

# Relationship between Intracranial Pressure and Critical Closing Pressure in Patients with Neurotrauma

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**Background:** The driving pressure gradient for cerebral perfusion is the difference between mean arterial pressure (MAP) and critical closing pressure (CCP = zero flow pressure). Therefore, determination of the difference between MAP and CCP should provide an appropriate monitoring of the effective cerebral perfusion pressure (CPP<sub>eff</sub>). Based on this concept, the authors compared conventional measurements of cerebral perfusion pressure by MAP and intracranial pressure (CPP<sub>ICP</sub>) with CPP<sub>eff</sub>.

**Methods:** Simultaneous synchronized recordings of pressure waveforms of the radial artery and blood flow velocities of the middle cerebral artery were performed in 70 head trauma patients. CCP was calculated from pressure-flow velocity plots by linear extrapolation to zero flow.

**Results:** Intracranial pressure measured by intraventricular probes and CCP ranged from 3 to 71 and 4 to 70 mmHg, respectively. Linear correlation between ICP and CCP was  $r = 0.91$ . CPP<sub>ICP</sub> was  $77 \pm 20$  mmHg and did not differ from CPP<sub>eff</sub>; linear correlation was  $r = 0.92$ . However, limits of agreement were only  $\pm 16.2$  mmHg. Therefore, in 51.4% of the patients, CPP<sub>ICP</sub> overestimated CPP<sub>eff</sub> by 19.8 mmHg at most.

**Conclusion:** Assuming that CPP<sub>eff</sub> (MAP - CCP) takes into account more determinants of cerebral downstream pressure, in individual cases, the actual gold standard of CPP determination (MAP - ICP) might overestimate the CPP<sub>eff</sub> of therapeutic significance.

SUFFICIENT cerebral perfusion pressure (CPP) is an important factor for the outcome of patients with severe brain injury.<sup>1,2</sup> Measurement of intracranial pressure (ICP) has therefore become established routine monitoring in these patients to determine CPP from the difference of mean arterial pressure (MAP) and ICP.

However, in the early 1960s, Permutt and Riley<sup>3</sup> pointed out that the effective downstream pressure is equal to the tissue pressure only in the absence of vasomotor tone. An estimation of CPP based on measurements of MAP and ICP may therefore be misleading, in particular if ICP is low, as recently demonstrated by Weyland *et al.*<sup>4</sup> From a physiologic point of view, the effective organ perfusion pressure is the difference between mean arterial and effective downstream pres-

sure.<sup>5</sup> The major component of effective downstream pressure is the critical closing pressure (CCP), which in turn might be influenced by tissue pressure, vasomotor tone, and venous pressure.<sup>3,5,6</sup> Cessation of organ blood flow is assumed to occur when CCP equals MAP and perfusion pressure therefore becomes zero.

Dewey *et al.*<sup>7</sup> and Early *et al.*<sup>8</sup> demonstrated in monkeys that CCP is the primary variable affecting cerebral blood flow. They identified vasomotor tone and ICP as the main determinants of CCP. Thus, as suggested by several investigators,<sup>4,9,10</sup> a physiologically more appropriate approach is the determination of "cerebral effective perfusion pressure" (CPP<sub>eff</sub>), which is the difference between MAP and CCP.

Cerebral CCP can be derived from pressure-flow relations because it has been proven by Early *et al.*<sup>8</sup> that cerebral pressure-flow relations in primates are straight lines and, when extrapolated, show a positive pressure intercept at zero flow. In these plots, the slope  $\Delta P/\Delta V$  of the regression curves is a function of vascular bed resistance and the intercept a function of transmural pressure, determined by vasomotor tone and ICP. Data of Dewey *et al.*<sup>7</sup> showed that extrapolation of curves that do not cross zero flow is scientifically sound because only cases in which arterial pressure (AP) decreased below CCP showed hysteresis caused by retrograde emptying of preresistance vessels. In cases in which AP did not cross CCP, pressure-flow relations were best described as straight lines.

