksson, S., Hagenfeldt, L., Law, D., Patrono, C., Pinca, E., and Wennmalm, A. (1983). Effect of prostaglandin synthesis inhibitors on basal and carbon dioxide stimulated cerebral blood flow in man. *Acta Physiol. Scand.* 117, 203–211.
- Faraci, F.M., and Brian, J.E., Jr. (1994). Nitric oxide and the cerebral circulation. *Stroke* 25, 692–703.
- Huber, P., and Handa, J. (1967). Effect of contrast material, hypercapnia, hyperventilation, hypertonic glucose and papaverine on the diameter of the cerebral arteries. *Angiographic determination in man. Invest. Radiol.* 2, 17–32.
- Kety, S.S., and Schmidt, C.F. (1948). The effects of altered arterial tensions of carbon dioxide and oxygen on cerebral blood flow and cerebral oxygen consumption of normal young men. *J. Clin. Invest.* 27, 484–492.
- Kim, D.J., Kaspruwicz, M., Carrera, E., Castellani, G., Zweifel, C., Lavinio, A., Smielewski, P., Sutcliffe, M.P., Pickard, J.D., and Czosnyka, M. (2009). The monitoring of relative changes in compartmental compliances of brain. *Physiol. Meas.* 30, 647–659.
- Kitazono, T., Faraci, F.M., Taguchi, H., and Heistad, D.D. (1995). Role of potassium channels in cerebral blood vessels. *Stroke* 26, 1713–1723.
- Marion, D.W., and Spiegel, T.P. (2000). Changes in the management of severe traumatic brain injury: 1991–1997. *Crit. Care. Med.* 28, 16–18.
- Marmarou, A., Shulman, K., and LaMorgese, J. (1975). Compartmental analysis of compliance and outflow resistance of the cerebrospinal fluid system. *J. Neurosurg.* 43, 523–534.
- Marmarou, A., Shulman, K., and Rosende, R.M. (1978). A non-linear analysis of the cerebrospinal fluid system and intracranial pressure dynamics. *J. Neurosurg.* 48, 332–344.
- Mokri, B. (2001). The Monro-Kellie hypothesis: applications in CSF volume depletion. *Neurology* 56, 1746–1748.
- Newell, D.W., Weber, J.P., Watson, R., Aaslid, R., and Winn, H.R. (1996). Effect of transient moderate hyperventilation on dynamic cerebral autoregulation after severe head injury. *Neurosurgery* 39, 35–43; discussion, 4.
- Petruk, K.C., Weir, B.K., Overton, T.R., Marriott, M.R., and Grace, M.G. (1974). The effect of graded hypocapnia and hypercapnia on regional cerebral blood flow and cerebral vessel caliber in the rhesus monkey: study of cerebral hemodynamics following subarachnoid hemorrhage and traumatic internal carotid spasm. *Stroke* 5, 230–236.
- Piechnik, S.K., Yang, X., Czosnyka, M., Smielewski, P., Fletcher, S.H., Jones, A.L., and Pickard, J.D. (1999). The continuous assessment of cerebrovascular reactivity: a validation of the method in healthy volunteers. *Anesth. Analg.* 89, 944–949.
- Poulin, M.J., and Robbins, P.A. (1996). Indexes of flow and cross-sectional area of the middle cerebral artery using doppler ultrasound during hypoxia and hypercapnia in humans. *Stroke* 27, 2244–2250.
- Reivich, M. (1964). Arterial Pco₂ and cerebral hemodynamics. *Am. J. Physiol.* 206, 25–35.
- Schaller, B. (2004). Physiology of cerebral venous blood flow: from experimental data in animals to normal function in humans. *Brain Res. Brain Res. Rev.* 46, 243–260.
- Smielewski, P., Czosnyka, M., Steiner, L., Belestri, M., Piechnik, S., and Pickard, J.D. (2005). ICM+: software for on-line analysis of bedside monitoring data after severe head trauma. *Acta Neurochir. Suppl.* 95, 43–49.
- Steiner, L.A., Balestreri, M., Johnston, A.J., Coles, J.P., Chatfield, D.A., Pickard, J.D., Menon, D.K., and Czosnyka, M. (2005). Effects of moderate hyperventilation on cerebrovascular pressure-reactivity after head injury. *Acta Neurochir. Suppl.* 95, 17–20.
- Steiner, L.A., Balestreri, M., Johnston, A.J., Czosnyka, M., Coles, J.P., Chatfield, D.A., Smielewski, P., Pickard, J.D., and Menon, D.K. (2004). Sustained moderate reductions in arterial CO₂ after brain trauma time-course of cerebral blood flow velocity and intracranial pressure. *Intensive Care Med.* 30, 2180–2187.
- Tain, R.W., and Alperin, N. (2009). Noninvasive intracranial compliance from MRI-based measurements of transcranial blood and CSF flows: indirect versus direct approach. *IEEE Trans. Biomed. Eng.* 56, 544–551.
- Valdúeza, J.M., Balzer, J.O., Villringer, A., Vogl, T.J., Kutter, R., and Einhaupl, K.M. (1997). Changes in blood flow velocity and diameter of the middle cerebral artery during hyperventilation: assessment with MR and transcranial Doppler sonography. *Am. J. Neuroradiol.* 18, 1929–1934.
- Wilkinson, I.B., MacCallum, H., Hupperetz, P.C., van Thoor, C.J., Cockcroft, J.R., and Webb, D.J. (2001). Changes in the derived central pressure waveform and pulse pressure in response to angiotensin II and noradrenaline in man. *J. Physiol.* 530, 541–550.
- Yura, T., Yuasa, S., Fukunaga, M., Badr, K.F., and Matsuo, H. (1995). Role for Doppler ultrasound in the assessment of renal circulation: effects of dopamine and dobutamine on renal hemodynamics in humans. *Nephron* 71, 168–175.

Address correspondence to:

Emmanuel Carrera, M.D.

Department of Clinical Neurosciences

Level 4, A Block

Addenbrooke's Hospital

Cambridge CB2 2QQ

United Kingdom

E-mail: emmanuel.carrera@chuv.ch