Continuous Monitoring of the Monro-Kellie Doctrine: Is It Possible?

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Abstract

The Monro-Kellie doctrine describes the principle of homeostatic intracerebral volume regulation, which stipulates that the total volume of the parenchyma, cerebrospinal fluid, and blood remains constant. Hypothetically, a slow shift (e.g., brain edema development) in the irregular vasomotion-driven exchanges of these compartmental volumes may lead to increased intracranial hypertension. To evaluate this paradigm in a clinical setting and measure the processes involved in the regulation of systemic intracranial volume, we quantified cerebral blood flow velocity (CBFv) in the middle cerebral artery, arterial blood pressure (ABP), and intracranial pressure (ICP), in 238 brain-injured subjects. Relative changes in compartmental compliances C_a (arterial) and C_i (combined venous and CSF compartments) were mathematically estimated using these raw signals through time series analysis; C_a and C_i were used to compute an index of cerebral compliance (ICC) as a moving correlation coefficient between C_a and C_i . Conceptually, a negative ICC would represent a functional Monro-Kellie doctrine by illustrating volumetric compensations between C_a and C_i . Clinical observations show that Lundberg A-waves and arterial hypertension were associated with negative ICC, whereas in refractory intracranial hypertension, a positive ICC was observed. In subjects who died, ICC was significantly greater than in survivors (0.46 ± 0.027 versus 0.22 ± 0.017 ; $p < 0.01$) over the first 5 days of intensive care. The mortality rate is 5% when ICC is less than 0, and 43% when above 0.7. ICC above 0.7 was associated with terminally elevated ICP (chi-square $p = 0.026$). We propose that the Monro-Kellie doctrine can be monitored in real time to illustrate the state of intracranial volume regulation.

Key words: cerebral blood volume; cerebral compliance; compensatory mechanism; CSF compartment; traumatic brain injury; vascular compartment

Introduction

THE CENTRAL NERVOUS SYSTEM can be divided into three compartments composed mainly of incompressible liquids: blood (arterial and venous), parenchyma (intracellular and extracellular), and cerebrospinal fluid (CSF). In adults, all components are contained within a rigid skull or semi-rigid structures surrounding the lumbar dural sac. The fast exchanges of compartmental volumes, ranging from seconds to a few minutes, mainly involve blood and CSF, which are responsible for slow vasogenic waves observed in intracranial pressure (ICP; Newell et al., 1997). Volumetric changes in the brain parenchyma usually take longer to develop (Ito et al.,

1990). Changes in volume of blood and CSF, assessed with corresponding changes in intracranial and arterial blood pressures, allow us to estimate the compartmental compliances of the brain.

Previous studies of cerebral compliance have used various techniques: systemic blood and cerebral perfusion pressure (CPP; Gray and Rosner, 1987a, 1987b), the pressure volume index (Marmarou et al., 1978) or the volume pressure response (Maset et al., 1987; Miller and Garibi, 1972); the Spiegelberg monitor (Piper et al., 1999); magnetic resonance imaging (MRI; Alperi et al., 2005; Baledent et al., 2006), and the combination of ICP, arterial blood pressure (ABP), and transcranial Doppler (TCD) ultrasonography (Kim et al.,

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2009b). Separate compartmentalization of brain compliance into venous/CSF and arterial compliances is a relatively new concept (Alperin et al., 2005; Kim et al., 2009b).

The total volume of the skull and lumbar sac does not stay absolutely constant within one cardiac cycle. However, it remains constant over a longer period of time, according to the Monro-Kellie doctrine (Greitz et al., 1992; Neff and Subramaniam, 1996), where an increase in the volume of one compartment is compensated for by a decrease in the volume of another. Intracranial hypertension occurs when such mutual intercompartmental volume compensation fails to occur. The interplay between compartmental compliances may be divided into the overall compliance of the arterial system (C_a , high-pressure compartment), and the compliance of the CSF space and venous system (C_i , low-pressure compartment). Combining the compliances of the CSF and the venous blood compartment is theoretically acceptable because intracerebral venous pressure follows ICP (Osterholm, 1970). Relative changes in compliances $C_a\%$ and $C_i\%$ can be monitored continuously over time. Previously we described reciprocal changes of these compliances during plateau waves (Kim et al., 2009b), and in inducing moderate hypocapnia (Carrera et al., 2011). We hypothesised that an average increase in $C_a\%$, causing a decrease in $C_i\%$ or vice-versa, would reflect the physiologic state of a system when the Monro-Kellie doctrine is applied. Using an observational study in a clinical setting, we evaluated an index of cerebral compliance (ICC, a moving correlation coefficient between C_a and C_i), and proposed that a positive ICC would reflect conditions in which both compartmental volumes increase, indicating a disturbance of the Monro-Kellie doctrine.

