PAPER

Temporal changes in cerebral tissue oxygenation with cerebrovascular pressure reactivity in severe traumatic brain injury

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Objective: To investigate the temporal relationship between cerebrovascular pressure reactivity and brain tissue oxygenation in patients with severe head injury.

Methods: In 40 patients, brain tissue oxygenation and intracranial pressure were monitored. Time-averaged values for intracranial pressure (ICP), mean arterial pressure (MAP), cerebral perfusion pressure (CPP) and brain tissue oxygenation (PtiO₂) were computed. The pressure reactivity index (PRx) was calculated. The mean values of the variables were obtained at the 6-h and 72-h post-injury time points, and the difference between the two time points for each of the variables was denoted as delta (δ).

Results: Of the 40 patients, 32 were survivors and 8 were non-survivors. Statistically significant differences were present between these two groups with regard to δ MAP ($p=0.013$), ICP at 6 h ($p=0.027$), CPP at 72 h ($p=0.018$), δ CPP ($p=0.033$), PRx at 6 h ($p=0.029$), PRx at 72 h ($p=0.002$), PtiO₂ at 72 h ($p<0.0005$) and δ PtiO₂ ($p=0.023$) values, reflecting an improvement with time in survivors and a deterioration with time in non-survivors. In non-survivors, the magnitude of change in PtiO₂ and CPP with time correlated in a negative linear fashion ($p=0.042$ and 0.029 , respectively) with the change in PRx with time, whereas no such relationship was seen in survivors.

Conclusion: The severity of brain tissue oxygenation derangement correlates with increasing cerebrovascular dysautoregulation in patients succumbing to severe head injury, supporting the utility of PRx as a monitoring variable and the rationale for a target-driven approach to head injury management.

Cerebral ischaemia is a critical contributory factor to secondary brain injury after trauma. In the presence of an unstable cerebral perfusion pressure (CPP), the autoregulatory cerebrovascular reactivity attempts to maintain an adequate cerebral blood flow. Increasing CPP may result in raised or lowered intracranial pressure (ICP), depending on whether cerebral autoregulation is preserved. Rosner *et al*¹ have described how increases in CPP within the autoregulatory range lead to compensatory vasoconstriction to maintain a stable cerebral blood flow. In so doing, cerebral blood volume and thus ICP levels fall. However, outside of these autoregulatory limits, a pressure-passive scenario exists where increases in CPP lead to vasodilatation and a rise in ICP. Investigators have defined an index comparing arterial blood pressure (ABP) and ICP to quantify this relationship between CPP and ICP, known as the pressure reactivity index (PRx).^{2,3} If a rise in ABP (and hence CPP) leads to a parallel increase in ICP, a good correlation exists, and the PRx is positive. However, in the face of intact cerebral autoregulatory capacity, vasoconstriction in the face of rising CPP leads to a drop in ICP, and hence PRx approaches zero or takes a negative value. Measurement of PRx could thus form the basis for target-driven management, as ABP can be manipulated.

Clinical studies on patients with head injury have shown the feasibility of continuous monitoring of local brain tissue oxygenation (PtiO₂) as a variable for cerebral oxygenation.^{4–6} Despite the limitations of such a local method of measurement, PtiO₂ indicates global cerebral oxygenation when the monitoring is carried out in a relatively uninjured part of the brain.⁶ The presence of autoregulation disturbance could conceivably lead to disturbance in oxygen tension in the tissue of interest by virtue of blood flow metabolism uncoupling as PtiO₂ reflects the net balance between oxygen supply and demand at the tissue level.⁷

We hypothesised that a worsening PRx indicative of increasing dysautoregulation during the temporal course of monitoring is related to mortality, and this may arise from specific patterns of change in various physiological variables including PtiO₂.