Based on this concept, we compared conventional measurements of CPP by MAP and ICP (CPP<sub>ICP</sub>) with CPP<sub>eff</sub>. The cerebral critical closing pressure was assessed in a minimal invasive fashion, *i.e.*, from transcranial Doppler flow tracings and radial artery pressure tracings.

## Methods

After approval by the Institutional Review Board (University of Bonn, Bonn, Germany) and informed consent, 70 consecutive neurosurgical patients who received invasive ICP monitoring because of head injury were included in the study. Patients with evidence of injured cervical or cerebral vessels or other pathologic findings of the cerebral circulation, such as aneurysms, were excluded from the study, as well as patients with increased blood flow velocity in the middle cerebral artery (mean  $V_{MCA} > 120$  cm/s), in whom posttraumatic vasospasm was suspected.

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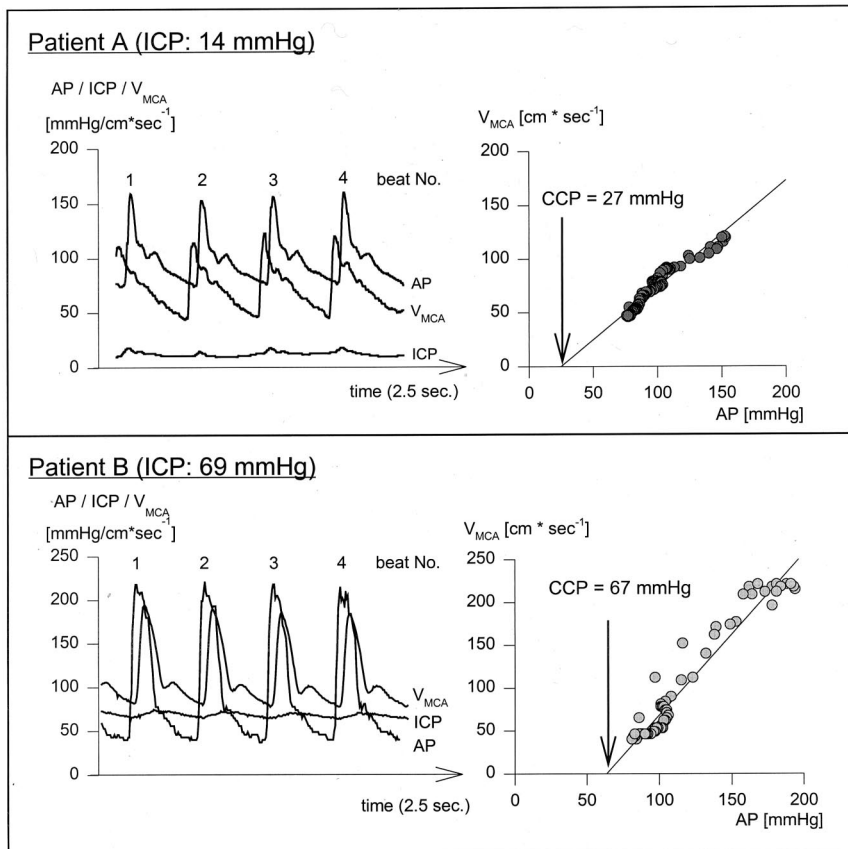


Fig. 1. Two examples of simultaneous recording of arterial blood pressure (AP) in the radial artery, blood flow velocity in the middle cerebral artery ( $V_{MCA}$ ), and intracranial pressure (ICP). Determination of the critical closing pressure (CCP) by extrapolation of the regression curve of the pressure-flow relation of a single heart-beat (beat 3 in both examples) to the x-axis (pressure). Patient A with generalized edema of the brain: ICP = 14 mmHg; CCP was calculated as 27 mmHg. Patient B after severe head trauma with multiple contusions of the brain: CCP was calculated as 67 mmHg. Simultaneous recorded ICP was 65 mmHg.

