Continuous monitoring of cerebrovascular pressure reactivity in patients with head injury

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Object. Cerebrovascular pressure reactivity is the ability of cerebral vessels to respond to changes in transmural pressure. A cerebrovascular pressure reactivity index (PRx) can be determined as the moving correlation coefficient between mean intracranial pressure (ICP) and mean arterial blood pressure.

Methods. The authors analyzed a database consisting of 398 patients with head injuries who underwent continuous monitoring of cerebrovascular pressure reactivity. In 298 patients, the PRx was compared with a transcranial Doppler ultrasonography assessment of cerebrovascular autoregulation (the mean index [Mx]), in 17 patients with the PET–assessed static rate of autoregulation, and in 22 patients with the cerebral metabolic rate for O₂. Patient outcome was assessed 6 months after injury.

Results. There was a positive and significant association between the PRx and Mx (R² = 0.36, p < 0.001) and with the static rate of autoregulation (R² = 0.31, p = 0.02). A PRx > 0.35 was associated with a high mortality rate (>50%). The PRx showed significant deterioration in refractory intracranial hypertension, was correlated with outcome, and was able to differentiate patients with good outcome, moderate disability, severe disability, and death. The graph of PRx compared with cerebral perfusion pressure (CPP) indicated a U–shaped curve, suggesting that too low and too high CPP was associated with a disturbance in pressure reactivity. Such an optimal CPP was confirmed in individual cases and a greater difference between current and optimal CPP was associated with worse outcome (for patients who, on average, were treated below optimal CPP [R² = 0.53, p < 0.001] and for patients whose mean CPP was above optimal CPP [R² = −0.40, p < 0.05]). Following decompressive craniectomy, pressure reactivity initially worsened (median −0.03 [interquartile range −0.13 to 0.06]) to 0.14 [interquartile range 0.12–0.22]; p < 0.01) and improved in the later postoperative course. After therapeutic hypothermia, in 17 (70.8%) of 24 patients in whom rewarming exceeded the brain temperature threshold of 37°C, ICP remained stable, but the average PRx increased to 0.32 (p < 0.0001), indicating significant derangement in cerebrovascular reactivity.

Conclusions. The PRx is a secondary index derived from changes in ICP and arterial blood pressure and can be used as a surrogate marker of cerebrovascular impairment. In view of an autoregulation–guided CPP therapy, a continuous determination of a PRx is feasible, but its value has to be evaluated in a prospective controlled trial.

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Key Words • cerebral perfusion pressure • cerebrovascular pressure reactivity • head injury • intracranial pressure monitoring • static rate of autoregulation

Cerebrovascular pressure reactivity reflects the capability of smooth muscle tone in the walls of cerebral arteries and arterioles to react to changes in transmural pressure (cerebral vessels constrict in response to an increase in CPP, and vice versa). Cerebrovascular pressure reactivity represents a key element of cerebral autoregulation, although the two terms should not be used interchangeably because vascular responses can occur outside the range of cerebral autoregulation. With increasing ABP, intact cerebrovascular pressure reactivity will lead to vasoconstriction and a reduction of cerebral blood volume. Under the condition of a finite pressure–volume compensatory reserve, this reduction of cerebral blood volume will produce a decrease in ICP, a condition that is usually not met in patients after a decompressive craniectomy or in those with an external ventricular drain. When cerebrovascular pressure reac-

Abbreviations used in this paper: ABP = arterial blood pressure; CBF = cerebral blood flow; CMRO₂ = cerebral metabolic rate for O₂; CPP = cerebral perfusion pressure; Mx = mean index of cerebrovascular autoregulation; GCS = Glasgow Coma Scale; PRx = cerebrovascular pressure reactivity index; SRO = static rate of autoregulation.
tivity is impaired, cerebral blood volume—and therefore ICP—will increase or decrease passively (in the same direction) in response to changes in ABP.

The assessment of cerebrovascular pressure reactivity (using the PRx) and its prognostic importance in patients with traumatic head injury have been recognized early, although its measurement remained a challenge without manipulation of ABP. Some authors have suggested that cerebrovascular pressure reactivity could be derived from the characteristic pulse waveform from ABP, although this has never been demonstrated to work in clinical practice. Perhaps changes in ABP are too fast (a fraction of a second) to mobilize an active vasoregulatory response. Slow waves of ABP, lasting from 20 seconds to 3 minutes, are almost always present in patients receiving mechanical ventilation and are of sufficient magnitude to provoke a vasomotor response. Taking advantage of this fact, cerebrovascular pressure reactivity can be determined continuously without manipulation of ABP by monitoring the response of ICP to such changes in mean ABP.

