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Clinical value of non-invasive monitoring of cerebral hemodynamics for evaluating intracranial pressure and cerebral perfusion pressure in patients with moderate to severe traumatic brain injury

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Abstract

Objective: To explore the clinical value of non-invasive monitoring of cerebral hemodynamics for evaluating intracranial pressure (ICP) and cerebral perfusion pressure (CPP) in patients with moderate to severe traumatic brain injury (TBI). *Methods:* Transcranial Doppler (TCD) was employed to detect the hemodynamics of bilateral middle cerebral arteries, including systolic blood flow velocity (Vp), diastolic blood flow velocity (Vd), average flow velocity (Vm), pulsatility index (PI) and resistance index (RI) in 52 patients with moderate to severe TBI. At the same time, the CPP, ICP and mean arterial blood pressure (MABP) were monitored. The correlations between hemodynamics and MABP, ICP as well as CPP were analyzed. *Results:* The PI and RI were positively related to the ICP ($r=0.881$, $P<0.0001$; $r=0.789$, $P<0.0001$). Multiple stepwise regression analysis showed PI was closely associated with ICP ($ICP=-8.593+24.295PI$; $t=13.216$, $P<0.0001$) and significant correlation was also found between CPP and PI as well as MABP ($CPP=15.596-22.886PI+0.910MABP$; $F= 76.597$, $P<0.0001$).
Conclusion: Non-invasive monitoring of cerebral hemodynamics by TCD can reflect the real time changes in the ICP and CPP and may be used as an effective tool to monitor the ICP and CPP. This method is non-invasive, safe, cheap, repeatable and applicable in clinical practice.

INTRODUCTION

Primary traumatic brain injury (TBI) is irreversible, so the therapeutic goal of TBI is to prevent and minimize secondary brain injury. The causes of secondary brain injury include: increased intracranial pressure (ICP); cerebral circulatory disorder and insufficient cerebral perfusion; pathophysiological changes in brain cells; dysfunctions of multiple systems following TBI. The key point in the treatment of TBI is to control the ICP, improve the cerebral circulation and perfusion. It has been demonstrated that effective monitoring of the ICP and cerebral perfusion pressure (CPP) is critical for the clinical treatment of TBI.[1,2] The recent trend in Neurosurgery is from invasive to minimally invasive or even non-invasive. In this prospective study, non-invasive monitoring of cerebral hemodynamics was performed and the relationships between hemodynamics and the ICP and CPP were analyzed. Our study aimed to explore the clinical value of non-invasive monitoring of ICP and CPP in patients with TBI.

METHODS

The patients

A total of 52 patients with acute TBI were recruited from December 2008 to December 2010 for this study. There were 43 males and 9 females with a mean age of 37 years (range: 17-72 years). The mean Glasgow Coma Scale (GCS) score was 7 (range: 3-12). The mechanism of the TBI were acceleration injury (n=26), deceleration injury (n=22), and mixed injury (n=4). The causes of the TBI were traffic accidents (n=36), fall (n=8), contusion (n=5) and others (n=3). The types of injury were acute subdural hematoma and brain contusion (n=21), epidural hematoma (n=4), diffuse brain contusion/primary brain stem injury (n=11), intraparenchymal hematoma (n=5), traumatic subarachnoid hemorrhage (n=4), brain

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contusion (n=5), and open brain injury (n=2).

There were 4 cases of traumatic subarachnoid hemorrhage accompanied by diffuse cerebral swelling due to cerebral contusion and laceration. Cerebral contusion and laceration was evident during treatment after cerebral swelling gradually disappeared. It was not common to diagnose traumatic subarachnoid hemorrhage alone, since it was often complicated by cerebral contusion and laceration. In the current study, intracranial pressure monitoring was done through a detector in the brain parenchyma. This was instead of a ventricular detector with ventricular drainage functionality. The parenchyma detector avoided cerebrospinal fluid loss which could affect the ICP.

