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EDITORIAL (BY INVITATION)

Pressure reactivity index: journey through the past 20 years

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Abstract Autoregulation after traumatic brain injury can be monitored continuously using simple signal processing of intracranial pressure and arterial blood pressure. The pressure reactivity index (PRx) showed several benefits when it was applied to continuous brain monitoring. Among them, a positive and strong correlation with the outcome and possibility of calculation of 'optimal cerebral perfusion pressure' have been listed. For this methodology, prospective clinical trials are missing—few of them are planned in the near future.

Keywords Traumatic brain injury · Intracranial pressure · Arterial blood pressure · Optimal cerebral perfusion pressure

The pressure-reactivity index was first described in 1995. Originally, we were inspired by the presentation of Erhard Lang and Randal Chestnut during the ICRAN conference at Gold Coast, Australia (1994). They reported that they could read a state of cerebral autoregulation from relative changes in mean arterial blood pressure (ABP) and intracranial pressure (ICP). They told us that it was enough to ask a research nurse to sit in front of a bedside monitor and instruct her to observe trends of ABP and ICP. The nurse needed to report when the values were changing in the same or opposite directions. When we arrived home, we programmed our computers, running ICM (intensive care monitor) software [7], to calculate a moving correlation coefficient from 30 consecutive 10-s averages of ICP and ABP waveforms. We called this the PRx index (pressure reactivity index) [6].

The rationale for averaging ICP and ABP waveforms over 10 s was that only slow waves, of frequencies lower than 0.05 Hz, can carry information about autoregulation [11]. Simple averaging is a sufficient method of filtration of all faster components (mainly respiratory and pulsatile), which do not contain or contain only a little of any autoregulation-related signatures.

The rationale for calculating the correlation coefficient from 5-min-long buffers (30 samples of 10 s produce correlation window of 5 min) is that longer periods (e.g., 30 or 60 min) may include too many reactions to drugs, nursing-related variations, metabolic reactions, etc. They are all not related to cerebral autoregulation and would produce distortion of the PRx.

When a few years later a postgraduate student from Switzerland, Luzius Steiner (now Professor of Anaesthesiology at University of Basel), came to our Laboratory of Brain Physics in Cambridge, asking whether he could be given a PhD project on PRx, we first took it for a joke. However, over the next 3 years we were proven very wrong. Works of Luzius and other clinical neuroscientists who followed in his footsteps brought to light perhaps the most important advantage of PRx, its ability to guide the management of cerebral perfusion pressure. The concept was so simple to understand and so appealing in the clinical setting that many more people than we initially anticipated embraced it enthusiastically and developed it further.

After 20 years, summarizing the milestone discoveries associated with PRx is tempting:

– PRx strongly and independently correlates with outcome after TBI [18].

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- Change of PRx from zero or a negative value to positive values (>0.3) is associated with a gold standard lower breakpoint of Lassen's curve (lower limit of autoregulation) in experimental settings [3].
- PRx correlates positively with traditional indices of autoregulation, measured with transcranial Doppler ultrasonography [4].
- PRx plotted against CPP shows a U-shaped curve, whose minimum is theoretically associated with the best state of autoregulation. This value was termed the 'optimal CPP' [19].
- Pressures lower than 'optimal CPP' are associated with increased mortality after TBI, and those above 'optimal CPP' have a greater rate of severe disability. At CPP close to the 'optimal CPP,' the rate of good/moderate disability shows a significant peak [1].
- PRx reacts to changes in ICP, showing deterioration of autoregulation with rising ICP, which potentially allows for establishing an individual threshold for detrimental ICP [15].
- PRx can be estimated noninvasively using near infrared spectroscopy. Total hemoglobin or hemoglobin volume correlated with ABP (with the same time averaging and correlating scales as for PRx), producing noninvasive equivalents of PRx: THx and HVx [16, 20]. They allow calculation of 'optimal ABP,' so far used in cardiac surgery [2] and brain protection of preterm neonates [8].
- PRx can also be estimated from 1-min averaged ABP and ICP signals as the so-called long PRx. It has a different (lower) clinical prediction power [14], but for calculation of 'optimal CPP' it seems to be useful [9].
- High ICP and/or low CPP insults of higher magnitude and duration can be better tolerated by an injured brain in the presence of preserved PRx [12].

Apart from its good points, PRx and its related methodologies suffer from several weaknesses, which should be kept in mind to interpret this index correctly:

- PRx cannot provide physiological information if there are no detectable coherent slow waves in ABP and ICP. Fortunately, such a situation is extremely rare.
- It is a noisy parameter. Without strong hemodynamic excitations (like incidental arterial hypotension or hypertension, etc.), it should be averaged in time (minimum 30 min of averaging is essential!).
- Its reliability can be improved at the cost of the complexity of calculations and interpretation, but only marginally. A good example is the recently proposed 'wavelet PRx' [17].
- Reliable 'optimal CPP' calculations require a sufficiently large span of CPP change, which may not be captured using fixed, relatively short (4-h) data periods. Fortunately, methods employing variable data periods have been recently proposed, which may help to overcome this problem [9].
- It has been demonstrated that 'optimal CPP' and 'optimal ABP' could potentially be calculated even from two uncorrelated noise series. However, the probability of such false positives is small and insignificant when real ABP and ICP measurements are used, where physiological information prevails consistently over the 'noise factor.'

We read a recent paper from Prof. Martin Schuhmann's group [13] with great interest. It describes thresholds of PRx in pediatric post-TBI brain monitoring and analyzes their association with outcome. Time spent with impaired autoregulation as compared to time with good autoregulation seems to be the best predictor of outcome. It is an innovative study, showing that research in pediatric patients should be carried out independently on adults. Positive results attained in such a small cohort (only 17 patients) are perhaps over-optimistic. Studies with larger samples are necessary to achieve greater confidence in a new methodology, particularly where outcome is concerned [5].

It is important to stress that PRx and 'optimal CPP' have never been subjected to a randomized, prospective clinical trial. Therefore, their strength is only supported by physiological reasoning, backed by retrospective analysis, with the exception of the prospective clinical protocols used in Porto [10] and Moscow (with no listed publications). The first multicenter trial on the feasibility of this method is about to start as we are writing this editorial (COGITATES: www.cppopt.org).

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