Intracranial Pressure: More Than a Number

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Many doctors involved in the critical care of head-injured patients understand intracranial pressure (ICP) as a number, characterizing the state of the brain pressure–volume relationships. However, the dynamics of ICP, its waveform, and secondarily derived indices portray useful information about brain homeostasis. There is circumstantial evidence that this information can be used to modify and optimize patients’ treatment. Secondary variables, such as pulse amplitude and the magnitude of slow waves, index of compensatory reserve, and pressure–reactivity index (PRx), look promising in clinical practice. The optimal cerebral perfusion pressure (CPP) derived using the PRx is a new concept that may help to avoid excessive use of vasopressors in CPP-oriented therapy. However, the use of secondary ICP indices remains to be confirmed in clinical trials.

KEY WORDS • cerebrovascular reactivity • head injury • intracranial pressure monitoring • pressure–volume compensation

Intracranial pressure is probably the most commonly monitored brain parameter in neurocritical care. The majority of the bedside monitors, including contemporary intraparenchymal transducer “boxes” (for example, the Codman Express or Sophysa Pressio) display the mean ICP numerically or its pulse waveform with an option of condensed time trends (as with the Camino ICP Monitor or Raumedic Datalogger). This may be sufficient to guide a CPP-oriented protocol31 or treat patients according to the Lund concept,1,2,3 but much valuable information regarding complex intracranial regulatory processes is lost. What is this information? Is its clinical validity proven or just suggested? Two generations of clinical neuroscientists have contributed to the fascinating subject of ICP waveform analysis. Lundberg20 taught us about various slow waves of ICP and their pathological meaning. Lang-fitt18 and Lofgren and Zwetnow19 introduced the pressure–volume curve and the term “compensatory reserve.” Other scientists32,22 laid the foundation for the clinical testing of brain compliance. Brain insults, such as short-term increases in ICP or decreases in CPP, were used as predictors of outcome after brain trauma. The pulse waveform of ICP was then used as a source of prognostic information.29 Is there any room for new concepts? Advances in multimodal bedside brain monitoring and data processing have made it possible to perform online, real-time analysis of the interdependence between the dynamic behaviors of various modalities. As information becomes more complex, it becomes notoriously difficult to detect and interpret phenomena of interest without computer bedside data analysis.33 In this review of our own observations, we attempt to highlight those phenomena and secondary ICP indices that may aid in the acute treatment of the severely head injured patient.

Clinical Material and Methods

Computer-supported bedside monitoring of ICP was introduced in Cambridge 16 years ago.12 Approximately 640 patients in a state of general anesthesia who were paralyzed and receiving ventilation have their ICP computer-recorded waveforms archived in our database. Continuous ICP recordings are supplemented by other modalities, including ABP (in all patients), blood flow velocity in the middle cerebral artery (recorded intermittently in ~ 300 patients), brain tissue oxygenation (using Neurotrend or Lycox, in ~ 90 patients), cortical laser Doppler blood flow (in 31 patients), data from brain microdialysis (in > 200 patients), and PET CBF and CMRO2 (in 55 patients). The study population included 416 male (65%) and 224 fe-

Abbreviations used in this paper: ABP = arterial blood pressure; CBF = cerebral blood flow; CMRO2 = cerebral metabolism O2 rate; CPP = cerebral perfusion pressure; ICP = intracranial pressure; PET = positron emission tomography; PRx = pressure-reactivity index; RAP = correlation between pulse amplitude and mean intracranial pressure; TBI = traumatic brain injury; TCD = trancranial Doppler.

Neurosurg. Focus / Volume 22 / May, 2007
male (35%) patients who ranged in age from 17 to 85 years (mean age 32 years). The median Glasgow Coma Scale score at admission was 6 and ranged from 3 to 13 (10% of patients had an initial Glasgow Coma Scale score > 9). Different treatment regimens and protocols were used within this period, beginning with treatment without any fixed protocol (1991–1993 in the so-called neurorehabilitation annex), then CPP-oriented therapy and mixed ICP/CPP protocol with a restricted use of vasopressors (from 2003) in a specialized 21-bed neurocritical care unit.