Inclusion criteria and exclusion criteria

The inclusion criteria of our study were: 1) Patients admitted within 48 hours after injury; 2) Age 14-75 years; and 3) GCS was ≤12 on admission. The exclusion criteria were: 1) Concomitant severe combined injury and shock; 2) Patients had definite stenosis of internal carotid arteries and vertebrobasilar artery system; 3) The temporal window was closed completely and blood flow signals were unable to be detected; 4) patients with heart or kidney dysfunction; and (5) Mortality within 3 days after injury.

Examinations and treatment

ICP was measured using an ICP monitor (MPM-1, USA) for 5~7 days. Dual-channel transcranial Doppler 2 HMz probe was employed to measure the cerebral dynamics ((DWL Multi-Dop X_2, German) through the bilateral temporal window and to detect the middle cerebral artery blood flow (depth: 45-60 mm). Multi-function monitor and intravascular fiber optic probe were used to detect the pressures of radial artery and dorsalis pedis artery and the mean arterial blood pressure (MABP) were calculated. The frequency spectrum and parameter of transcranial Doppler ultrasound (TCD) for cerebral vasospasm were significantly different from those for intracerebral blood pressure. For the former, the systolic and diastolic blood flow velocity increased simultaneously, and the pulsatility index (PI) and resistance index (PI) were normal. For the latter, the systolic Vm increased, while the diastolic Vm decreased, though PI and RI were obviously increased. Thus TCD features for cerebral vasospasm did not impact the evaluation of ICP. Routine neurosurgical interventions were performed in all patients. Under the favorable airway management, sufficient sedation/hibernation or hypothermia therapy was carried out.

Observations and data collection

The hemodynamics including pulsatility index (PI), resistance index (RI), peak flow velocity (Vs), end-diastolic velocity (Vd) and mean flow velocity (Vm) were measured at both middle cerebral arteries. At the same time, the ICP and MABP were measured. This was followed by determination of CCP as follow: CPP=MABP-ICP. The non-invasive CPP (nCPP) was determined based on: nCPP=MABP*Vd/Vm+14; the non-invasive ICP (nICP) was determined based on: nICP=MABP *(1-Vd/Vm).[3,4] Cerebral blood flow parameters were determined based on mean values of middle cerebral artery blood flow. In our study, pH and PCO2 were in the normal range to prevent their influence on hemodynamic measurements. The measures to control pH and PCO2 included endotracheal intubation, tracheotomy, machine-assisted breathing, and oxygen inhalation with different flows. In our study, the patient's heart rhythm and respiratory rate were controlled during the TCD, so as not to affect the PI and other TCD readings.

Statistical analysis

Statistical analysis was performed using SPSS version 11.5 and data were expressed as mean ± standard deviation (x ± SD). The comparisons between CPP and nCPP as well as between ICP and nICP were done with paired t test. Correlations between ICP, CPP and PI as well as RI, between CPP and nCPP and between ICP and nICP were also analyzed with linear correlation analysis. The relationships between hemodynamics and MABP, ICP as well as CPP were analyzed using multiple regression analysis. The comparisons of the remaining parameters were done with paired or independent samples t test. A value of $P<0.05$ was considered statistically significant. For stepwise regression analysis, a preset $\alpha=0.15$ was used as a minimum threshold for inclusion.

RESULTS

After TBI, the ICP increased with the elevation of PI and the changes in the blood flow were first characterized by the reduction of Vd. The Vm was relatively low. With the increase of ICP, the Vs also declined and was characterized by high and sharp systolic peak, fusion of S1 and S2, deepened