All patients received controlled mechanical ventilation. Patients received midazolam and sufentanil for sedation and analgesia, respectively. Special care was taken to ensure that determinants of the cerebral circulation, such as MAP, central venous pressure, arterial oxygen tension ( $P_{aO_2}$ ), and arterial carbon dioxide tension ( $P_{aCO_2}$ ), remained constant 30 min before and throughout the measurements. To minimize the influence of venous pressure on the cerebral circulation, the patient's upper body was elevated 15°. ICP was monitored by means of conventional intraventricular probes (Duisburger Nadel; Pilling Weck, Karlstein, Germany). Arterial pressure was monitored *via* radial artery cannulas. Arterial and intracranial pressure transducers were calibrated at the level of the skull.  $V_{MCA}$  ipsilateral to the site of ICP monitoring was measured by means of a 2-MHz transcranial Doppler probe (Multidop T; DWL, Sipplingen, Germany). The Doppler probe was fixed to the patient's head using a specially designed holder apparatus (DWL) to ensure a constant angle of insonation during the study period. Transcranial Doppler adjustments of depth, sample volume, gain, and power were kept constant during the investigation. Instantaneous data of AP, ICP, and  $V_{MCA}$  were stored simultaneously *via* analog-digital converters with a sample rate of 114 Hz using the integrated hard disk of the transcranial Doppler device. Digital signals were then processed off-line using software developed in house (M. S.). CCP was

calculated by heartbeat-to-heartbeat analysis from zero flow velocity pressure as extrapolated by regression analysis of AP- $V_{MCA}$  plots (fig. 1). For determination of CCP, the time lag between the AP and  $V_{MCA}$  curves had to be compensated so that corresponding beats had the same origin. This was performed by shifting the  $V_{MCA}$  curve and iterative regression analysis. The correct time lag compensation for calculation of zero flow pressure was achieved when the hysteresis of AP- $V_{MCA}$  plots was minimal, *i.e.*, the shift of the  $V_{MCA}$  curve resulted in a maximum correlation coefficient of the AP- $V_{MCA}$  plots (average shift 60 ms). Because AP, ICP, and CCP are dynamic values that fluctuate from beat to beat, *e.g.*, because of ventilation, CCP calculations were averaged over a period of two randomly selected respiratory cycles. Thus, depending on ventilation frequency and heart rate, the number of heartbeats averaged for calculation of CCP ranged from 11 to 19.

Cerebral perfusion pressure, estimated as the difference between MAP and mean ICP, and  $CPP_{eff}$ , determined as the difference between MAP and critical closing pressure, were analyzed as suggested by Bland and Altman<sup>11</sup> for assessing agreement between two methods of clinical measurement.

Assuming that CCP is the effective downstream pressure for calculation of CPP, we evaluated to what extent  $CPP_{ICP}$  reflects  $CPP_{eff}$ . Sensitivity and specificity of test results<sup>12</sup> of  $CPP_{ICP}$  for different  $CPP_{eff}$  thresholds were

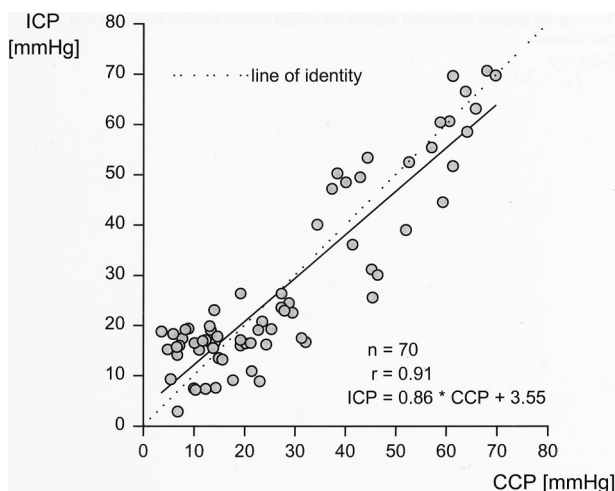


Fig. 2. Linear relation between intraventricular measured intracranial pressure (ICP) and critical closing pressure (CCP) as determined by pressure-flow plots from arterial pressure in the radial artery and blood flow velocity in the middle cerebral artery. Correlation coefficient  $r = 0.91$ ;  $n = 70$ .