Results

Waveform Analysis of ICP

The ICP waveforms include three distinct quasiperiodic components: heart rate pulse, respiratory waves, and slow vasogenic waves. Although these components overlap on a background of randomly changing mean ICP, they can be isolated and quantified using spectral analysis. By definition, a frequency spectrum is a graph showing the intensity of individual phasic components plotted against their specific frequency. In the case of the ICP waveform, the area under the curve can be used to quantify the magnitude of each specific component at their characteristic range (that is, heart rate 50–180 bpm, respiratory waves 8–20 cycles/minute, and slow waves 0.3–3 cycles/minute).

The pulse waveform has a fundamental frequency equivalent to the heart rate, and several harmonic components (Fig. 1). The amplitude of the fundamental component is useful for the evaluation of various indices describing cerebrospinal dynamics. Time-domain analysis is an alternative for evaluation of the pulse waveform. It is used to calculate the peak-to-peak amplitude of ICP pulsation during one heartbeat. Both methods seem to be equivalent, as there is an excellent linear relationship between the amplitude of the fundamental component and peak-to-peak time-domain amplitude (R = 0.97 in a group analysis of 79 head-injured patients). The amplitude of the fundamental component seems to be less influenced by the presence of noise and contamination from other components (such as respiratory and slow waves), but it may be affected by an irregular heart rate.

The respiratory waveform is related to the frequency of the respiratory cycle (8–20 cycles per minute). Slow waves are usually not as precisely defined as in the original Lundberg thesis. All components that have a spectral representation within the frequency limits of 0.05 to 0.0055 Hz (20 seconds–3 minutes) can be classified as slow waves.

In group analysis, the amplitude of the fundamental component correlates with mean ICP (the correlation coefficient ranges from 0.6 to 0.7). In patients with refractory intracranial hypertension, the amplitude of the fundamental component plotted against mean ICP shows an upper breakpoint (Fig. 2) above which physiological cerebrovascular mechanisms deteriorate. This is usually associated with a decrease in cortical blood flow.

Pulse amplitude relates to outcome similarly as mean ICP, that is, the greatest mean ICP and amplitude of the fundamental component are seen in patients who died. This probably results from the proportional relationship between mean ICP and the amplitude of the fundamental component. In multivariate analysis, mean ICP rather than pulse amplitude is indicated as a variable independently correlated with outcome.

The positive relationship between the amplitude of the fundamental component and the pulse amplitude of CBF velocity is significant (R ~ 0.4, 300 patients) and seems to be stronger than the relationship between pulse wave in ABP and the amplitude of the fundamental component (R ~ 0.2). There is a significant positive correlation between the amplitude of the fundamental component and autoregulatory reserve (R ~ 0.4, 300 patients), indicating that greater pulse amplitude associates with weaker autoregulation (assessed using TCD ultrasonography). Slow waves in ICP seem to decrease in patients exhibiting refractory intracranial hypertension. A relationship between lower magnitude of slow waves and worse outcome was found to be significant in a group analysis.
Pressure–Volume Compensatory Reserve

Theoretically, the compensatory reserve can be studied through the relationship between the mean ICP and changes in volume of the intracerebral space, known as the pressure–volume curve (Fig. 3). The index called “RAP” (correlation coefficient [R] between the amplitude of the fundamental component [A] and mean pressure [P]) can be derived by calculating the linear correlation between consecutive, time-averaged (a 6–10-second averaging period is usually used) data points of the amplitude of the fundamental component and ICP (usually 40 of such samples are taken). This index indicates the degree of correlation between the amplitude of the fundamental component and the mean ICP over short periods of time (~ 4 minutes).

An RAP coefficient close to 0 indicates a lack of synchronization between changes in the amplitude of the fundamental component and mean ICP. This denotes a good pressure–volume compensatory reserve at low ICP, where a change in volume produces no or very little change of the pressure (see Fig. 3).

When the RAP increases to +1, the amplitude of the fundamental component varies directly with ICP, indicating that further deterioration when brain edema occurs (RAP becomes consistently close to +1; Fig. 4). During plateau waves, when maximal vasodilation occurs, RAP decreases from +1 to 0 or lower (Fig. 5), indicating a state of cerebrovascular deterioration.

Similarly, during refractory intracranial hypertension, switching from positive to low or negative RAP values indicates that the critical level of ICP has been exceeded. Above this threshold, normal cerebrovascular mechanisms fail and cerebral ischemia may cause irreversible brain damage (Fig. 6).

A comparison of RAP to PET-assessed CBF in a limited group of patients with TBI (22 patients, unpublished report) indicated that there was a significant correlation between CBF and the RAP index (R = 0.47, p < 0.025), suggesting that severe cerebrovascular disturbance was associated with inadequate brain perfusion.