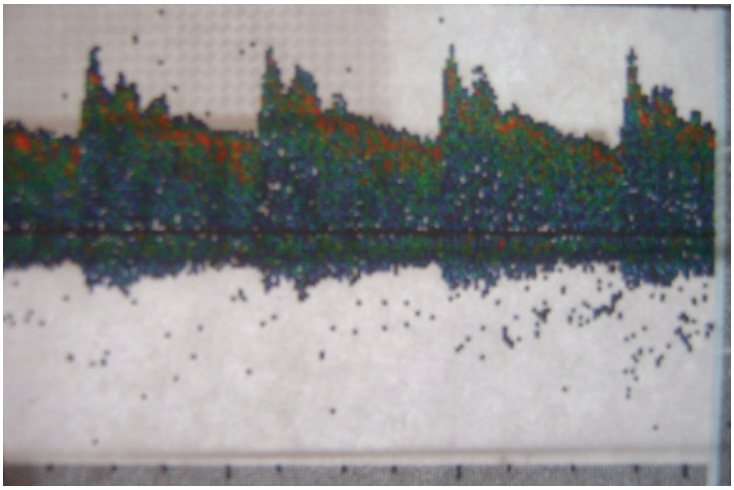

Figure 1: Normal blood flow spectrum. Three peaks were obvious, Vd was relatively high, PI and RI were relatively low and spectrum had approximate right triangle-like feature. S1: Peak systolic; S2: Vascular pulse wave in the systolic phase; D: peak in the early diastolic phase.

diastolic anterior notch and increased pulsatility. When the ICP was near to the diastolic pressure, the diastolic blood flow signals were absent and typical frequency spectrum of brain death was present as oscillating blood flow or nail blood flow (Figure 1-4).

In the present study, ICP=20 cm H_2O was defined as the threshold, and the patients with ICP>20 cm H_2O were compared with those with ICP<20 cm H_2O. Results showed statistical significant differences in the PI, RI and Vd between the two groups (P<0.01 or P<0.05), but there were no statistical significant differences in the Vs and Vm between the groups (P>0.05) (Table 1).

There were linear correlations between ICP and PI as well as RI (r =0.881, P<0.0001; r =0.789, P<0.0001). The coefficients of determination were R=0.777 and R=0.623, respectively (Figure 5). The regression equations between ICP and PI as well as between ICP and RI were as follows: ICP=-8.593+24.295PI (t=13.216, P<0.0001); ICP=-47.948+109.208RI (t=9.098, P<0.0001). Multiple stepwise regression analysis

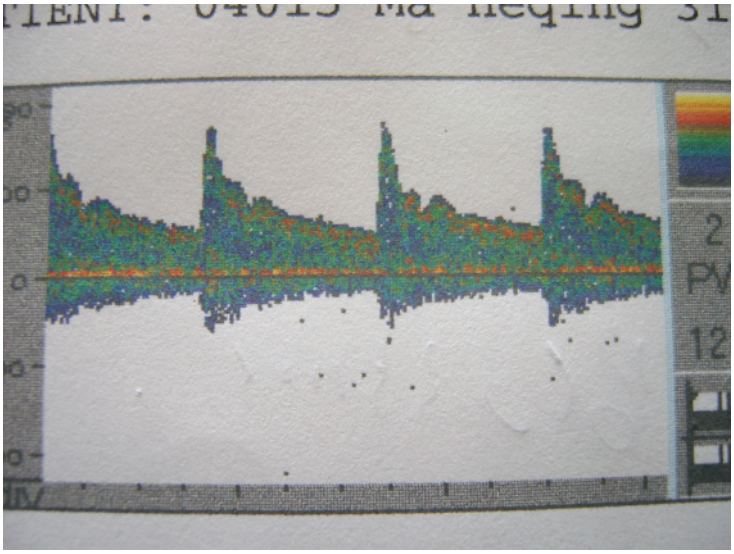

Figure 2: ICP increased and the peak systolic was high and sharp. S2 tended to disappear, and had deep anterior notch in the diastolic phase. D level reduced, Vd and Vm decreased accompanied by increase of PI and RI.