calculated. Sensitivity was defined as the fraction of patients with a  $CPP_{eff}$  less than or equal to a predefined  $CPP_{eff}$  threshold in which  $CPP_{ICP}$  was also less than or equal to this threshold of  $CPP_{eff}$ . Specificity was defined as the fraction of patients with a  $CPP_{eff}$  greater than or equal to a predefined  $CPP_{eff}$  threshold in which  $CPP_{ICP}$  was also greater than or equal to this  $CPP_{eff}$  threshold. All results are presented as mean  $\pm$  SD.

## Results

Seventy measurements were performed in 70 patients (26 women, 44 men; aged 18–64 yr, mean age, 35 yr). All patients had diffuse brain edema, 22 had epidural or subdural hematomas without necessity of neurosurgical intervention, and 52 had simple or multiple contusions of the brain. The mean interval between head injury and measurements of CCP was  $4.2 \pm 1.8$  days (mean  $\pm$  SD). All patients received sedation and analgesia with  $0.24 \pm 0.06$  mg  $\cdot$  kg $^{-1} \cdot$  h $^{-1}$  midazolam (mean  $\pm$  SD) and  $0.6 \pm 0.2$   $\mu$ g  $\cdot$  kg $^{-1} \cdot$  h $^{-1}$  sufentanil, respectively. In 25 patients with an ICP greater than 25 mmHg,  $3.1 \pm 0.3$  mg  $\cdot$  kg $^{-1} \cdot$  h $^{-1}$  thiopentone was administered in addition. A CPP (= MAP – ICP) of 70 mmHg or less was maintained by infusion of  $0.1 \pm 0.08$   $\mu$ g  $\cdot$  kg $^{-1} \cdot$  min $^{-1}$  norepinephrine (range: 0.02–0.25  $\mu$ g  $\cdot$  kg $^{-1} \cdot$  min $^{-1}$ ). CPP less than 70 mmHg was tolerated and not treated by catecholamine infusion only in patients in which ICP and CCP were 15 mmHg or less. In 24 of the patients, cerebrospinal fluid withdrawal until 30 min before the measurements was used to manage intracranial hypertension. In eight patients in whom ICP greater than 25 mmHg had been treated with 0.5 g/kg mannitol, measurements were performed 3 h after the infusion. During the measurements, all patients were mechani-

cally normoventilated or slightly hyperventilated with a mean  $Paco_2$  of  $35 \pm 1$  mmHg (range, 32–38 mmHg). Central venous pressure was  $13 \pm 4$  mmHg (range, 7–19 mmHg).

Mean AP measured in the radial artery was  $104 \pm 13$  mmHg and ranged from 72 to 134 mmHg. ICP recordings *via* intraventricular probes in the 70 patients varied from 3 to 71 ( $28 \pm 18$ ) mmHg. Mean CPP, calculated as the difference between MAP and ICP ( $CPP_{ICP}$ ), was  $77 \pm 20$  mmHg (range, 37–109 mmHg). Mean  $V_{MCA}$  was  $62 \pm 24$  cm/s and varied from 38 to 112 cm/s. CCP calculated from pressure-flow velocity relations ranged from 4 to 70 ( $28 \pm 19$ ) mmHg. Mean CPP calculated from MAP and CCP ( $CPP_{eff}$ ) was  $77 \pm 20$  mmHg (range, 39–110 mmHg).