PATIENTS AND METHODS

Patient selection

We prospectively studied a cohort of 40 patients with severe non-penetrating head injury (Glasgow Coma Score ≤ 8) admitted to our 18-bed neurocritical care unit at the Tan Tock Seng Hospital campus of the National Neuroscience Institute, Singapore. The research protocol was approved by the institutional review committee and signed informed consent was obtained from all relatives of the patients. All patients were managed according to a severe traumatic brain injury management protocol, emphasising rapid detection and evacuation of mass lesions, aggressive treatment of intracranial hypertension and maintenance of an adequate CPP, that conforms to the American Association of Neurological Surgeons Guidelines⁸ for the management of severe head injury. All patients were intubated and placed on volume-controlled ventilation under sedation, with continuous infusion of midazolam to maintain an arterial carbon dioxide pressure of about 35–40 mm Hg. Morphine was given as an analgesic. The lowest fraction of inspired oxygen was used to keep the arterial oxygen saturation $>95\%$ and the haematocrit was maintained at about 35%. Paralytic agents were not routinely used. ICP, which was >20 mm Hg, was after exclusion of mass lesions treated with

Abbreviations: ABP, arterial blood pressure; CPP, cerebral perfusion pressure; ICP, intracranial pressure; MAP, mean arterial pressure; PRx, pressure reactivity index; PtiO₂, brain tissue oxygenation

an incremental algorithm using mannitol, mild to moderate hyperventilation and, as a last resort, barbiturates. Target CPP was aimed at >60 mm Hg with intravascular volume expansion and, if necessary, with use of vasopressors such as noradrenaline. The outcome (survivors *v* non-survivors) was ascertained at 6 months. Relationships between PRx and PtiO₂ were not assessed for the various subdivisions of survivors in the Glasgow Outcome Scoring system.

PtiO₂ monitoring

Brain tissue oxygen was monitored using a polarographic Clarke type electrode (Licor, Integra Lifesciences, New Jersey, USA). The catheter was inserted through a triple lumen bolt, allowing the simultaneous introduction of a strain gauge intraparenchymal ICP monitor (Codman & Shurtleff, Raynham, Massachusetts, USA) in the frontal region away from the lesion. Catheter-specific calibration settings were installed according to the manufacturer's specifications. Monitoring was started when the oxygen tensions were noted to be in a steady state, and it ended when continuous ICP monitoring was no longer required.

Data capture and PRx computation

All variables obtained from the multimodality monitoring were digitally extracted using an open-systems server platform that was developed in-house. This enabled extraction of all data at 5-s intervals from our generic data management system in the unit (Carevue, Phillips Medical System, The Netherlands) as well as from specialised monitoring devices (the Licor system) in an appropriate time-stamped fashion. These data were then integrated and displayed on a Windows-based interface, which allowed for automatic mathematical computation of the PRx. Time-averaged values of ICP, ABP, CPP and PtiO₂ were calculated using waveform time integration (an average of 256 consecutive samples) for 5-s intervals. Linear (Pearson's) moving correlation coefficients between 40 past consecutive 5-s averages of ICP and ABP were computed to give the PRx. Computations were automatically repeated with a moving window every 5 s. PRx was thus expressed as values ranging from +1 to -1. This index permitted a quantitative comparison of the state of pressure reactivity, where a positive value denoted a pressure-passive behaviour of the arterial walls and a negative value indicated a vascular bed with active vasomotor responses.

All data were then transferred offline for further analysis. Summary values of variables were averaged over 6-h blocks and the data analysed.

Statistical analysis

SPSS V. 12.0 was used for statistical analysis. All data are presented as mean (standard deviation (SD)). Differences between categorical data were analysed using the χ^2 test. Comparison of means was performed using the *t* test when normality distribution was shown. This was refined by applying Levene's test for equality of variances to test the null hypothesis that the sample data from the survivor and non-survivor groups were from populations with the same variances. An *F* value was obtained, which was used to test the null hypothesis that the survivor and non-survivor populations had the same variances. Levene's test was applied because of the discrepancy in size between the survivor and non-survivor groups. The observed significance level would determine if we could reject the null hypothesis and hence allowed us to select the appropriate *p* value depending on whether or not equal variances were assumed. Correlation analysis using Spearman's correlation was performed for continuous variables; statistical significance was set at *p*<0.05.