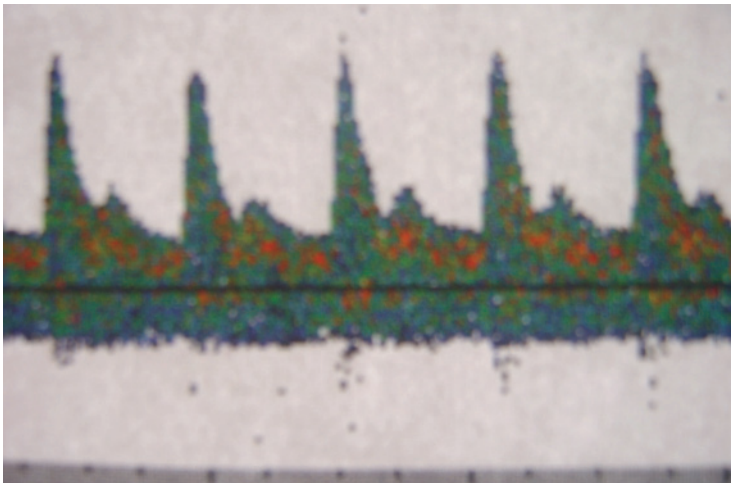

Figure 3: ICP further increased and the SI was steep. The S2 merged with S1, the D level reduced and Vd and Vm decreased. The anterior notch in the diastolic phase was deepened. Both PI and RI increased.

showed significant correlation only between ICP and PI, and the multiple correlation coefficient and coefficient of determination were 0.882 and 0.777 respectively ($F=174.652$, $P<0.0001$). These findings suggest PI is a good variable that can reflect the changes in the ICP and PI, and is positively and closely correlated to the ICP. In addition, ICP was positively correlated to the Vm, and negative correlation was noted between Vp and Vd. However, there were no clear correlations between ICP and RI as well as MABP.

Statistical analysis showed no marked difference between CPP and nCPP ($P>0.05$) but nCPP was closely correlated to the CPP ($r=0.815$, $P<0.0001$). In addition, ICP was significantly different from nICP ($P<0.01$) (Table 2). These results reveal nICP is unfeasible to evaluate the ICP but nCPP can be applied to assess the CPP. Correlation analysis also displayed ICP was closely related to the nICP with large correlation coefficient ($r=0.831$, $P<0.01$) demonstrating that nICP can reflect the changes in ICP.

CPP was negatively associated with PI and RI ($r=-0.559$, $P<0.01$; $r=-0.508$, $P<0.01$) (Figure 6), and the regression equations were as follows: CPP=90.099-14.561PI ($t=-4.768$, $P<0.0001$),

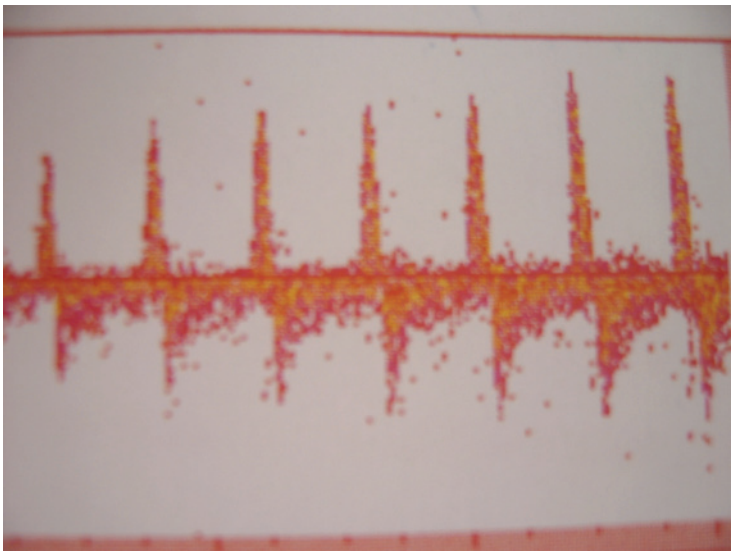

Figure 4: ICP increased and was higher than the diastolic pressure and MABP. This represented a clinical brain death state. The Vd was absent and revere flow was found in the diastolic phase. The effective cerebral perfusion was absent predicting brain death.