Following successful decompressive craniotomy, a decrease in RAP (from ~ +1 to 0) indicates recovery of good compensatory reserve. In cases of closed head injury, RAP correlates positively with the width of the ventricles and negatively with the total volume of contusion. This may suggest that cerebrovascular deterioration happens more frequently when ventricles close due to brain edema or contusion occupies more space in a cranium.

It has been shown that high ICP (> 20–25 mm Hg) is associated with fatal outcome. Similarly, low average RAP is associated with worse outcome, independent of ICP.

The product of the mean ICP × (1–RAP) has been suggested to be an indicator of dangerous intracranial hypertension in head injured patients (true ICP). Indeed, the mm Hg indicates a terminal cerebrovascular disturbance with a deterioration in pulse pressure transmission from the arterial bed to the intracranial compartment.

Generally, there is no correlation between the pressure–volume index and RAP. The pressure–volume index seems to characterize the steepness of the pressure–volume curve. The RAP indicates where on the curve—that is, on its flat or rising part—the cerebrospinal system currently works (see Fig. 3).

In most head-injured patients, the RAP index indicates good compensatory reserve over a few hours after admission that further deteriorates when brain edema occurs (RAP becomes consistently close to +1; Fig. 4). During plateau waves, when maximal vasodilation occurs, RAP decreases from +1 to 0 or lower (Fig. 5), indicating a state of cerebrovascular deterioration.

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relationship of $ICP \times (1 - RAP)$ and outcome seems to be stronger than ICP and RAP alone.\textsuperscript{11}

**Cerebrovascular Pressure Reactivity**

Another ICP-derived index is the PRx, which incorporates the philosophy of assessing cerebrovascular reactions by observing the response of ICP to slow spontaneous changes in ABP.\textsuperscript{9,17,30} When the cerebrovascular bed is normally reactive, any change in ABP produces an inverse change in cerebral blood volume and hence ICP. When reactivity is disturbed, changes in ABP are passively transmitted to ICP. Using computational methods similar to those used for the calculation of the RAP index, PRx is determined by calculating the correlation coefficient between 40 consecutive, time-averaged data points of ICP and ABP. A positive PRx signifies a positive gradient of the regression line between the slow components of ABP and ICP, which we hypothesize to be associated with passive behavior of a nonreactive vascular bed (Fig. 7). A negative value of PRx reflects a normally reactive vascular bed, as ABP waves provoke inversely correlated waves in ICP.

This index correlates well ($R \approx 0.6$, 300 patients) with indices of autoregulation based on TCD ultrasonography.\textsuperscript{9} A PRx indicating poor cerebrovascular reactivity correlates with a low static rate of autoregulation assessed with PET CBF.\textsuperscript{35}

Poor reactivity correlates with low CMRO$_2$ and CBF assessed with PET studies.\textsuperscript{34} Furthermore, abnormal values of both PRx, indicating poor autoregulation and disturbed cerebrospinal pressure reactivity, have been demonstrated to be predictive of a poor outcome following head injury.\textsuperscript{4} This predictive potential, when tested using multivariate analysis, is independent of mean ICP, age, or severity of injury.\textsuperscript{3}

Like TCD-derived indices, the PRx indicates temporary loss of autoregulatory reserve on top of ICP plateau waves\textsuperscript{10} and permanent autoregulatory failure during refractory intracranial hypertension (Fig. 8).\textsuperscript{5}

The PRx conveys information about pressure reactivity as long as the pressure–volume curve has an exponentially increasing shape. Following decompressive craniotomy, the PRx deteriorates partially because the curve becomes flat due to mechanical decompression.\textsuperscript{38} The PRx is robust in neurointensive care. The ICP and arterial pressure are usually monitored continuously without measurement artifacts over a long time. Changes in PRx observed over time indicate changes in pressure reactivity and may guide the treatment of patients (Fig. 9).

Anecdotally, brain microdialysis seems to agree with pressure reactivity: a high lactate/pyruvate ratio and low cerebral glucose correlate with failing pressure reactivity (I Timofeyev et al., unpublished data).

The PRx plotted against CPP shows a U-shaped curve.\textsuperscript{25,36} This indicates that in the majority of patients
there is a value of the CPP at which pressure reactivity is optimal (Fig. 10). This optimal perfusion pressure can be estimated by plotting and analyzing the PRx-CPP curve in a sequential time-moving window.

