Literaure review

# Pressure Reactivity Index (PRx): A Concept to Optimize Cerebral Perfusion Pressure in Traumatic Brain Injury

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**Abstract**

Two common factors contributing to poorer outcomes in TBI patients are high intracranial pressure (ICP) and low cerebral perfusion pressure (CPP). These two factors constitute a vicious circle that will have a negative impact on TBI patients. An increase in ICP will cause a decrease in CPP, while a reduction in CPP will cause ischemia, which will worsen the high ICP. However, increasing the CPP by increasing MAP will not help the situation; in fact, it may worsen the impact due to impairment of cerebral autoregulation (CA). Therefore, it is critical to manage TBI patients with an ideal CPP. Pressure reactivity index (PRx) is a measurement of the linear relationship between the mean arterial pressure (MAP) and ICP. A positive correlation between ICP and MAP indicates an impairment of CA, which suggests a suboptimal CPP value. The basis of PRx theory is that the rise, because of the presence of CA, an increase in MAP should not be followed by the rise in ICP because there is a compensatory effect in the form of a decrease in cerebral blood volume, so that ICP does not increase. That being said, this mechanism will not work when the limit of autoregulation is exceeded. Based on PRx and CPP, an optimal CPP could be obtained by using a U-shaped curve. The outcomes of TBI patients can be enhanced by treating them according to their optimal CPP (CPPopt).

**Keywords**: Cerebral perfusion pressure, intracranial pressure, mean arterial pressure, pressure reactivity index, traumatic brain injury

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## Introduction

Cerebral perfusion pressure (CPP) is defined as mean arterial pressure (MAP) minus intracranial pressure (ICP). Therefore, an increase in ICP can cause a decrease in CPP, and an increase in MAP can cause an increase in CPP. Both of these conditions (decreased or increased CPP) can have an adverse impact on traumatic brain injury (TBI) patients. A decrease in CPP will cause ischemia and damage brain neurons, while an increase in CPP can cause edema and worsen the increase in ICP, which will lead to further ischemia.[1–3] Actually, there is a compensatory mechanism to maintain CPP when ICP increases, namely by carrying out vasodilation in the distal cerebral arterioles with the aim of reducing cerebrovascular resistance (CVR) in order to maintain cerebral blood flow (CBF), and if this is not enough, the body will increase arterial blood pressure. However, both of these mechanisms have the effect of increasing cerebral blood volume (CBV), which could increase ICP further until a complete cessation of cerebral blood flow occurs and eventually leads to worsening ischemia.[4] Therefore, an ideal CPP which didn't increase ICP or causing ischemia is required in TBI patients' management.[5,6] Pressure reactivity index (PRx) is defined as the relationship

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between slow changes in MAP and ICP derived from the dynamic slow variations in cerebral blood volume (CBV) by cerebral autoregulation. This index is considered as cerebrovascular reactivity reserve which could be a guidance to find optimal CPP in TBI patients.[7] The pressure reactivity index was first described by Marek Czosnyka and colleagues in their study in 1997. They were using continuous monitoring to track the relationship between slow spontaneous waves in the ICP and arterial blood pressure (ABP).

The pressure reactivity index was obtained by calculating a moving correlation coefficient between 40 consecutive samples of values for ICP and ABP averaged for a period of 5 seconds using a computer program. A positive PRx indicates that the slow components of ABP and ICP have a positive association, which suggests that the vascular bed is acting passively and non-reactively. On the other hand, a vascular bed that is normally reactive is indicated by a negative PRx value, where ABP waves cause inversely correlated waves in ICP.[8] rain traumatic foundation (BTF) recommended to keep CPP between 60 and 70mmHg in TBI patients due to cerebral autoregulation. Cerebral autoregulation is the ability to maintain CBF over a wide range of CPPs by changing CVR. Thus, as long as the CPP stays within the upper and lower limits of autoregulation, no change in flow would be expected, assuming that the CPP serves as the stimulus for cerebral autoregulation.[6] Nevertheless, given that different patients have different autoregulation limits, it is unclear whether these limitations can be applied in any circumstance. Thus, determining the ideal CPP value could lead to improved regulation of cerebral blood flow (CBF).[7,9]