Linear correlation between ICP and CCP was  $r = 0.91$  (fig. 2). Linear correlation between  $CPP_{ICP}$  and  $CPP_{eff}$  was  $r = 0.92$  (fig. 3). Comparison of both methods for determination of CPP according to Bland and Altman<sup>11</sup> showed almost no systematic difference between both approaches ( $-0.28$  mmHg). However, limits of agreement were only  $\pm 16.2$  mmHg (fig. 4). In 36 of 70 patients (51.4%),  $CPP_{eff}$  values lower than  $CPP_{ICP}$  were obtained. For a  $CPP_{eff}$  threshold of 70 mmHg, sensitivity of  $CPP_{ICP}$  was 0.9, and specificity was 0.67 (table 1).

## Discussion

The results of this comparison of  $CPP_{eff}$  determined from MAP and CCP and  $CPP_{ICP}$  calculated from MAP and ICP show a close linear correlation between  $CPP_{eff}$  and  $CPP_{ICP}$ . Nevertheless, in 51.4% of the patients,  $CPP_{ICP}$  overestimated  $CPP_{eff}$ , which more likely should reflect the physiologic relevant driving pressure gradient.

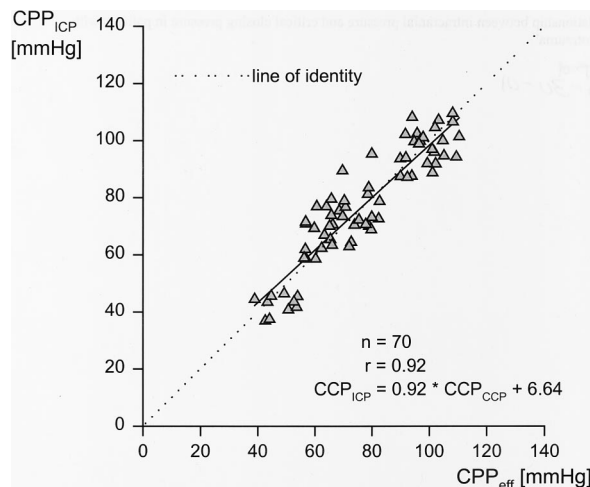


Fig. 3. Linear relation between cerebral perfusion pressure estimated from the difference between mean arterial pressure and intracranial pressure ( $CPP_{ICP}$ ) and physiologically correct determined cerebral perfusion pressure calculated from the difference between mean arterial pressure and critical closing pressure ( $CPP_{eff}$ ). Correlation coefficient  $r = 0.92$ ;  $n = 70$ .



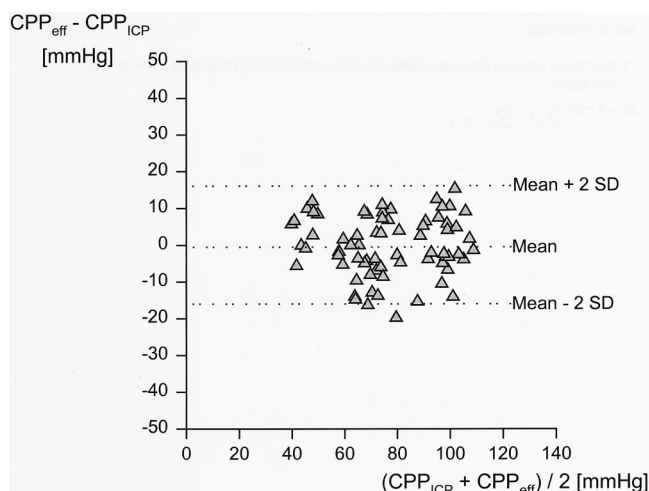


Fig. 4. Clinical measurement comparison according to Bland and Altman<sup>11</sup> of cerebral perfusion pressure as estimated from mean arterial pressure and intracranial pressure ( $CPP_{ICP}$ ) and cerebral perfusion pressure as determined from mean arterial pressure and critical closing pressure ( $CPP_{eff}$ ). Bias:  $-0.28$  mmHg; limits of agreement:  $\pm 16.2$  mmHg;  $n = 70$ .