The objective of this study was to evaluate the ICC in a cohort of subjects with traumatic brain injury (TBI), and to observe its computational behavior during typical pathological events (arterial hypo- and hypertension, plateau waves in ICP, and refractory hypertension). In addition, we sought to analyze the relationship between ICC and clinical outcome after TBI.

Methods

Clinical data and outcome

This study was performed using data derived from an anonymized database of digitally recorded clinical signals. The data were prospectively recorded from routine clinical multimodality monitoring and audit of subjects in the Neuro Critical Care Unit of Addenbrookes Hospital, Cambridge, U.K. The use of the data for research was approved by the local ethics board and the multidisciplinary Neuro Critical Care Users Group; the need for individual consent was waived in accordance with institutional regulations.

Recordings from 238 consecutive subjects with continuous arterial blood pressure (ABP), ICP, and intermittent TCD monitoring, and with known outcomes, were analyzed. Between 1992 and 2003, clinical management used CPP- and ICP-controlled protocols (Patel et al., 2002). The target CPP was above 65–70 mm Hg, and ICP was intended to be kept below 25 mm Hg. In cases of intracranial hypertension, the subjects were managed with an increase of ventilation volume to achieve mild hypocapnia ($Paco_2$ range 28–35 mm Hg), moderate hypothermia, boluses of mannitol (200 mL of 20%, over a period of 2 min or longer), and thiopentone. To avoid

systemic hypotension, ABP was maintained by fluid loading and vasoactive drugs (e.g., dopamine 2–15 $\mu\text{g kg}^{-1}\text{min}^{-1}$ and/or norepinephrine 0.5 $\mu\text{g kg}^{-1}\text{min}^{-1}$). TCD examination after TBI was performed daily in subjects without craniectomy, since mounting of the TCD probe holder in these subjects was not feasible. In addition, in a few patients ($n=7$) with extra-ventricular drainage, recordings were done with drainage closed 30 min before, provided ICP did not increase above 20 mm Hg during this period; otherwise recording was aborted.

Data acquisition and computations

ICP was measured by using micro-transducers (Codman MicroSensor; Johnson & Johnson Professional, Rynham, MA or Camino Direct Pressure Monitor; Camino Laboratories, San Diego, CA), inserted in the parenchyma of the frontal region (Gopinath et al., 1993; Koskinen and Olivecrona, 2005; Luerssen and Vos, 1989; Marmarou and Dunbar, 1994). ABP was measured directly from a peripheral artery (System 8000; S&W Vickers Ltd., Sidcup, U.K. or Solar 6000 System; Solar, Marquette, MI).

The blood flow velocity was measured from the middle cerebral artery (MCA) using TCD ipsilateral to the ICP device, for a period ranging from 10 min to 2 h, starting from the day of admission. The middle cerebral artery carries nearly 70% of the supratentorial cerebral blood inflow to each hemisphere (Kirkpatrick et al., 1996). The M1 segment of the middle cerebral artery was insonated daily to estimate the blood flow velocity during steady-state periods; these intervention-free periods were remote from medication or transfusion delivery or changes in mechanical ventilation in order to assess the underlying status of autoregulation (Czosnyka et al., 2001). The duration of continuous application of TCD probes is limited by the following factors: the need to minimize side effects associated with the examination, and the need to record valid measurements. Measurements were performed following standard safety regulations applied to ultrasound use in human subjects (ALARA principles), while minimizing the effects of the application of the probes directly on the skin (indentation, skin abrasion, and/or burn). The headset used to hold the probes placed over the temporal window allows for repeated measurements within a subject to be performed in similar conditions. The depth of insonation was between 40 and 60 mm. Signals were recorded when respiratory parameters were stable and there was no physiotherapy, tracheal suction, or other disturbances. TCD recordings were performed and collected for up to 7 days for each patient. We used the PCDop 842 Doppler Ultrasound Unit (Scimed, Bristol, U.K.) or Neuroguard (Medasonics, Fremont, CA) with their respective headsets.