Increasing intracranial pressure is a risk in patients with brain injury, regardless of the cause. Traumatic brain injury (TBI), large acute ischemic stroke, and intracerebral hemorrhage are just a few of the cerebral pathologies that can cause an acute increase in intracranial pressure. The increase in intracranial volume is the most common factor among these pathological processes. This condition is linked to worse outcomes, regardless of the cause.[3] Theoretically, maintaining optimal CBF is necessary to meet the metabolic needs of the injured brain. The aim is to prevent the escalation of secondary insults while maintaining the ischemic penumbra. Both low and high CPP have their own set of drawbacks and potential causes of complications. Now, the question of the ideal CPP must be addressed in order to balance the CPP.[10,11] The Optimal CPP Guided Therapy: Assessment of Target Effectiveness (COGiTATE) czosnykastudy is one of the key studies on the ideal CPP in TBI. The results of this study indicated that using both PRx and CPP-PRx curved in individualised care to target a dynamic optimal CPP based on cerebral autoregulation is both safe and practicable.7 The author aims to review the fundamentals of PRx utilization in order to determine the optimal CPP in TBI patients and to explore its application in routine practice.

**Physiology of cerebral autoregulation**

The term cerebral autoregulation (CA) describes the brain's and the cerebral vasculature's homeostatic capacity to control both regional and global blood flow in accordance with its metabolic needs under a variety of physiological circumstances. The issue with this strategy is the lack of precise understanding regarding the mechanisms underlying CBF maintenance. Regardless of the underlying mechanism, one may contend that autoregulation essentially means matching flow to metabolism. It seems that the cerebral vascular bed plays a significant role in balancing the demands of flow and metabolism. While the "proximal vasculature" guarantees sufficient blood delivery across a range of perfusion pressures, the "distal vascular" bed is able to react quickly to abrupt changes in the metabolic needs of the tissue. The non-adrenergic, non-cholinergic neurons that innervate the distal penetrating arterioles most likely play a role in the communication between the two systems. According to the Monro-Kellie doctrine, CBF is strictly regulated in healthy individuals since it is a significant determinant of ICP. In healthy individuals, CBF remains constant although CPP changes significantly between

subjects and ranges from 50 to 150 mmHg. However, changes in CBF will passively follow CPP after cerebral blood vessels reach their maximum capacity. This condition also applies if extreme circumstances occur. In fact, vessel collapse and passive vascular dilatation may amplify the expected decrease or rise brought on by variations in CPP. Resistance and pressure are no longer linearly related as a result. While the overall idea presented in figure 1 is significant, it merely provides a statistical account of the responses of the general population, and even in a normotensive person, a value of 50 mmHg does not ensure that the cerebral circulation of a given patient stays within the "autoregulatory plateau." Individual reactions differ greatly from one another.[12,13]

Although the precise mechanism underlying autoregulation is still unclear, four theories—myogenic, endothelial, neurogenic and metabolic—are thought to be involved. The most widely accepted mechanism hypothesis is the myogenic. This hypothesis predicts that the basal tone of vascular pole muscles is influenced by changes in transmural pressure. A rise in MAP causes a rise in transmural pressure, which depolarizes vascular smooth muscle and constricts the precapillary resistance vessels to maintain a constant CBF. On the other hand, when the MAP and consequently the transmural pressure decrease, these vessels dilate to increase CBF. These alterations are brought about almost instantly by nitric oxide (NO). Variations in MAP will be resulted in different levels of vascular tone based on the type of blood vessel. Arterioles are more susceptible to variations in MAP because they have a higher proportion of smooth muscle fibers than their venous counterparts. Since venous vessels behave more like capacitance vessels and affect the cerebral blood volume (CBV), their primary role is to regulate CBF.[2,14]