Measurement of ICP-derived CPP has proved to be a valuable tool for the management of patients with intracranial hypertension.<sup>1,2</sup> The rationale for applying ICP for calculation of the blood flow driving pressure gradient is based on the concept of Burton,<sup>5</sup> who noted that the effective downstream pressure in any part of the circulation is not only determined by the venous back pressure, but also by vasomotor tone and tissue pressure. Using the same concept in a more sophisticated manner, Dewey *et al.*<sup>7</sup> and Early *et al.*<sup>8</sup> demonstrated in monkeys that CCP is the primary variable affecting cerebral blood flow and identified vasomotor tone and ICP as the main determinants of CCP.

Burton's concept<sup>5</sup> of the critical closing pressure seems to be appropriate in particular for the cerebral circulation, in which venous pressure might even be subatmospheric and tissue pressure might easily become the limiting factor in case of brain swelling because of the rigid skull. Nevertheless, it has been noted by several investigators that ICP might not always correctly indicate

effective downstream pressure.<sup>4,9,10</sup> Weyland *et al.*<sup>4</sup> have demonstrated that during hypocapnia, ICP might decrease while the effective downstream pressure increases. Therefore, it seems rational to assess the effective downstream pressure more directly. Theoretically, the effective downstream pressure can be derived from instantaneous pressure-flow relations by determination of the CCP. True pressure-flow relations can only be measured in animal experiments by means of flow probes. Because only linear but not calibrated flow signals should suffice for assessment of the zero flow pressure, flow velocity measurements by transcranial Doppler can be applied for this purpose.

Aaslid<sup>13</sup> proposed extrapolation of a linear regression line between AP and  $V_{MCA}$  to the pressure axis for calculation of CCP. In more simplified methods, time-averaged values of systolic and diastolic pressure and systolic and diastolic blood flow velocities were used for calculation of CCP<sup>14</sup> as well as sequential mean AP and blood flow velocity values.<sup>10</sup> We calculated CCP by linear regression analysis of the instantaneous AP and  $V_{MCA}$  envelope curves.<sup>4,13,15</sup> This method, using the data points of the complete cardiac cycle, should be less sensitive to artifacts of blood pressure measurements than methods dependent on systolic and diastolic AP values. Furthermore, it allows a simple and reliable automatic compensation of the time delay between corresponding waves by shifting the  $V_{MCA}$  curves with an iterative regression analysis until hysteresis is minimized. An alternative method for calculation of the CCP based on Fourier analysis and the first harmonics of the pulse waveforms of AP and flow velocity was suggested by Michel *et al.*<sup>16</sup> The validity of the Fourier analysis-based CCP was confirmed in patients<sup>14</sup> as well as in an animal experimental setting.<sup>17</sup> Determination of CCP by Fourier analysis might be of particular advantage in pediatric populations<sup>16</sup> in which the time resolution of the Doppler signal might become marginal because of higher heart rates. Nevertheless, manual compensation for the time shift between AP and flow velocity was still necessary. In principle, graphically derived CCP and spectral analysis-derived CCP are identical. Whether the latter offers advantage with respect to the signal-to-noise ratio in adults remains unknown.

In this study, in some patients, ICP was observed as being higher than CCP. This observation is in principle contradictory to the theory of CCP; CCP, because of contributing vasomotor tone, should always be higher than ICP.<sup>3,4,7</sup> Similar observations of CCP values lower than ICP by Richards *et al.*<sup>17</sup> and Czosnyka *et al.*<sup>14</sup> have been attributed to autoregulatory vasodilatation during hypoxia or cerebral vasoparalysis. Cerebral vasoparalysis caused by neurotrauma seems to be an unlikely explanation, especially during normal ICP. Other reasons for autoregulatory vasodilatation (extremely low CPP, hypoxia, or hypercarbia) can be excluded in our investiga-