Signals from the pressure monitors (ABP and ICP), the TCD unit (maximal frequency envelope), and analogue outputs (e.g., ICP, ABP, and CBFv) were sampled and digitized using analogue-to-digital converters (DT 2814; Data Translation, Marlboro, MA), which were connected to an IBM laptop computer (Amstrad ALT 386 SX). A 50-Hz sampling frequency was used to record the signal samples using custom software (WREC, W. Zabolotny, Warsaw University of Technology). The data recorded were then analyzed off-line using ICM+ (Neurosurgery Unit, University of Cambridge, <http://www.neurosurg.cam.ac.uk/icmplus>) and Matlab (The MathWorks, Natick, MA) software.

MCA blood flow velocity signals were transformed to pulsatile cerebral arterial blood volume (CaBV) divided by the cross-sectional area of the insonated artery (S_a). Blood volume is calculated by time integration of the difference between the instant value of blood flow velocity and time-averaged flow velocity (over 10 to 12 heart beat cycles; for details see Appendix). The absolute serum osmolality or arterial carbon dioxide tension were not integrated in the model; the aim of the recordings was to estimate the state of auto-regulation, which would reflect the underlying exposure to therapeutic management delivered in the periods of care before the recording. Then the amplitudes of fundamental components of pulse waves of CaBV/ S_a , ABP, and ICP were calculated using Fourier transformations. Dividing the amplitude of blood inflow volumes by the amplitude of corresponding pressures, which are responsible for the observed volume change (amplitude of ABP or ICP), variables expressing changes in compartmental compliances can be evaluated (Kim et al., 2009b):

$$\frac{AMP_{CaBV}}{AMP_{ABP}} = \frac{C_a}{S_a} \quad \frac{AMP_{CaBV}}{AMP_{ICP}} = \frac{C_i}{S_a} \quad ([Eq.1])$$

where C_a represents compliance of the arterial blood component, and C_i represents combined compliance of the venous blood and CSF compartment. The latter compliance is mainly associated with the extensible lumbar subarachnoid space (Alperin et al., 2005).

Because the cross-sectional area of the insonated artery (S_a) is not known, the cerebral arterial blood volume (CaBV) cannot be expressed in absolute units. Calculated variables are useful for monitoring the variation of compartmental compliances within a subject over time, and may not be suitable for making comparisons between subjects. Formally, the right-hand side of the formulas given above indicates compliances per unit of cross-sectional area of insonated vessel. They can be expressed as a percentage change of the initial value, and are denoted in Figures 1 and 2 as $C_{a\%}$ and $C_{i\%}$.

Calculation of $C_{a\%}$ and $C_{i\%}$ was repeated every 10 sec. The ICC was calculated as a Pearson correlation coefficient between consecutive $C_{a\%}$ and $C_{i\%}$ samples from a 4-min period (amounting to 24 data points). In this way ICC is calculated every 10 sec with the current and the 23 previous $C_{a\%}$ and $C_{i\%}$ values used to obtain ICC values over time.

A negative value of ICC signifies that $C_{a\%}$ and $C_{i\%}$ change in an inverse direction, which hypothetically indicates that the Monro-Kellie doctrine's principle applies. Close to zero ICC indicates a situation in which mutually inverse changes in compartmental compliances cannot be detected, which hypothetically suggests that the state of volume processes described by Monro-Kellie principles may not be estimated reliably. Finally, when ICC is close to +1, hypothetically the Monro-Kellie principle is not upheld. Because ICC is a coefficient with a normalized value from -1 to +1, it allows for comparison between subjects.

For the duration of each recording, ICC was observed as a time-varying index, and was also time-averaged. The recording-averaged values of ICC were averaged again over multiple recordings, performed in each patient for outcome analysis and relationships with ICP, ABP, and pressure reactivity index (PRx; Czosnyka et al., 1997b). PRx was calcu-

lated as the moving correlation coefficient between 24 consecutive 10-sec averages of mean ABP and ICP.