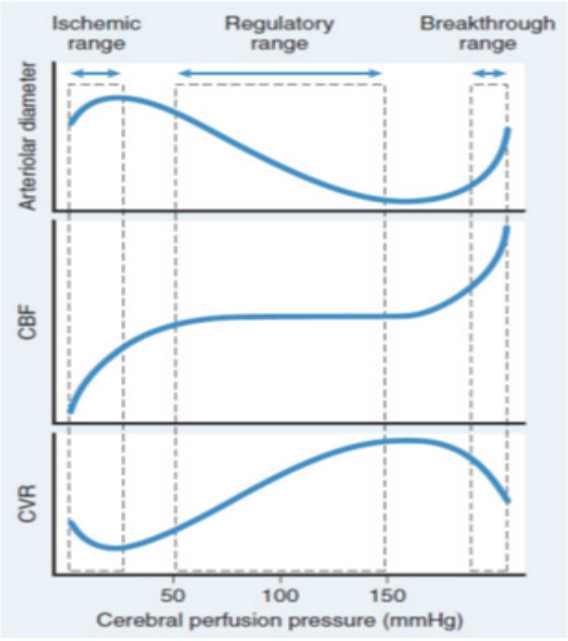


**Figure 1 A simplified illustration of pressure autoregulation as it relates to arteriolar diameter, CVR, and CBF.[13]**

As seen in wereFigure 1, hypoperfusion would arise if the CPP was below the lower limit (50 mmHg), and hyperperfusion would arise if the CPP was above the upper limit (150 mmHg). Hypoperfusion causes ischemia, while hyperperfusion causes cerebral oedema, and neither of these consequences is suitable for neuro-critical patients. Yet, given that there is a process of metabolic compensation and flow-metabolism coupling, those processes do not happen instantly.[2,13] As CPP approaches the lower bound of autoregulation, vascular resistance widens and cerebral blood volume rises. But when autoregulation reaches its lowest point, vasodilation becomes impossible, the circulation can no longer lower resistance to maintain flow, and CBF begins to passively decline while CPP keeps declining. Initially, there will be an increase in oxygen extraction to compensate for the decline in CBF. $CMRO_2$ levels will begin to fall when maximum oxygen extraction occurs. As a result, synaptic transmission deteriorates and eventually fails completely.

Currently, there is enough energy to sustain the neurons, but their “work” has been disrupted. As flow levels are reduced further, "membrane failure" occurs, causing potassium to leave the cells and sodium, calcium, and water to enter, resulting in cytotoxic oedema. If left untreated, these CBF reductions are in the fatal range and cause infarction. The degree of flow reduction to

ischemic levels and the duration of that reduction determine the development of cerebral infarction. As opposed to this, the flow increases initially with a fixed maximal arteriolar resistance when CPP rises above the upper limit. As the pressure builds up, the arteriolar bed eventually dilates, and the resistance decreases. Clinically, intravascular engorgement may cause brain swelling, BBB opening may cause vasogenic oedema, and vessel rupture may cause intracerebral haemorrhage.[13,14]

**Pressure Reactivity Index (PRx)**

As mentioned before, PRx was first introduced by Marek Czosnyka and colleagues in their study. In their study, PRx was obtained by calculating a moving correlation coefficient between 40 consecutive samples of values for ICP and ABP for a period of 5 seconds. However, along with time, Czosnyka suggested calculating PRx using a moving correlation coefficient from 30 consecutive samples with a 10-second average of ICP and ABP waveforms. The idea behind averaging the ICP and ABP waveforms for ten seconds was that autoregulation information could only be conveyed by slow waves, or waves with frequencies less than 0.05 Hz. The reasoning behind using 5-minute-long buffers to calculate the correlation coefficient (30 samples of 10 s produce a correlation window of 5 min) is that longer times (30 or 60 min, for example) might include too many confounding factors such as drugs, nursing care, metabolites, and others.[8] Thereafter, this notion was presented in numerous studies.

According to a Polish study, PRx and cerebral autoregulation have a moderate correlation. The mean flow velocity index (Mx) was used in this investigation to measure CA. The mean flow velocity index was obtained by calculating a moving correlation coefficient between mean cerebral artery flow velocity (MCAFv) and CPP from a window of 30 consecutive samples (each averaging 10 seconds). CPP was obtained by calculating the formula of MAP from arterial blood pressure minus ICP from intraparenchymal probe monitoring (IPM). In this study, there is a moderate correlation between PRx and Mx (r = 0,58), with an area under the receiver-operator characteristic (ROC) curve of 0.700 (95%CI 0,607-0,880).[15] Another study demonstrated the potential clinical utility and adaptability of a mean PRx using an ultra-low frequency to a range of age groups. In this study, PRx was measured using an ultra-low frequency due to difficulty in getting data in such a short period of time (lower than 1 minute); therefore, the authors attempted to use an ultra-low frequency minute-by-minute ICP and MAP data as a surrogate approach for estimating CA.[16]