RESULTS

Patient demographics

Of the 40 patients in our cohort, 32 were survivors and 8 were non-survivors. There were 28 men and 4 women in the survivors group and 6 men and 2 women in the non-survivor group. The mean ages in these two groups were 46.23 (SD 16.94) and 44.33 (SD 23.15) years, respectively. The mean Glasgow Coma Score values were 5.00 (SD 1.69) and 5.50 (SD 1.89), respectively. The median Glasgow Coma Scores in both groups were 5. Pupillary abnormalities (presence of a dilated or non-reactive pupil) were recorded on admission in 12 survivors and 5 non-survivors. The presence of hypoxia (oxygen saturation <90% by pulse oximetry) and hypotension (systolic blood pressure <90 mm Hg) on admission was noted in one survivor and two non-survivors. Of the 40 patients, 29 (72.5%) underwent craniotomy for mass lesions. The mean period of monitoring was 137 (SD 21.82) h. The mean time from the start of surgery to the start of monitoring was 5.79 (SD 4.63) h and the mean time from the end of surgery to the start of monitoring was 3.54 (SD 3.81) h. Barbiturate coma was induced in 18 patients (11 survivors and 7 non-survivors), and inotropes were used in 28 patients (20 survivors and 8 non-survivors). The differences between the survivor and non-survivor groups with respect to age, Glasgow Coma Score, presence of pupillary abnormalities at admission, presence of hypoxia and hypotension at admission, and use of barbiturates and inotropes were not significantly different (*p*>0.05).

Temporal changes in monitored variables between survivors and non-survivors

Comparison of the MAP difference (δ MAP) between the two time points showed a significant disparity, in that there was a relatively large drop in MAP with time in non-survivors compared with a small rise in MAP with time in survivors (*p* = 0.013; table 1). The ICP at 6 h was significantly higher in non-survivors compared with survivors (*p* = 0.027). The CPP at 72 h was considerably higher in survivors than in non-survivors (*p* = 0.018), with a comparatively larger drop in CPP with time (δ CPP) in non-survivors versus a small rise with time in survivors (*p* = 0.033). PRx at 6 h was significantly more positive in non-survivors than in survivors (*p* = 0.029) and patients showed a worsening PRx with time. At 72 h, a significant difference (*p* = 0.002) persisted between non-survivors and survivors, with non-survivors having more positive values than survivors. The mean PRx at 72 h for non-survivors was >0.3, whereas the mean PRx at the same time point for survivors was <0.3. Previous work had defined 0.3 as the cut-off value between disturbed and intact autoregulation.² Although PtiO₂ was not significantly different between the two groups at 6 h, a drop in PtiO₂ to below ischaemic levels was recorded for non-survivors at 72 h in contrast with an improvement in oxygenation in survivors over time, such that PtiO₂ values at 72 h were significantly different between the two groups (*p*<0.005). The mean difference between PtiO₂ values at the two time points was also significantly different, with a larger absolute drop in tissue oxygenation in non-survivors compared with the extent of improvement in survivors (*p* = 0.023).

Relationship between derived parameters

After calculating the absolute changes that occurred with time in MAP, ICP, CPP, PRx and PtiO₂— δ MAP, δ ICP, δ CPP, δ PRx and δ PtiO₂, respectively—we ascertained whether any correlation existed between these temporally derived parameters. Correlation analysis showed that for the entire cohort of patients, a significant negative linear relationship existed between δ CPP and δ PRx (r^2 = -0.431; *p* = 0.001; fig 1). No apparent linear relationship existed between δ PtiO₂ and δ PRx (r^2 = -0.198; *p* = 0.220) or δ CPP (r^2 = 0.299; *p* = 0.061).