The introduction of a computer-aided approach to calculate cerebrovascular pressure reactivity and to monitor it continuously was introduced in 1997. Since then, the use of the PRx in patients with head injury has progressed. A collection of almost 400 cases with continuous monitoring of the PRx has been created, supplemented by intermittent recordings of blood flow velocity in the middle cerebral artery. We intended to review our own findings regarding the PRx and to outline the potential use of this index to facilitate intensive care treatment of patients with severe head injuries.

**Methods**

Patient Characteristics and Pressure Reactivity Monitoring

Our head injury database includes 398 patients with head injuries admitted to the Neuro-Rehabilitation Annex and Neuro Critical Care Unit of Addenbrooke’s Hospital, Cambridge, between 1991 and 2007. Several different treatment protocols were used within this period. From 1991 to 1993, the treatment regimen was the so-called “neurorehabilitation annex.” Later, a CPP-oriented therapy was administered. Since 2003, a mixed ICP/CPP protocol has been in use with a restricted use of vasopressors.

The database population included 314 men (79%) and 84 women (21%), ranging in age from 16 to 79 years old (median age 33 years). The median GCS score at admission was 7 and ranged from 3 to 13; 22% of patients had an initial GCS score > 8, but their condition deteriorated later, requiring neurocritical care.

Beginning in September 1996, continuous cerebrovascular pressure reactivity monitoring was included in the computer-assisted algorithm. In 2003, an improved version of the bedside software (ICM+; http://www.neurosurg.cam.ac.uk/icmplus) was launched. In 298 patients the PRx was retrospectively calculated from intermittent computer raw data recordings of ABP and ICP. Continuous monitoring of ICP using Codman intraparenchymal ICP sensors (in 87%) or Camino ICP intraparenchymal sensors or external transducers connected to an extraventricular drain (before 1995) was supplemented by other modalities, including direct ABP from the radial artery (in all patients), brain tissue oxygenation (using Neurorotrend or Licox, in 74 patients), cortical laser Doppler blood flow (in 31 patients), and PET CBF and CMRO₂ (in 39 patients).

Data Analysis

Using computational methods, the PRx was determined by calculating the correlation coefficient between 40 consecutive, time-averaged data points (8-second periods) of ICP and ABP. A positive PRx signified a positive gradient of the regression line between the slow components of ABP and ICP, which has been shown to be associated with a passive behavior of a nonreactive vascular bed. A negative value of PRx reflected normally reactive cerebral vessels, as ABP waves provoke inversely correlated waves in ICP (Fig. 1).

Similarly, in patients with intermittent transcranial Doppler ultrasonography recordings, the Mx was calculated as a Pearson correlation coefficient of 40 consecutive samples (320 seconds, or 5 minutes and 20 seconds) of time-averaged (8 seconds) CPP and flow velocity values. The correlation between CPP and middle cerebral artery mean flow velocity values was measured using transcranial Doppler ultrasonography. Flow velocity over...
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A limited period can be analyzed using a regression plot of flow velocity (y-axis) versus CPP (x-axis). If points show a linear model, the correlation coefficient is reasonably positive or negative. A positive association between CPP and flow velocity (positive Mx values) indicates passive dependence of blood flow on CPP, and therefore defective autoregulation. Zero or negative Mx values implicate active cerebrovascular responses to changes in CPP, and therefore preserved autoregulation.

In both indices (PRx and Mx) the time interval over which ICP, ABP, CPP, and flow velocity are averaged (8 seconds in this study) is not very crucial. Any period from 6–10 seconds works in practice. Averaging is used to suppress the influence of the pulse wave and part of the respiratory wave. All slower waves potentially contain information about cerebrovascular pressure reactivity and autoregulation of CBF. The length of the time window (5 minutes) is long enough to contain a period of the longest waves (3 minutes) but not too long to be affected by long-term trends in pressure.

In PET CBF studies, SROr was calculated as the percentage change in cerebrovascular resistance (cerebrovascular resistance = CBF/CPP) divided by the percentage change in CPP; thus, a value of 100% represents ideal autoregulation and 0% represents completely nonfunctional autoregulation.