Table 1: Comparisons of different parameters of cerebral hemodynamics between patients with ICP<20cm H_2O and those with ICP≥20cm H_2O

Group	N	PI	RI	Vd	Vm	Vs
ICP<20cmH_2O	28	1.01±0.19	0.59±0.07	50.39±20.01	71.79±26.73	119.71±39.02
ICP≥20cmH_2O	23	1.96±1.28	0.74±0.14	38.04±23.40	67.35±32.47	142.25±48.51
t		3.893	4.876	2.032	0.536	1.847
P		0.000	0.000	0.048	0.595	0.071

CPP=114.284-66.352RI (t=-4.165, P<0.0001). Multiple stepwise regression analysis showed the significant correlations between CPP and PI as well as MABP and the multiple correlation coefficient and coefficient of determination was R=0.870 and R^2=0.758, respectively (F=76.597, P<0.0001). The optimal regression equation was CPP=15.596-22.886PI+0.910MABP (F= 76.597, P<0.0001). The CPP was closely related to the PI and MABP with large correlation coefficients. CPP was negatively related to PI but positively associated with MABP.

DISCUSSION

The moderate to severe TBI is a common disease in Department of Neurosurgery and usually has terrible disease condition and high disability and mortality. Thus, the treatment of moderate to severe TBI has been challenging in the clinical practice. About 40-82% of patients with severe TBI have increased ICP, which is the main cause of reduction of CPP and cerebral blood flow (CBF) and frequently cause the dysfunction of central nervous system or even death. Thus, it is important to monitor the post-injury ICP and CPP. The control of ICP and maintenance of CPP are critical for the successful treatment of TBI. ICP cannot be reliably estimated from any specific clinical feature or computed tomography (CT) finding and must actually be measured. Different methods of monitoring ICP have been described but two methods are commonly used in clinical practice: intraventricular catheters and intraparenchymal catheter-tip.[5] The "gold standard" technique for ICP monitoring is a catheter inserted into the lateral ventricle, usually via a small right frontal burr hole. However, placement of the catheter may be difficult if there is ventricular effacement or displacement due to brain swelling or intracranial mass lesions. The use of intraventricular catheters is complicated by infection in up to 11% of cases.[6,7] This is a serious complication resulting in significant morbidity and mortality. The risk for infection and intracranial hemorrhage and high cost for invasive monitoring significantly limit the wide application of this technique. With the development of minimally invasive and non-invasive concepts in the neurosurgery, it is imperative to develop an effective and non-invasive technique to monitor the ICP and CPP. Nowadays, increasing attention has been paid to the detection of hemodynamics by TCD and the blood pressure and electrocardiogram to evaluate the ICP and CPP, which are then applied to guide the clinical treatment and evaluate the prognosis in moderate to severe TBI.

Changes in the cerebral hemodynamics of patients with moderate to severe TBI

TCD provides useful information on cerebral circulation even under raised ICP[8]. Normal cerebral blood flow spectrum is characterized by approximate right triangle with steep ascending wave and relatively flat descending wave. Three

Table 2: Comparisons between nCPP and CPP as well as between nICP and ICP

Variable	n	value	variable	n	value
nCPP	52	72.81±16.49	nICP	52	36.83±16.42
CPP	52	70.17±16.14	ICP	52	24.65±17.71
t		1.727			8.791
p		0.090			0.000