Table 1 Measured and derived parameters in survivors and non-survivors

	Non-survivors	Survivors	p Value
MAP			
6 h	98.54 (16.90)	86.98 (10.46)	0.100
72 h	75.28 (25.74)	95.66 (10.44)	0.061
δ MAP	-23.26 (27.44)	8.68 (12.57)	0.013
ICP			
6 h	36.90 (20.49)	16.75 (9.24)	0.027
72 h	34.26 (28.91)	16.86 (7.73)	0.134
δ ICP	-2.64 (18.27)	0.11 (8.99)	0.690
CPP			
6 h	61.64 (20.95)	70.23 (10.85)	0.111
72 h	46.66 (29.80)	78.80 (11.42)	0.018
δ CPP	-14.97 (25.07)	8.57 (13.700)	0.033
PRx			
6 h	0.52 (0.28)	0.28 (0.26)	0.029
72 h	0.56 (0.28)	0.17 (0.30)	0.002
δ PRx	0.04 (0.36)	-0.11 (0.21)	0.126
PtiO ₂			
6 h	12.50 (13.84)	17.88 (12.16)	0.238
72 h	4.09 (4.18)	24.10 (13.25)	<0.005
δ PtiO ₂	-8.41 (14.05)	6.22 (15.92)	0.023

Values are mean (SD).

δ 6 h and 72 h; mean value of variables at the 6-h and 72-h post-injury time points, respectively; CPP, cerebral perfusion pressure; δ , the difference between mean values (ie, value at 72 h – value at 6 h); ICP, intracranial pressure; MAP, mean arterial pressure; PRx, pressure reactivity; PtiO₂, brain tissue partial pressure.

Next, we analysed whether there were any differences between the two groups. For the non-survivors, a negative linear relationship was seen between δ PRx and δ PtiO₂ ($r^2 = -0.685$; $p = 0.042$; fig 2) and also between δ PRx and δ CPP ($r^2 = -0.720$; $p = 0.029$; fig 3). This suggested that as the δ PRx value became larger, reflecting an increasing magnitude of deterioration of cerebrovascular reactivity with time, the reduction in CPP and PtiO₂ with time became accordingly larger when all the patients were collectively analysed and also when considering only the patients who did not survive. The negative slope was, however, smaller for the entire cohort than for the non-survivors. In the group of survivors, we found no significant relationships when δ ICP ($p = 0.132$), δ CPP ($p = 0.148$), δ PRx ($p = 0.143$) and δ PtiO₂ ($p = 0.238$) were correlated.

Figure 1 Relationship between the difference in pressure reactivity (PRx) with time (δ PRx) and the difference in cerebral perfusion pressure (CPP) with time (δ CPP) for the entire cohort of patients. **Figure 2** Relationship between the difference in pressure reactivity (PRx) with time (δ PRx) and the difference in brain tissue oxygen tension (PtiO₂) with time (δ PtiO₂) for non-survivors.

DISCUSSION

Cerebral autoregulation is the ability of cerebral arterioles to adapt their diameters to meet the metabolic requirements of the brain independent of CPP.⁹ Cerebrovascular pressure reactivity has been validated in a prospective study on patients with head injuries with regard to monitoring and quantification of cerebral blood flow velocity and the phenomenon of cerebral autoregulation.¹⁰ It is one of the major mechanisms responsible for brain protection in cases where CPP is unstable in patients with acute brain injury.¹⁰ Cerebral ischaemia is recognised as one of the keys factors in the development of secondary brain injury after severe head injury. The increased susceptibility of the injured brain to secondary insults is partly due to altered cerebral autoregulation.^{2, 11–16}

Defective cerebral autoregulation aggravates, secondary ischaemia after head trauma, leading to a worse outcome.^{17–20} In our study, patients who did not survive tended to have a worsening PRx, denoting worse pressure reactivity with time. The magnitude of the change in PRx was mirrored by a corresponding magnitude of change in CPP. The fact that autoregulation may be partially disrupted but not completely

Figure 3 Relationship between the difference in pressure reactivity (PRx) with time (δ PRx) and the difference in cerebral perfusion pressure (CPP) with time (δ CPP) for non-survivors.

lost has been used in Rosner *et al*'s¹ argument for CPP-directed management in patients with severe traumatic brain injury, by keeping CPP above the lower breakpoint of autoregulation to minimise secondary insults arising from hypoperfusion. Nevertheless, CPP maintenance above a single value may be simplistic. In the face of intact cerebrovascular reactivity, manipulating the vasomotor response by raising ABP and so CPP to attain a drop in ICP by reducing cerebral blood volume is a common manoeuvre practised in intensive care units. Lang *et al*¹⁷ have showed that cerebral blood flow velocity remains stable despite varying ABP or CPP in patients with preserved cerebrovascular reactivity, and that blood flow velocity is correlated linearly with ABP and CPP when cerebrovascular reactivity is disturbed. It has also been shown that an optimal CPP may be ascertained for individual patients by monitoring of cerebrovascular reactivity.²¹