Table 1. Sensitivity and Specificity of  $CPP_{ICP}$  for Different  $CPP_{eff}$  Thresholds

$CPP_{eff}$ Threshold (mmHg)	Prevalence	Sensitivity of $CPP_{ICP}$	Specificity of $CPP_{ICP}$
$\geq 50$	0.91	0.94	1.0
$\geq 60$	0.77	0.98	0.75
$\geq 70$	0.57	0.9	0.67
$\geq 80$	0.39	0.93	0.91
$\geq 90$	0.33	0.87	0.96
$\geq 100$	0.17	0.42	0.93

Suitability of the cerebral perfusion pressure when estimated from mean arterial pressure and intracranial pressure ( $CPP_{ICP}$ ) as a substitute of the cerebral effective perfusion pressure determined from mean arterial pressure and critical closing pressure ( $CPP_{eff}$ ) in clinical monitoring. Sensitivity and specificity of  $CPP_{ICP}$  for different  $CPP_{eff}$  thresholds ( $n = 70$ ).

tion because of the steady state conditions 30 min before the measurements. Another possible explanation for our observations could be resonance phenomena of the arterial blood pressure measurements, which were performed in the radial artery. The increased pressure amplitude at peripheral sites would lead to an underestimation of CCP. Furthermore, this phenomenon could explain the only slight systematical error that, from theoretical considerations, had been expected to be more distinct.

Although principally linear relations between CCP and ICP were demonstrated in several investigations,<sup>14,17</sup> acceptable results for detection of ICP quantitatively by calculation of CCP could not be obtained. The data of our study confirm these observations. However, a close correlation between CCP and ICP was not expected, especially when ICP is low and CCP is relatively more determined by vasomotor tone. Therefore, we did not intend to view CCP as a less-invasive method for determination of tissue pressure (ICP), but we considered ICP as an indirect estimate of the hemodynamically effective downstream pressure (CCP). Thus, we intended to assess the effective cerebral perfusion pressure as the difference of MAP and CCP representing the sum of tissue pressure, vasomotor tone,<sup>5,7,8</sup> and backward venous pressure.<sup>6</sup> Our comparison of  $CPP_{ICP}$  and  $CPP_{eff}$  revealed limits of agreement of  $\pm 16.2$  mmHg. In 36 of 70 patients,  $CPP_{ICP}$  overestimated  $CPP_{eff}$  by 19.8 mmHg at most. Taking into consideration the importance of CPP for therapeutic management in patients with intracranial hypertension,<sup>1,2</sup> this would have considerable consequences.

In a previous study, Czosnyka *et al.*<sup>18</sup> compared  $CPP_{ICP}$  and  $CPP_{eff}$ , which had been estimated graphically as well as by spectral analysis as proposed by Aaslid *et al.*<sup>19</sup> Considerable 95% confidence limits for predictors led to the conclusion that  $CPP_{eff}$  could predict "real CPP" ( $= CPP_{ICP}$ ) with a certain error margin and that this would be of potential benefit for continuous monitoring merely of changes in "real CPP" over time.

Although the ICP is an established and validated standard of neuromonitoring, in principle, it remains an indirect estimate of the effective downstream pressure, which is better represented by the CCP. Therefore, in contrast to Czosnyka *et al.*,<sup>18</sup> we chose to consider MAP minus CCP the "real" cerebral perfusion pressure in this investigation, although we are aware of the fact that this

concept has not been shown to be superior in terms of patient outcome. Still, this view is supported by many other investigators,<sup>4,9,10</sup> and it seemed worthwhile for us at least to point out that differences between the two approaches of CPP assessment might exist, which could potentially lead to differing therapeutic decisions. Besides the more physiologic concept of CCP-derived  $CPP_{eff}$ , clearly, the less invasive nature is an advantage of CPP assessment by transcranial Doppler and pressure waveform analysis.

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