Clinical outcome was assessed 6 months after injury using the GOS (Jennett and Bond, 1975) in interviews of subjects or caregivers. The GOS is graded from 1–5: 1, died; 2, persistent vegetative state; 3, severe disability; 4, moderate disability; and 5, good outcome. For analytical purposes, outcome was either dichotomized as died (GOS 1) or survived (GOS 2–5), or grouped into four categories (GOS 1, GOS 2, GOS 3–4, and GOS 5).

Statistical analysis

Mean or median values and standard deviations or 95% confidence intervals of all parameters were calculated. Groups of subjects who survived or were fatally injured were compared.

Chi-square or Kruskal-Wallis tests were used to compare rates of mortality and intracranial hypertension for different ranges of ICC index. All statistical analyses were performed using SPSS statistical software (SPSS Inc., Chicago, IL; Pallet, 2001), and statistical significance was inferred at two-sided $p = 0.05$.

Results

Demographics

The baseline characteristics of the subjects are summarized in Table 1. The median age was 27 years (range 3–78, less than 6% of the sample was below age of 16). We performed the analyses with and without the pediatric (age < 16 years) sample and the results were unchanged (data not shown). Thus we analyzed based on the entire study sample. The range of GCS was 3–15 (15.5% of the subjects had GCS scores above 8, and deteriorated later needing full intensive care); 26% were female and 76% of the cohort survived. When considering the daily average ICP, 30.6% of the sample had a daily average ICP ≥ 25 mm Hg for a minimum of a day (mean 1.77 days, SD 1.23), and 50% of the sample had a daily average ICP ≥ 20 mm Hg for a minimum of a day (mean 1.93, SD 1.23).

Observations

The following specific three clinical conditions were examined in detail: arterial hypertension, plateau waves associated with sustained increases in arterial pressure, and intracranial hypertension (Figs. 1 and 2).

Pronounced hemodynamic responses were associated with major changes in cerebral blood volume, for example during episodes of transient arterial hypertension (Fig. 1a), or plateau waves of ICP (Fig. 1b).

In the case of arterial hypertension, sudden increases in ABP were associated with a decrease in ICP followed by a change in CBFv, as shown in Figure 1a. Changes in velocity influence the reduction of cerebral blood volume (see Eq. 2 in the Appendix). The spatial capacitances of the vascular ($C_{a\%}$) and CSF ($C_{i\%}$) systems change in opposite directions and are thereby capable of compensating for further abnormal physiological fluctuation. This leads ICC to be solidly negative.

During plateau waves or Lundberg A waves, changes in CBFv may be due to a substantial reduction of cerebral blood volume, which subsequently leads to the raised ICP shown in

FIG. 1. Changes of ICC, $Ca\%$, and $Ci\%$ during strong, hemodynamically-relevant stimulation: (a) Arterial hypertension due to transient change in arterial blood pressure (ABP). Changes in Ca and Ci have clearly inverse direction, index of cerebral compliance (ICC) is negative, and therefore the Monro-Kellie doctrine works. (b) Plateau wave of ICP index ICC becomes negative. This is caused by increasing Ca (vasodilation), and a further decrease in Ci (rise in intracranial pressure [ICP]; CBFVa, cerebral blood flow velocity in basal arteries).

FIG. 2. Example of rising intracranial pressure (ICP) in a subject who died of intracranial hypertension. The index of cerebral compliance (ICC) is continuously positive during uniformly rising ICP. Both C_a and C_i decrease (ABP, arterial blood pressure; CBFva, cerebral blood flow velocity in basal arteries; $C_a\%$ and $C_i\%$, compliances per unit of cross-sectional area of insonated vessel).

Fig. 1b. Although the early part of the event illustrates poor spatial capacitance due to raised ICP, the intracranial system becomes equilibrated during the plateau wave. C_a increases (vasodilatation) and C_i increases (further intracranial hypertension). We speculate that a decreasing ICC may indicate a reasonable capacity of the intracranial system to withstand abnormal physiological events thanks to the Monro-Kellie doctrine being fulfilled.