Since CPP is one of the regulatory factors of CBF, PRx can assist in determining the optimal specific CPP for each patient. As previously mentioned, cerebral oedema can be resulted from either a high or low CPP, so finding the ideal value is crucial. According to the Brain Trauma Foundation, keeping CPP between 60 and 70 mmHg is essential for TBI patient survival. Nonetheless, there is ongoing discussion about whether this value is appropriate for all patients.[9,10] The optimal CPP value (CPPopt) could be determined automatically by using the U-shaped curve (Figure 2d) obtained from the CPP and PRx values. The CPPopt is where cerebral autoregulation is best preserved.[7,12] In order to obtain the CPPopt, a 5-minute median CPP time trend was calculated alongside PRx, next, the binned data were subjected to an automatic curve fitting method in order to identify the CPP value that had the lowest corresponding PRx value. This method of computing the CPPopt time trend was applied to a moving 4-hour time window, which was updated once every minute. It is conceivable that the determination of the CPPopt value may be unattainable as a result of the CPP value falling beyond the CPPopt range or due to an inadequate quantity of data sets.[17,18] Optimal cerebral perfusion pressure could be traced, just like in figure 2D; the green line indicates good autoregulation where PRx is less than 0,15 (figure 2C). The prognosis is better in patients whose autoregulation is still functioning normally, as indicated by an average daily CPP value close to CPP opt.[17–19]

**Clinical utility of PRx in TBI**

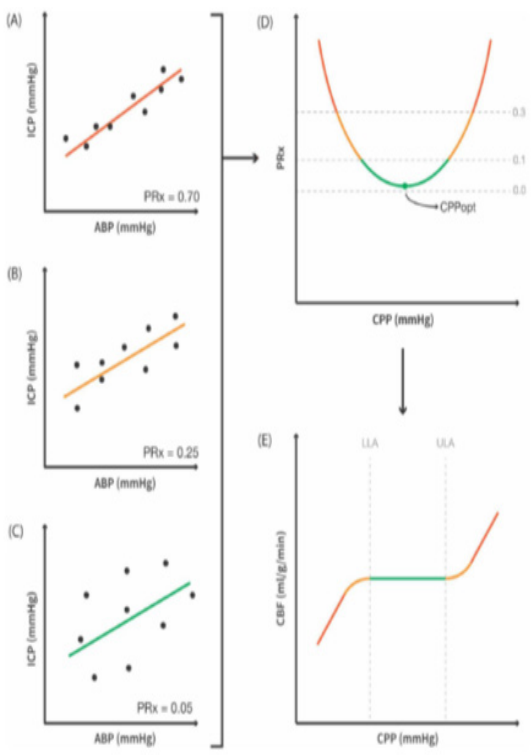


**Figure 2. Principles for calculating CPPopt with the PRx. (A) Scattered plots of ICP and ABP when PRx = 0,70; (B) Scattered plots of ICP and ABP when PRx = 0,25 (C) Scattered plots of ICP and ABP when PRx = 0,05; (D) The U-shaped curve of CPP and PRx (E) The Lassen curve (autoregulation curve) and its conceptualization from the U-shaped curve.[12]**

Pressure reactivity has been employed for the determination of the $CPP_{opt}$ in patients with TBI. As mentioned earlier, the CPPopt value can be calculated from a U-shaped curve showing the relationship between ICP and CPP (Figure 2D). A decrease in cerebral perfusion pressure below the lower limit of autoregulation (LLA) may be resulted in ischemia, while surpassing the upper limit of autoregulation (ULA) could be resulted in hyperaemia and a subsequent elevation in intracranial pressure (ICP).[1,12] Nevertheless, some research indicateed that CPP below the LLA produces worse results than CPP above the ULA. Donnely and colleagues introduced the term "ΔCPPopt," which simply means the mean CPP over a 5-min buffer minus the estimated current CPPopt value. According to their research, patients who had a below the LLA for a shorter period of time had a better outcome than the others. A U-shaped curve between and PRx based on Glasgow outcome scale (GOS) at 6 months in this study can be seen in figure 3.[19] The COGiTATE study (the first randomized control trial about $CPP_{opt}$) showed that targeting a dynamic CPP based on its PRx will lead to less time spent in lower area (CPP less than 60mmHg) than recommended one (6,71% vs 11,7%), even though there aren't any differences in the outcome.