Comparison Between the PRx and the Mx

We compared the PRx with the transcranial Doppler–derived Mx in 298 patients with head injuries. The PRx showed a relatively good correlation with the Mx (R² = 0.36, p < 0.001). Both indices presented similar changes during recording intervals (Fig. 2). In an example of episodes of refractory intracranial hypertension, the PRx was capable of detecting temporary or permanent impairment of autoregulation (Fig. 3).

Comparison of PRx with PET CBF and CMRO₂

The hypothesis that the PRx is an indicator of autoregulation was further validated in PET studies. The PRx was simultaneously compared with the global SROr measured using PET CBF, which has shown a significant association (R² = 0.31, p = 0.02; 17 patients), especially for low static values. After using PET to determine CMRO₂, CMRO₂ has been shown to be negatively associated with PRx (R² = 0.21, p = 0.018; 22 patients). The correlation between PRx and the O₂ extraction fraction was fitted into a quadratic model (R² = 0.55, p = 0.0001). This model suggests that both low O₂ extraction fraction (indicating luxury perfusion, hyperemia, or necrotic tissue) and high O₂ extraction fraction (representing poor perfusion or ischemia) are associated with disturbed pressure reactivity.

Comparison of PRx With Intracranial Hypertension, CT, and Outcome

Abnormal cerebrovascular pressure reactivity is associated with a fatal outcome after head injury. In a retrospective analysis of 193 patients with head injuries with continuous monitoring of PRx, pressure reactivity was worse in patients who died (22%) compared with those who survived (0.19 ± 0.26 vs 0.04 ± 0.18, respectively; p < 0.0002). Mortality modeled as a function of PRx was unevenly distributed (Fig. 4). The PRx values greater than 0.25 indicated a mortality rate of 69%, as opposed to a
mortality rate < 20% in patients with a PRx value < 0.25 (p < 0.0001; chi-square test). These results confirmed those in previous studies, showing that PRx is one of the most important predictors of death after brain trauma.31,33

In this updated analysis of 398 patients, outcome showed a close linear relation to PRx, whereas outcome was unevenly distributed with ICP (Fig. 5); this finding supports the assumption of the contribution of PRx to patient outcome.

In a stepwise multivariate analysis, PRx as well as ICP emerged as independent predictors of outcome ($R^2 = 0.37; p < 0.0001$). Other independent predictors were age and GCS score,4 whereas GCS score was not an independent predictor in a recent patient cohort.3

In a study comparing outcome with PRx and the CT classification (according to the Marshall CT classification system), PRx showed a better correlation with outcome ($R^2 = -0.36, p < 0.0002$) than the CT classification ($R^2 = -0.23, p = 0.018$) in a subgroup of 107 patients.13 Separating patients into 2 groups (one with positive and the other with negative PRx values) shows that the mortality rate differed considerably (28.6% in those with positive PRx values vs 9.5% in those with negative PRx values), even though both groups did not show statistically significant differences in ICP and CPP values and CT scores.

Optimal CPP Therapy

The relationship between cerebrovascular pressure reactivity and CPP shows a U-shaped curve, suggesting that too low or too high CPP values are unsuitable from the point to maintain good cerebrovascular reserve. Figure 6 upper shows PRx (averaged per patient) in a group of 398 patients with continuous PRx monitoring. Both too low (ischemia) and too high CPP (hyperemia and a secondary increase in ICP) are adversarial, hence, CPP should be optimized to maintain CPP in the most favorable state. The question has been asked of whether such optimal CPP (the CPP that assures the best condition for cerebrovascular pressure reactivity) can be identified in individual patients and followed over time. Steiner and colleagues33 reported that in two-thirds of 114 patients with head injuries (a subgroup of patients from 1997–2000), PRx plotted against CPP displayed a U-shaped curve. Consequently, optimal CPP can be evaluated in most individual cases (Fig. 6 lower). In this retrospective evaluation cohort, patient outcome correlated with the difference between the averaged CPP and optimal CPP for patients who were treated on average below optimal
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CPP (R² = 0.53, p < 0.001) and for patients whose mean CPP was above optimal CPP (R² = −0.40, p < 0.05).

An algorithm was proposed in which the PRx/CPP relationship was evaluated for 4–6 hours to find optimal CPP and minimize (by altering ABP) the distance between CPP and optimal CPP. Such adjustments of CPP should not be made too frequently, but hourly corrections may be feasible. This concept needs to be tested in a prospective trial.