During an episode of intracranial hypertension (Fig. 2), a sustained positive ICC reflects the changes in $C_a\%$ and $C_i\%$, both decreasing with raised ICP. Hypothetically, a lack of exchange of values of compliance indicates a violation of the Monro-Kellie doctrine: the primary theoretical reason for refractory intracranial hypertension.

TABLE 1. BASELINE CHARACTERISTICS OF INCLUDED PATIENTS

Age, median years (range)	27 (3–78)
Male	74%
Glasgow Coma Scale (GCS) score	(207/238)
GCS > 8	32
GCS 5–8	106
GCS 3–4	69
Glasgow Outcome Scale (GOS) score	(238/238)
Good (G)	69
Moderate (M)	52
Severe disability (S.D.)	60 (55/5)
Dead (D)	57

Relationship between cerebral compliance, ICP, and outcome

The relationship between ICC and outcome at 6 months (Fig. 3) shows that ICC in survivors was significantly greater than in fatally-injured subjects (0.22, SD 0.017) versus 0.46 (SD 0.027; $p=0.01$).

Overall correlation of ICC with ICP, mean ABP, or CPP was not significant. However, ICC correlated significantly with PRx ($R=0.47$; $p<0.01$) (Table 2). When ICC was positive, a significant positive correlation was found between ICC and mean ICP ($R=0.65$; $p=0.001$). The incidence of intracranial hypertension (average ICP > 20 mm Hg for entire ICU stay) was 65% when ICC was greater than 0.7. When ICC was < 0.7, intracranial hypertension was seen in only 30% of subjects (chi-square test with Yates' correction, $p=0.026$).

In subjects with ICC > 0.7, the mortality rate was higher than 50%, and 19% in the remaining subjects ($p=0.006$ by chi-square test with Yates' correction). These findings are illustrated in Figure 4.

Discussion

Three intracranial compartments are involved in the pressure-volume equilibrium: brain parenchyma, cerebral vasculature, and cerebrospinal fluid space. The Monro-Kellie Doctrine (Mokri, 2001; Monro, 1783) proposes that the

FIG. 3. Distribution of index of cerebral compliance (ICC) among four different Glasgow Outcome Scale (GOS) groups (G, good outcome; M, moderate disability; S.D., severe disability; D, died). Vertical bars indicate 95% confidence intervals for means.

relationship between compartments is normally mutually balanced. The mathematical models (Czosnyka et al., 1997a; Ursino and Lodi, 1997) imply that expansion of arterial cerebral volume is compensated by decreasing the volume of the venous compartment and the expansion of the CSF compartment associated with a displacement of CSF from the cranial to the lumbar space. Our results suggest that monitoring of ICC formulated by a moving correlation coefficient between arterial and CSF + venous compliances is feasible in real time. Disrupted volume-regulating mechanisms described by the Monroe-Kellie doctrine and indicated as positive ICC lead to intracranial hypertension associated with a significantly increased mortality rate after TBI.

Technical implications

Faster brain volume regulation implies short-term volume compensation (from a few seconds to 3–5 min), and involves reciprocal changes in arterial and venous blood as well as CSF displacement. We presume that volumetric changes of the intracranial compartment are time-constant and are reasonably long (longer than hours and definitely longer than tens of minutes; Overgaard and Tweed, 1976; Pollay and Roberts, 1980).

Theoretically, the essential contribution of the fast brain volume regulation is cerebral blood volume, which is formulated by the time lag between pulsatile inflow and outflow. Conceptually, during the cardiac cycle, approximately 80% of cerebral inflow may be compensated for by venous outflow and 20% by the CSF system.

To estimate CBV, several methods are available. Phase-coded MRI (PC-MRI; Alperin et al., 2005) can inform us of

changes in CBV and is probably more precise than any other available method. However, only short-term measurement is available, and this cannot be done at the bedside in real time. A TCD-based technique is an alternative method used to obtain CBV. This technique requires additional assumptions that venous blood outflow is uniform over time and that the cross-sectional area of the insonated MCA remains constant (Alperin et al., 2005). On the other hand, TCD allows for longer monitoring times at the bedside in real time.