Patients treated with CPPopt-based management spent less time in ICP more than 22 mmHg (1,27% vs 2,25%), administered less fluid (1330ml vs 1470ml), and a lower dose of noradrenaline (10,4mg vs 12,2mg) than the recommended one, despite having higher average MAP and CPP.[7] Recently, it was discovered that the length of time the patient experienced outside-recommended CPP (60–70 mmHg or ± 20 mmHg among recommended mmHg) or an increase in ICP (more than 20 mmHg) were the factors influencing the mortality and morbidity of TBI patients of all ages. The findings of this investigation demonstrated a relationship between the hourly dosage and the proportion of time during which the ICP exceeds 20 mmHg, alongside the CPP being above 70 mmHg or below 60 mmHg, with the outcome of TBI patients across all age groups. Additionally, this study demonstrates that the mean CPP is correlated with patient outcome. In addition, the percentage

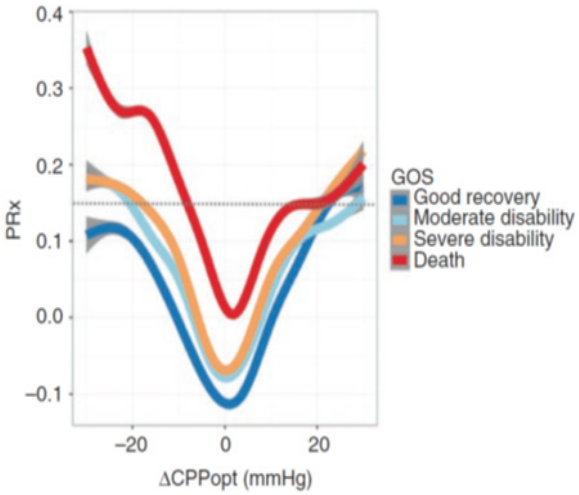


**Figure 3. A curve between ΔCPPopt and PRx, stratified by 6-month GOS.[19]**

of time that patients with TBI spend above or below CPPopt is correlated with their outcome.[16] Pressure Reactivity Index has also demonstrated the ability to predict TBI patients' outcomes. Numerous investigations have demonstrated that in TBI patients, a positive PRx is likely to have unfavourable outcomes. These investigations used a variety of cutoff point values, most of which are greater than 0,15 up to 0.30.[1,15,19] The initial investigation conducted by Marek Czosnyka and colleagues revealed that PRx exhibited a significant association with the outcome and the Glasgow Coma Scale (GCS) of the individuals. Based on the correlation coefficient, there exists a moderate relationship (r = 0.484) between PRx and the outcome, where an elevated PRx value is indicative of poorer outcomes.

Conversely, a weak inverse correlation is observed between PRx and GCS (r = -0.29), suggesting that higher PRx values are linked to lower GCS scores.8 The PRx has been used in conjunction with Mx to assess CA, based on these studies, positive values of Mx and PRx indicate impaired CA. In this study, which measured CA every day, it was found that Mx and PRx in TBI patients who survived were lower until the third day after trauma (Mx 0,01±0,25; PRx -0,06±0,30 vs Mx 0,25±0,28; PRx 0,17±0,44). However, there was no discernible differentiation on the following day between survivors and non-survivors. In this study, intact autoregulation is defined as PRx less than 0,3.15 Another study showed that there are association between static rate of autoregulation (SRoR) with PRx (R2 = 0,31) and cerebral metabolic rate of oxygen ($CMRO_2$) with PRx (R2= -0,21). Both of those parameters (SRoR and $CMRO_2$) were examined by PET scan. According to this study, a change in $CMRO_2$ (low or high extraction) and low CBF was also linked to impaired cerebrovascular pressure reactivity.[18]