In the dysautoregulatory state, cerebral hypoxia is more likely to be present at the tissue level. While monitoring ICP and CPP, with real-time appreciation of cerebrovascular autoregulatory capacity using indices such as PRx and Maxwell Medex (Maxwell Medex is calculated as a moving correlation coefficient between ABP and cerebral blood flow velocity), has shown to be beneficial in critical care, the next logical step is to ascertain whether these indices bear a direct correlation with PtiO₂.²² Lang *et al*¹⁷ have investigated the relationship between cerebral autoregulation and tissue oxygen reactivity after blood pressure manipulation with norepinephrine. They defined a static rate of regulation as an index that described the change in cerebrovascular resistance using cerebral blood flow velocity in relation to changing CPP. In essence, the static rate of autoregulation was used as a quantitative index that expressed the stability of changes in cerebral blood flow velocity when ABP or CPP varied, hence approximating the concept of autoregulation. This index was then correlated with the rate of change in PtiO₂, which related the percentage change in PtiO₂ to the percentage change in CPP. They discovered that both cerebral blood flow velocity and PtiO₂ showed a plateau phase, representing intact autoregulation, between mean ABP values of 70 and 90 mm Hg. The presence of the PtiO₂ plateau phase and the significant correlation between their static index of autoregulation and tissue oxygen reactivity suggest a close relationship between cerebral blood flow and oxygenation. We used another well-established index, PRx, for evaluation of cerebrovascular reactivity, which approximates cerebral autoregulatory capacity. As vasodilative phenomena reach a peak at ABP values below the lower threshold for a constant cerebral blood flow, the two terms cerebrovascular reactivity and cerebral autoregulation strictly differ from each other.²³ The PRx was shown to correlate well with the cerebral autoregulation index, Maxwell Medex.¹⁰ In this study, no correlation was noted between ABP or CPP and cerebral blood flow velocity in patients with intact cerebrovascular reactivity as determined by PRx. Conversely, the correlation between these variables was significant in patients with disturbed cerebrovascular reactivity. In essence, when cerebral blood flow velocity is independent of ABP or CPP, we may infer that the patient's autoregulatory set point is operating at the plateau phase of cerebral autoregulation, and the opposite also applies in that when the set point shifts away in either direction off the plateau phase, cerebral blood flow velocity becomes purely dependant on ABP or CPP.

In our study, we showed that apart from the indices of cerebral autoregulation such as Maxwell Medex and the static rate of regulation, an index of vasomotor reactivity, PRx, shows time trends consistent with appropriate changes in PtiO₂. In addition, there is a link between these disturbed indices and outcome. Specifically, the mean PRx at both 6 and 72 h was considerably higher in non-survivors than in survivors. PRx

decreased with time in survivors, reflecting improved cerebrovascular reactivity, and increased with time in non-survivors, reflecting a worsening of cerebrovascular reactivity. In line with the presence of increasing dysregulation in non-survivors, PtiO₂ decreased with time and the mean PtiO₂ at 72 h was below the accepted ischaemic threshold. Additionally, the magnitude of change in PtiO₂ was negatively correlated with the change in PRx—that is, the greater the derangement manifested as a larger PRx change, the greater the reduction in PtiO₂. By contrast, in the survivors, PtiO₂ increased with time and the mean PtiO₂ at 72 h was above the ischaemic threshold. We may speculate that the observations seen in our patients represent intact physiological autoregulation in survivors within the plateau phase, hence no correlation could be obtained between δ PtiO₂ and δ CPP with δ PRx. In non-survivors, however, these two variables showed good correlation, in line with the argument outlined above as to the dependence of cerebral blood flow velocity on ABP or CPP in PRx-disturbed and PRx-favourable patient populations. With the correlation between δ PRx and δ PtiO₂ being independent of δ CPP in non-survivors, the fall in PtiO₂ in non-survivors with time was unlikely to have been accounted for by the drop in MAP with time. Our study also supports the usefulness of PRx, a relationship variable between ABP or CPP and ICP, as a useful bedside monitoring modality. This relationship between PRx and PtiO₂ emphasises the potential utility of a target-driven approach to management of patients with head injury.