In this method, $C_{a\%}$ and $C_{i\%}$ are mathematically calculated using the pulse amplitude of the cerebral blood volume obtained from TCD, ABP, and ICP. Absolute values of both compliances are still unknown, as there is currently no bedside technique that makes it possible to estimate the precise areas of the insonated vessels. Therefore, $C_{a\%}$ and $C_{i\%}$ values allow for assessments of relative changes only. Phase-related changes between $C_{a\%}$ and $C_{i\%}$, as illustrated in Figures 1 and 2 are significant. A shift of 180 degrees is demonstrated specifically when the Monroe-Kellie Doctrine is followed: when one compartment expands the other decreases in volume, and vice-versa. It is important to understand that a 180° phase shift is not always equivalent to good stabilization of ICP. For example, $C_{a\%}$ and $C_{i\%}$ change in opposite directions during arterial hypertension when ICP decreases (Fig. 1a), but also during the plateau wave (Fig. 1b) when ICP increases.

ICC is a moving correlation coefficient of slow interactions between $C_{a\%}$ and $C_{i\%}$ (up to 4 min). It has a normalized value; therefore the comparison between subjects is straightforward. Negative ICC can be interpreted as evidence of a working Monroe-Kellie doctrine. It is rather unrealistic that all positive values of ICC denote a disturbed doctrine. It may be that changes in $C_{a\%}$ and $C_{i\%}$ are too small and hidden in noise formed by the nature of

FIG. 4. (a) Distribution of intracranial pressure (ICP), and (b) mortality rate over the range of observed values of index of cerebral compliance (ICC). For negative ICC, the mortality rate is 0 and mean ICP is lower than 20 mm Hg. The mortality rate increases when ICC is greater than 0.7.

the signal process. During strong intracranial hypertension ICC is often positive (Fig. 2), but it is negative during intracranial hypertension related to plateau waves of ICP (Fig. 1b).

Clinical significance

The failure of the equilibrated intracranial system may be due to the exhaustion of the physiological and physical (or spatial) compensatory mechanisms. Subjects with TBI of a space-occupying nature (e.g., extradural or/and subdural

hematoma and intracerebral abscess and edema; Frank, 1995) often develop either systemic or intracranial hypertension when the intracranial system is no longer in equilibrium. Although some subjects show ICP or CPP within desired limits, their clinical outcomes still remain suboptimal. Historically, exponential curves (Guinane, 1972,1974,1975; Marmarou, 1973; Sklar and Elashvili, 1977; Sullivan et al., 1977) are used to conceptualize the pressure-volume relationship in the intracranial system. Although it is generally accepted as a typical pressure-volume relationship, some contradictory results

TABLE 2. RELATIONSHIP BETWEEN VARIABLES (RECORDED AND CALCULATED) AND CLINICAL OUTCOMES AS ASSESSED BY THE GLASGOW OUTCOME SCALE (GOS)

Parameter	Survived (SD)	Fatal outcome (SD)	p Value
ICP (mm Hg)	18.4 (8.6)	25.3 (16)	<0.001
ABP (mm Hg)	90.4 (13)	91.1 (16)	0.81
CPP (mm Hg)	74.3 (13.5)	67.2 (20.2)	<0.001
CBFv (cm/sec)	60 (25.4)	62.6 (26.6)	0.13
PRx	0.04 (0.25)	0.29 (0.35)	<0.001
ICC	0.22 (0.36)	0.46 (0.30)	<0.001

CBFv, cerebral blood velocity at the middle cerebral artery, PRx, pressure reactivity index; ICC, index of cerebral compliance; ICP, intracranial pressure; CPP, cerebral perfusion pressure; ABP, arterial blood pressure.