**Optimal Cerebral Perfusion Pressure-Based Therapy**

The first CPP-based management in TBI was introduced by Rosner and colleagues in 1995. Based on their study, maintaining CPP about 70 mmHg up to 85 mmHg (in some individuals could be about 100 mmHg) gives a better outcome for TBI patients. Moreover, artificial hypertension to raise CPP did not exacerbate or worsen intracranial hypertension; rather, the mortality rate could rise by as much as 20% for every 10 mmHg decline in CPP.[10,20] However, till now this finding is still debatable. The theory underlying CPP-based care is that meeting the metabolic requirements of the injured brain requires maintaining optimal CBF. Cerebral perfusion pressure is the stimulus for cerebral vascular autoregulatory responses; thus, maintaining CPP within the functional CA range is important in the care of neuro-intensive patients. The goal is to maintain sufficient flow to the ischemic penumbra while preventing the exacerbation of secondary insults, such as excitotoxicity, the production of free radicals, and inflammation. Keep in mind that brain injury can shift the CA curve to the right, requiring a higher CPP to achieve normal CBF. Thus, the lower limit of autoregulation is not only higher than normal, but also decreased at a time when brain tissue is most vulnerable to ischemic insults. In addition, cerebral vascular resistance is generally higher, and the critical closure pressure is also much higher. Furthermore, there is a blunting of the autoregulatory latent period, which occurs when the vasculature has not had time to dilate or constrict in response to a change in pressure.[10]

The "Lund concept" therapy is another concept that is comparable to the CPP-based management; this concept is based on ICP management. The Lund concept, while falling under the category of CPP-targeted therapy, contends that elevated CPP simply serves to exacerbate intracranial hypertension and worsen cerebral oedema. Reduced CPP (lower than LLA) will induce vasodilatory compensation of the autoregulatory response, which will worsen the oedema and increase the ICP through a vasodilation cascade.[10] According to a recent study, the prognosis of TBI patients is correlated with the length of time the patient had high ICP (more than 20 mmHg) and CPP (below 60 mmHg or above 70 mmHg) outside recommended levels. According to recent research, the mortality of TBI patients correlates with the length of time the patient experiences high ICP (more than 20 mmHg) and CPP outside

recommended levels (below 60 mmHg or above 70 mmHg). However, CPP below 60 mmHg or above 70 mmHg is not associated with neurological outcomes.[6,16] As mentioned previously, there are negative effects on the brain from both low and high CPP. Thus, the concept of figuring out the ideal CPP ($CPP_{opt}$) emerged. The first study to determine CPPopt in each individual patient was done in 2002. According to that study, it can be concluded that there is a correlation between CPPopt and GOS (r = -0.51). This implies that the greater the difference between CPP and CPPopt, the worse the outcome.

However, the correlation coefficients for ΔCPPopt less than 0 and more than 0 are different (0.53 vs. -0.40). Patients with good outcome (GOS 5) have a mean ΔCPPopt (CPP – CPPopt) of 3 mmHg, whereas patients with moderate disability (GOS 3-4) have a mean CPPopt of 7 mmHg, and dead patients have a mean CPPopt of 16 16mmHg.[18] A follow-up study conducted ten years later revealed that keeping CPP around CPPopt (less than 2 mmHg) is a better value than using a fixed threshold (between 60 and 70 mmHg) to manage CPP of TBI patients. A follow-up study conducted ten years later revealed that keeping CPP around CPPopt (less than 2 mmHg) is a better value than using a fixed threshold (between 60 and 70 mmHg) to manage the CPP of TBI patients. This study also demonstrated that patients with CPPs higher than $CPP_{opt}$ (hyperperfusion) frequently experienced severe disability, and that mortality rates rose when CPP was lower than CPPopt (hypoperfusion).[17]