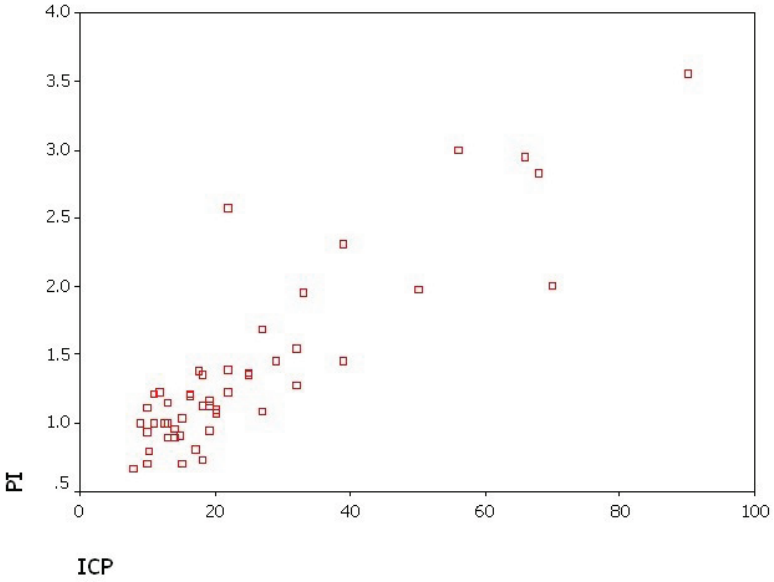

Figure 5: Correlation between ICP and PI. ICP was positively related to PI (r=0.881, P<0.01) and there was positively linear correlation between ICP and PI. The regression equation was ICP=-8.593+24.295PI (t =13.216, P<0.001).

peaks can be found in this spectrum: peak systolic (S1), second systolic (S2), and peak diastolic (D). When the ICP increases, the abnormal cerebral hemodynamics is characterized by decreased Vd, high and sharp S1 and decreased Vm. In addition, the PI and RI are also increased. The changes in the frequency spectrum are related to the extent of ICP increase. In the present study, with the increase of ICP, the Vd decreased first and Vs slightly increased at the early stage but the Vm was normal. Subsequently, the systolic and diastolic notchs were deepened, the S2 and D are absent and the S1 was high and sharp. Finally, the reverse flow at the diastolic stage and nail-like flow might be present. Thus, we can determine the changes in the ICP according to the cerebral blood flow spectrum which are then applied to guide the clinical treatment. Of course, ICP together

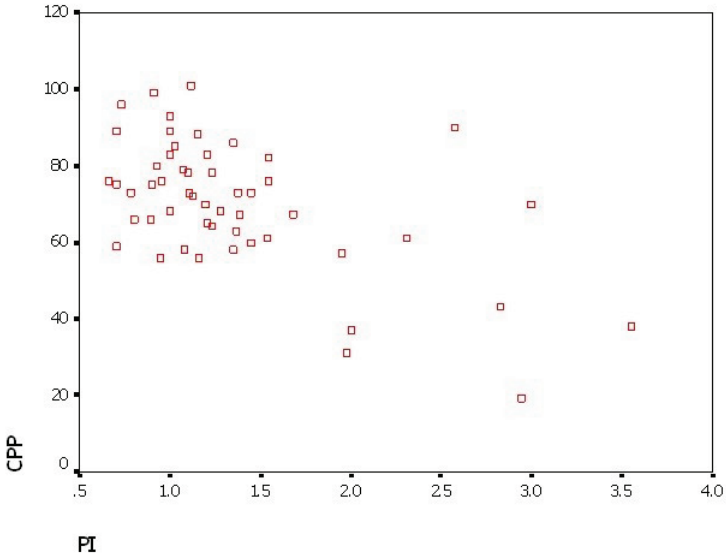

Figure 6: Correlation between CCP and PI. CPP was negatively related to PI (r=-0.559, P<0.01), and there was negatively linear correlation between CPP and PI. The regression equation was CPP=90.099-14.561PI (t=-4.768, P<0.001).

with hemodynamics including PI, RI and Vm may elevate the accuracy in the determination of ICP. Our results showed significant differences in the PI and RI between patients with ICP>20 mmHg and those with ICP<20 mmHg. These findings demonstrate PI and RI can be used to reflect the ICP.