are still shown in animal experiments (Burton, 1954; Davson, 1967). Several types of pressure-volume curves are probably found after TBI (Kim et al., 2009a), due to various abnormal boundary conditions, which are formed by all pathophysiological elements subject to mechanical stress of different temporal and spatial profiles in the neurological system. Examples of the boundary conditions include the compression of parenchyma due to brain swelling, hematoma, and skull fracture, and the therapeutic interference with neurophysiology due to medications, ventilation, and temperatures. Although ICP is one of the main clinical endpoints used for clinical management, it incompletely represents the status of the actual intracranial system in pathological conditions associated with the development of cerebral edema. For example, Figure 4a shows the wide range of ICC ($-0.5 < \text{ICC} < 0.7$), while ICP is around 20 mm Hg and the different ICC values correspond to the different mortality rates seen in Figure 4b. Despite similar ICPs, subjects experienced different clinical outcomes. ICC may be a complementary parameter that could provide information about the relative volumetric conditions reflecting the alterations in pressure. The clinical significance of ICC needs further clinical investigation, and we recognize that the meaning of this index may be theoretically hampered by the fact that TCD is a technique that presents challenges when used as continuous monitoring. Although this is a highly scientific-oriented study, we speculate that this parameter could potentially be relevant in clinical cases associated with therapies related to hemodynamics and CSF dynamics.

Limitations

Our current investigation was performed using prospective analyses and computation performed after the recordings were completed. Therefore, the study disallows precisely presenting the impact of therapeutic interventions associated with specific medication regimens.

Our study is focused on a proof of principle: when the Monro-Kelly doctrine does not work, we observe uncontrollable and often fatal intracranial hypertension.

Conclusion

We propose that the state of the Monro-Kellie doctrine, understood as brain volume-regulating mechanism evolving

over time, can be measured with an index of cerebral compliance. This initial clinical investigation shows that a disrupted Monro-Kellie doctrine was associated with severe intracranial hypertension and increased mortality rate after TBI.

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Author Disclosure Statement

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(Appendix follows →)

APPENDIX. DATA ANALYSIS SUPPLEMENT

Using blood flow velocity, the cerebral blood volume can be mathematically approximated. According to Avezaat and Van Eijndhoven (Avezaat and van Eijndhoven, 1984; Avezaat et al. 1979), the change of cerebral blood volume over one cardiac cycle can be formulated as an integral of the subtraction between the arterial inflow and the venous outflow:

$$\Delta CBV(\tau) = \int_{\tau_0}^{\tau} (CBFa(t) - CBFv(t)) dt \quad ([Eq.1])$$

where $\Delta CBV(\tau)$ is the change in cerebral blood volume, $CBFa(t)$ is the cerebral arterial blood flow, $CBFv(t)$ is the cerebral venous blood outflow, and all variables are expressed as functions of time (τ_0 denotes the beginning of one cardiac cycle). The volumetric flow rate of the cerebral blood can be expressed as the measured velocity multiplied by the regional cross-sectional area per unit of time. For digitally-sampled signals (represented by time series), the integral of different cerebral flows can be approximated by:

$$\Delta CBV(n) = \sum_{i=m_i}^{m_n} [CBFva(i) \cdot S_a - CBFvv(i) \cdot S_v] \cdot \Delta t(i) \quad ([Eq.2])$$

where m_n is the first sample of the heart interval, n is the number of consecutive samples, Δt is the time interval

between two consecutive samples, $CBFva(i)$ is the cerebral arterial blood flow velocity, $CBFvv(i)$ is the cerebral venous blood flow velocity, and S_a and S_v are the cross-sectional areas of arteries and veins, respectively.

Two assumptions become critical in this method: (1) The cross-sectional area of the insonated artery remains constant during the cardiac cycle (Toth et al., 2000); and (2) The low-pulsatile venous outflow can be written as an averaged arterial inflow (Avezaat and van Eijndhoven, 1984), and thus the venous outflow can be approximated by:

$$S_v \times CBFvv(n) = \text{mean}(CBFva) \times S_a \quad ([Eq.3])$$

where $\text{mean}(CBFva)$ is a time-averaged cerebral arterial blood flow velocity for a period longer than one cardiac cycle.

Under these assumptions, the pulsatile change CBV can be calculated from the cerebral artery pulsatile flow profile, assuming a constant venous outflow, and thus CBV becomes CaBV, which can be expressed as:

$$CaBV(n) = S_a \cdot \sum_{i=m_i}^{m_n} [CBFva(i) - \text{mean}(CBFva)] \cdot \Delta t(i) \quad ([Eq.4])$$

where $CaBV(n)$ is the cerebral blood volume as a function of time index n , and $CBFva(i)$ is the cerebral blood flow velocity as a function of time index i .