CONCLUSION

A relationship exists between a poor vasodilative reserve, as reflected by PRx indices in non-survivors, and poor PtiO₂, denoting the potential benefit of PRx recording in the management of patients with severe head injuries.

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HISTORICAL NOTE

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Robert Bárány

Magnus Gustaf Retzius (1842–1919) initiated the anatomical studies of the semicircular apparatus. The physiologist Jean Pierre Flourens (1794–1867) in 1825 had observed that when a pigeon's horizontal semicircular canal was destroyed, it went on turning horizontally in a circle. Purkinje (1787–1869) proved that changing the head position induced vertigo in man. However, no experiments on rotating the head in animals were performed, and as Bárány noted:

Science stood still in this respect for nearly 40 years.

In 1861, Ménière (1799–1862) had observed vertigo and tinnitus in inner ear disease. However, Goltz in 1870 deduced that if the destruction of the semicircular canal apparatus caused vertigo and imbalance, then the normal function of this apparatus must be to maintain equilibrium.

In the wake of these historical landmarks, Bárány discovered the caloric reaction, which initiated the systematic investigation of the vestibular apparatus. If the reaction was positive, the canals were excitable—that is, not totally destroyed; if it was negative then they were, with few exceptions, destroyed.¹ The caloric reaction arose from the semicircular canals, where the endolymph increases in specific gravity with cooling, showing a tendency to sink, whereas with warming, the specific gravity decreases and the fluid shows a tendency to rise.

Bárány found that syringing of the ear produced nystagmus and giddiness. The explanation came to him by pure accident.

A patient whose ears he was syringing said to me: "Doctor, I only get giddy when the water is not warm enough. When I do my own ears at home and use warm enough water I never get giddy." I then called the nurse and asked her to get me warmer water for the syringe. She maintained that it was already warm enough. I replied that if the patient found it too cold we should conform to his wish. The next time she brought me very hot water in the bowl. When I syringed the patient's ear he shouted: "But Doctor, this water is much too hot and now I am giddy again." I quickly observed his eyes and noticed that the nystagmus was in an exactly opposite direction from the previous one when cold water had been used. It came to me then in a flash that obviously the temperature of the water was responsible for the nystagmus.

Bárány's work followed that of Josef Breuer (1842–1925) in Vienna, Mach, and Crum Brown, who independently in 1874 had concluded that the semicircular canal was a sensory organ for the perception of rotary motion and vertigo was the result of abnormal excitation of this sensory organ.

Bárány was not slow to extend the use of his caloric reactions in labyrinthine disorders² that included "benign positional vertigo".³ In 1921, he described this syndrome of episodic vertigo, induced by sudden movement of the head; the vertigo was abrupt in onset and lasted a few seconds. Dix and Hallpike^{4,5} in 1952 gave a more detailed account, and named the syndrome "benign paroxysmal positional vertigo".

Robert Bárány (1876–1936)

Born on 22 April 1876, in Vienna,⁶ Bárány read Medicine at Vienna, graduating in 1900.⁷ He trained in otology under Politzer (1835–1920), founder of Austrian otology. He investigated the functions of the vestibular apparatus, the cerebellum and the muscular apparatus, establishing the vestibular reactions to movement, and Bárány's pointing test. His work greatly expanded the physiology of the vestibular mechanisms. His work is reflected in the eponymous Bárány's chair, Bárány's law, Bárány's pointing test Bárány's caloric test and Bárány's theory of endolymphatic flow.

In 1914, he was awarded the Nobel Prize (Some new methods for functional testing of the vestibular apparatus and the cerebellum) while incarcerated in a prisoner-of-war camp. After the personal intervention of Prince Carl of Sweden, he was released to receive the prize in 1916. From 1917, he worked in Stockholm and died in Uppsala on 8 April 1936. He was cremated in the Stockholm crematorium.

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