Relationship between cerebral hemodynamics and ICP

Both RI and PI can reflect the elasticity, compliance and resistance of intracranial blood vessels. The increase of PI or RI suggests the elevation of cerebral vascular resistance, decrease of cerebral perfusion and reduction of cerebral blood flow. After TBI, the increase of ICP may result in the elevation of cerebral vascular resistance which affects the cerebral perfusion and reduces the cerebral blood flow. In addition, the cerebral blood flow velocity is also changed to a certain extent, which may be reflected in some parameters of hemodynamics (Vp, Vd, Vm). These are characterized by increase of PI and RI. Gura et al [9] found the ICP was closely related to the PI following TBI. For patients unable to receive invasive monitoring of ICP, monitoring the PI with non-invasive method can be applied to effectively guide the clinical treatment. Homburg *et al*.[10] speculated that when the $PaCO_2$ was stable, PI was positively associated with ICP, and when the ICP ranged from 5 cmH_2O to 60 cmH_2O, approximate linear correlation was found between PI and ICP. Schmidt *et al*.[11] applied multiple regression analysis to generate a mathematical formula for calculating the ICP according to the arterial blood pressure and cerebral hemodynamics in TCD. Their results showed the corresponding pressure trends with a mean absolute difference of 4.0 ± 1.8 mm Hg between computed and measured ICP, and shapes of pulse and respiratory ICP modulations were clearly predicted. Our results showed the linear correlation between ICP and PI as well as RI with large coefficient. Multiple regression analysis showed PI was more important in reflecting the changes in the ICP because the Vm was included in the calculation of PI and thus the PI was sensitive to the changes in ICP.

Relationship between cerebral dynamics and CPP

Following TBI, the increased ICP and/or hypotension may cause the decrease of CPP and reduction of CBF resulting in secondary cerebral ischemia and hypoxia. Melo *et al*.[12] reported that the sensitivity of TCD in the evaluation of high ICP was 94%, that in the assessment of normal ICP was 95% and that in the evaluation of abnormal CPP was 80%. Voulgaris et al found the PI was closely related to the CPP and ICP when the ICP>20 cmH_2O.[13] When the CPP<70mmHg, CPP was negatively associated with PI. In the present study, CPP was negatively relevant with PI and RI. Our results indicate the increased ICP and decreased CPP can be reflected in the parameters of cerebral hemodynamics. However, it is still difficult to accurately determine the CPP level according to the PI and RI. Thus, multivariate analysis and quantitative analysis of CPP are necessary.

CPP is usually affected by numerous factors, of which ICP, MABP and cerebral autoregulation are the most important. Therefore, the parameters of cerebral hemodynamics detected by TCD, together with MABP, can effectively be used to evaluate the changes in the CPP and cerebral autoregulation. In the present study, multivariate analysis showed CPP was negatively related to PI, but positively associated with MABP with large coefficients. PI mainly reflects the ICP which is consistent with the source of CPP: CPP=MABP-ICP. Thus, PI and MABP together with regression equation can be applied to assess the CPP reliably.

Quantitative evaluation of ICP and CPP

Czosnyka et al proposed that nCPP and nICP could be calculated as follows: nCPP=MABP×Vd/Vm+14 and nICP =MABP×(1- Vd/Vm)-14.[2] Their results showed the difference between nCPP and actual CPP was less than 10 mmHg in 82% of patients and less than 13 mmHg in 90% of patients. When the CPP was lower than 60 mmHg, the accuracy of nCPP in the evaluation of CPP was as high as 94%, and the changes in CPP over time and the disease condition were also reflected accurately by the nCPP ($r > 0.8$; $P < 0.001$). However, the difference between nCPP and actual CPP was less than 10 mmHg in only 68%. Our results showed the nCPP could be accurately calculated based on the formula above and the nCPP level was similar to the actual CPP level. These findings suggest MABP, Vd and Vm can be used to accurately evaluate the CPP. Thus, the CPP can be evaluated with a non-invasive method, which is then feasible to guide the clinical treatment. However, the difference between nICP and actual ICP is still obvious, which implies ICP is difficult to be assessed by MABP, Vd AND Vm. This may be attributed to that ICP is not related to

MABP when the cerebral autoregulation is intact, and the PI, a sensitive indicator reflecting ICP, is not included in the formula. Thus, the evaluation of ICP using parameters of cerebral hemodynamics should be explored in future studies.

In conclusion, the evaluation of ICP and CPP using non-invasive parameters of cerebral hemodynamics is safe, practical, repeatable, cheap and easy to carry out, but further studies are required to confirm our findings. Our results demonstrate parameters of cerebral hemodynamics together with MABP can be applied to effectively evaluate the ICP and CPP, which has important clinical implications.

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