It has been demonstrated in a group of retrospectively evaluated patients that the greater the distance between the current and the optimal CPP the worse the outcome. This potentially useful method is used in an attempt to refine CPP-oriented therapy. Both too low (ischemia) and too high CPP (hyperemia and secondary increase in ICP) are detrimental. The CPP should be optimized to maintain cerebral perfusion in the most favorable state.

There is early evidence that brain tissue oxygenation increases with increasing CPP but only until the level of the optimal CPP. A further increase in CPP does not improve tissue oxygenation (M Jaeger and M Schuhmann, unpublished data). We have observed that when CPP increases from below the optimal CPP to the optimal CPP range, $O_2$ increases and reaches a plateau. The range of optimal CPP in broad terms (negative or slightly positive PRx) is wide. Within this range one can see stable (or plateau) $O_2$, but if CPP is pushed further, to values that are associated with PRx disturbance, an increase in brain oxygenation seems to occur, probably reflecting hyperemia.

Analysis of the lactate/pyruvate ratio as a function of CPP shows the lowest ratio at optimal CPP level (I Timofeev et al., unpublished data).

**Discussion**

**Other Methods of ICP Analysis**

One of the main priorities in brain monitoring is to develop a technique that helps in predicting decompensation or herniation. Apart from the aforementioned assessment of compensatory reserve and cerebrospinal pressure reactivity, there are other methods of ICP analysis that are worthy of mention.

The authors of early work focused on intracranial volume–pressure response, which subsequently evolved into continuous monitoring of brain compliance. This method relies on the evaluation of the pressure response to known small volume additions, by inflating and deflating a balloon inserted within the cerebrospinal space. The method has been implemented in the Spiegelberg Brain Compliance monitor, and the initial trials have indicated that compliance monitoring may be useful in various scenarios. Its correlation with outcome remains to be demonstrated.

The analysis of the pulse waveform of ICP, known as the high-frequency centroid, was based on evaluation of the power spectrum of a single-pulse ICP waveform and calculation of its power-weighted average frequency within the range of 5 to 15 Hz. The high-frequency centroid was demonstrated to decrease with increasing ICP and then increase in the state of refractory intracranial hypertension where the blood flow regulation mechanism failed.

Various groups of authors have investigated the transmission between arterial pressure and mean ICP. This correlation depends on assumptions about the linearity of the transmission model. Such assumptions are probably unrealistic, particularly in pathological circumstances.

The ratio of respiratory wave to pulse amplitude of ICP was believed to be predictive of outcome after head injury. Modulation of pulse waveform by the respiratory cycle has been demonstrated to correlate with brain compliance and has been used in an attempt to make a diagnosis in patients suffering from hydrocephalus.
Intracranial pressure is a complex modality that contains combined information about cerebral compensatory and CBF regulation mechanisms. Control of ICP requires continuous monitoring and, preferably, online calculation of secondary indices. Although promising at the present stage, the practical value of these indices should be confirmed in randomized clinical trials.

Acknowledgments

We thank the following colleagues participating in head injury monitoring programs in Cambridge, UK, in 1991–2007, whose experience, knowledge, and clinical material helped us to write this review: Mrs. P. Al-Rawi, Mrs. D. Chatfield, Mrs. C. Turner, Mrs. M. Balestreri, Miss. M. Hiler, Dr. S.K. Piechnik, Dr. L.A. Steiner, Mr. P.C. Whetfield, P. Minhas, Dr. M. Soehle, Dr. R. Kett-White, Dr. E. Schmidt, Dr. B. Schmidt, Mr. A. Kumar, Mr. A. Raabe, Mr. M. Schuhmann, Mr. P. J. Kirkpatrick, Dr. F. K. Matta, Dr. A. Gupta, Professor D. K. Menon, and the nursing and research staff from the Neuro Critical Care Unit and Wolfson Brain Imaging Centre.

Disclosure

Software for brain monitoring ICM+ (www.neurosurg.cam.ac.uk/icmplus) is licensed by the University of Cambridge (Cambridge Enterprise), M. Czosnyka and P. Smielewski have a financial interest in a part of its licensing fee.

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This study was supported by Medical Research Council Grant No. G9439390, ID 65883 (to J.D.P., M.C., P.S., and P.H.). Dr. M. Czosnyka is on leave from Warsaw University of Technology, Poland.
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