Cerebrovascular Pressure Reactivity After Decompressive Craniotomy

The pressure-volume curve has an exponentially increasing shape, which is particularly steep after head injury. This curve becomes flat after decompressive craniectomy, making a prerequisite assumption for PRx as an index of cerebrovascular reactivity probably invalid. In a retrospective study with 17 patients who underwent decompressive craniectomy, PRx deteriorated postoperatively from a median of −0.03 (interquartile range 0.13 to 0.06) to 0.14 (interquartile range 0.12–0.22; p < 0.01) initially and improved in the later postoperative course.

Cerebrovascular Pressure Reactivity During Hypothermia and Rewarming

The clinical benefit of hypothermia in the treatment of refractory intracranial hypertension is not clear yet. In 24 patients with head injuries, PRx was monitored during hypothermia/rewarming. Hypothermia helped to control increased ICP and did not impair pressure reactivity. Slow rewarming up to 37.0°C (rate of rewarming 0.2°C/hr) did not significantly increase ICP (18.6 ± 6.2 mmHg) or PRx (0.06 ± 0.18). However, in 17 (70.8%) of 24 patients who underwent rewarming and whose brain temperature exceeded 37°C, ICP remained stable, but the average mean PRx increased to 0.32 ± 0.24 (p < 0.0001), indicating a significant derangement in cerebrovascular pressure reactivity (Fig. 8).

Discussion

Continuous ICP monitoring is an essential modality in neurointensive care, even though no randomized controlled trial has proven an effect of ICP monitoring on overall patient outcome. Intracranial pressure is a complex variable that comprises useful information about cerebrospinal pathophysiology. The association of slow waves of ABP and ICP has been previously described as an index of the cerebral autoregulatory state. Using a computed moving correlation technology to relate ICP to ABP, PRx can be determined as a coefficient ranging from −1 (intact pressure reactivity) to +1 (impaired pressure reactivity).

In our patient database, there was a significant correlation of PRx and the transcranial Doppler–derived Mx, which confirmed that PRx was a valid alternative for continuous autoregulation assessment. However, whereas Mx assesses vascular responses of an individual branch of a basal artery, PRx reflects a global vasomotor reactiv-
Impaired cerebrovascular pressure reactivity was also associated with reduced capacity in a heterogeneous distribution preserved, and therefore PRx is a useful indicator of a trend toward an improving or deteriorating global cerebrovascular dilatory reserve. In addition, continuous (24-hour) autoregulation monitoring using Mx is technically very difficult because the present technology requires a trained person at the patient’s bedside to adjust the Doppler probes during monitoring. This technical difficulty makes Mx impractical for continuous long-term monitoring. The PRx, on the other hand, is not restricted by such technical limitations.

Cerebrovascular pressure reactivity correlates well with outcome after brain trauma. Whereas ICP only differentiates patients with fatal outcome from those who survive at 6 months, PRx distinguished between patients with good outcome, moderate disability, severe disability, and death. The correlation of PRx with patient outcome is independent of mean ICP: in a stepwise multivariate analysis both variables were included in the model independently. Moreover, patients with head injuries who are treated close to the optimal CPP—as determined by the PRx calculation—had a better outcome in a retrospectively performed study. The concept of pressure reactivity–guided intensive care therapy has to be proven. Initial worsening of PRx after decompressive craniectomy should be confirmed in other studies and is not yet fully understood, but outcome was significantly correlated with postoperative PRx values.

Using cerebrovascular pressure reactivity as a surrogate marker could also be very useful under particular intensive care conditions such as hypothermia. The results of our cohort have emphasized the importance of management of systemic temperature after rewarming. Although an average PRx changing from 0.06 to 0.32 might appear to represent a rather unimpressive increase, as we show in Fig. 4, the mortality rate increases steeply at a PRx value > 0.3.

Prospective data in the literature on a pressure reactivity–guided intensive care therapy are missing, which is also the major limitation of our data given that all analyses were performed retrospectively. The concept of pressure reactivity–guided intensive care therapy has to be proven in a prospective randomized trial. A further limitation of this study is the use of a very specific, although standard, intensive care management strategy, which limits the transfer of our results to centers that use distinctly different management strategies.

Conclusions

The PRx is a secondary index calculated using ICP and APB and can be used as a surrogate marker of cerebrovascular impairment. Continuous long-term monitoring of PRx allows the determination of the CPP at which cerebrovascular pressure reactivity reaches its optimal value in individual patients. The benefit of such an autoregulation–oriented approach should be evaluated in a prospective study.

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