Recently, COGiTATE study shown that dynamic CPP (CPPopt) targeted therapy have shown a promising result even though they are not statistically significant. This study found that targeting CPPopt have a better outcome such as lower mortality rate than recommended CPP (22% vs 39%), GCS less than 8 at ICU discharge (9% vs 11%), mortality at 6 month (23% vs 44%) and higher favorable outcome (GOS 4–5) at 6 month (50% vs 34%). Even though, percent time CPP higher than 70mmHg was longer 64,9% (44 - 82,5) in $CPP_{opt}$ group and 30,7% (23 - 44,6) in recommended CPP. The average CPP trendline value was higher in $CPP_{opt}$ group with 72(66 – 77) mmHg than CPP recommended with 69(67 - 73) mmHg.[7] The results of this study support previous research. In those study, it was found that mortality was associated with ΔCPPopt ≤ -5 mmHg, and 0 to 10 mmHg was the ideal ΔCPPopt with good results (GOS 4-5). Additionally, a percentage of time ΔCPPopt ≤ -5 mmHg was associated with an unfavorable outcome (GOS 2-3) and death. The critical value for an unfavorable outcome is below 27%, while the critical threshold for death is above 45%.[20]

The idea behind CPPopt-based therapy is to rely on the CA's ability, which can be obtained from PRx, to maintain CPP based on its CPPopt (± 5 mmHg). Cerebral autoregulation refers to the brain and cerebral vasculature capacity to control blood flow by adjusting to its metabolic requirements under diverse physiological circumstances. The pressure reactivity index (PRx) is a commonly employed surrogate technique for continuous bedside estimation of CA. Hence, PRx is a measurement of the linear relationship between the MAP and ICP slow-wave components. A rise in MAP causes an increase in ICP, which is indicative of impaired CA, and this results in a positive correlation coefficient between MAP and ICP, or positive PRx. Normally, this rise would not occur with an intact CA. If the PRx is negative, it suggests that there is a compensatory cerebrovascular response to an elevated MAP, which lowers the ICP. Cerebral autoregulation is often compromised by acute neurological lesions and systemic pathologic conditions. In patients with traumatic brain injury, large ischemic stroke, and spontaneous subarachnoid hemorrhage, impaired autoregulation is associated with a worse prognosis.[12,16]

**What can be inferred from PRx (in situations where this measurement cannot be done)**

As mentioned previously, PRx is the correlation coefficient between MAP and ICP. According to physiological principles, if MAP rises, CA will physiologically counteract by lowering CBV in order to keep ICP from rising. A decrease in CBV will cause a decrease in CBF, causing

the brain to compensate by increasing MAP to compensate for the decrease in CPP. This procedure will keep happening until the limit on autoregulatory compensation is exceeded. If this happens, CA will be disrupted and impact PRx. If CA is disturbed, an increase in MAP will cause an increase in CBV, thereby increasing the increase in intracranial volume. According to the Monroe-Kelly doctrine, an increase in ICV will be followed by compensation from other compartments (CSF, blood, and brain tissue). However, if the compensation limit is exceeded, there will be a rapid increase in ICP. Therefore, figuring out the limit of optimal CPP where CA is still intact can be aided by understanding the values at which increasing MAP is not associated with increasing ICP (PRx).[2,8,13]

Therefore, even without PRx, we can determine CA by monitoring changes in ICP and MAP. ICP monitoring can be performed by direct (intraventricular catheter or IPM) or indirect (optic nerve sheath diameter, pulsatility index, and pupillometry) assessment. Although indirect assessment cannot determine the exact value of ICP, we can still determine the incidence of increased ICP with the help of those parameters.[3,11] Additional factors may also be taken into consideration in CPPopt-based management, such as assessment of ischemia with near infrared spectroscopy (NIRS), cerebromicrodialysis (CMD), or jugular vein oxygen saturation (SjvO2), which shows a decrease in CPP. Meanwhile, it is possible that the CPP is too high if there are indications of an increasing ICP.[10,19,20]

## Conclusion

Pressure reactivity index (PRx) is a relationship between MAP and ICP derived from dynamic, slow variations in cerebral blood volume (CBV) by cerebral autoregulation. The U-shaped curves of PRx and CPP can help determine CPPopt values. Numerous studies have demonstrated that the PRx value is correlated with the outcome of TBI patients and that controlling CPP between CPPopt can improve the outcome of TBI patients. The pressure reactivity index plays an important role in managing TBI patients.

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