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# Cerebral perfusion pressure in head-injured patients: a noninvasive assessment using transcranial Doppler ultrasonography

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*Object.* The authors studied the reliability of a new method for noninvasive assessment of cerebral perfusion pressure (CPP) in head-injured patients in which mean arterial blood pressure (ABP) and transcranial Doppler middle cerebral artery mean and diastolic flow velocities are measured.

*Methods.* Cerebral perfusion pressure was estimated (eCPP) over periods of continuous monitoring (20 minutes–2 hours, 421 daily examinations) in 96 head-injured patients (Glasgow Coma Scale score $< 13$) who were admitted to the intensive care unit. All patients were sedated, paralyzed, and ventilated. The eCPP and the measured CPP (ABP minus intracranial pressure, measured using an intraparenchymal microsensor) were compared.

The correlation between eCPP and measured CPP was $r = 0.73$; $p < 10^{-6}$. In 71% of the examinations, the estimation error was less than 10 mm Hg and in 84% of the examinations, the error was less than 15 mm Hg. The method had a high positive predictive power (94%) for detecting low CPP ($< 60$ mm Hg). The eCPP also accurately reflected changes in measured CPP over time ($r > 0.8$; $p < 0.001$) in situations such as plateau and B waves of intracranial pressure, arterial hypotension, and refractory intracranial hypertension. A good correlation was found between the average measured CPP and eCPP when day-by-day variability was assessed in a group of 41 patients ($r = 0.71$).

*Conclusions.* Noninvasive estimation of CPP by using transcranial Doppler ultrasonography may be of value in situations in which monitoring relative changes in CPP is required without invasive measurement of intracranial pressure.

**KEY WORDS • transcranial Doppler ultrasonography • ultrasound • cerebral perfusion pressure • head injury**

ALTHOUGH many factors may affect outcome in the patient with head injury, an increase in intracranial pressure (ICP) and a reduction in arterial blood pressure (ABP) are both independently predictive of poor outcome.[11] Both systemic hypotension and intracranial hypertension lead to a reduction in cerebral perfusion pressure (CPP) and a potential decrease in cerebral blood flow (CBF), causing secondary ischemic insults.[3,8,9,12,19] Therefore, the goal of intensive care of head-injured patients is to optimize CPP, a targeted therapy that shows promise as a method to improve outcome after head trauma.[19]

Direct measurement of CPP is complex; the difference between ABP and ICP, although considered the "gold standard," may prove inaccurate in clinical practice. Errors in the measurement of ICP may result from long-term or temperature-induced drifts of the transducer used[4] or, in case of using contemporary microtransducers, from uneven distribution of intraparenchymal pressure within the brain.[18] The less invasive epidural probes have been shown to produce case- and time-dependent errors up to 20 mm Hg.[14] There are also potential errors in the measurements of ABP. Arterial pressure at the level of the brain is often underestimated because all invasive pressure monitoring devices measure readings from peripheral vessels prone to vasospasm and atherosclerosis. Therefore, "real CPP" should not be considered a number but rather a condition for cerebral blood to flow.

Varying CPP produces specific changes in CBF velocity (FV) measured by transcranial Doppler (TCD) ultrasonography[2,6] with stable systolic and falling diastolic values. These changes may be observed in the so-called pulsatility index (defined either as Gosling pulsatility index [GPI], the peak-to-peak amplitude of FV pulsations divided by time-averaged FV, or as "spectral" pulsatility index [SPI], the first harmonic component of FV pulsations divided by mean FV), which has been reported to be inversely proportional to CPP.[2,6]

In 1986 Aaslid, et al.,[1] proposed a formula for estimating CPP by relating the first harmonic component of the ABP pulse waveform to SPI. Although sufficiently sensitive to detect changes of CPP over time, this method proved to have a limited absolute accuracy (the 95% prediction error is as wide as $\pm$ 27 mm Hg[5]).

The present study aimed to address the following ques-

*List of Abbreviations*

ABP = arterial blood pressure
ABPm = time-averaged (mean) arterial blood pressure
aCPP = estimate for CPP based on formula discussed in Aaslid, et al.
A1 = first harmonic component of arterial blood pressure pulse wave
CBF = cerebral blood flow
CPP = cerebral perfusion pressure
eCPP = authors' estimate for CPP
aICP = estimate for ICP using formula presented in Aaslid, et al.
eICP = authors' estimate for ICP
F1 = first harmonic component of blood flow velocity pulse wave
FV = (blood) flow velocity
FVd = diastolic flow velocity
FVm = time-averaged (mean) flow velocity
FVs = systolic flow velocity
GPI = Gosling pulsatility index (GPI = [FVs − FVd]/FVm)
ICP = intracranial pressure
SPI = "spectral" pulsatility index (SPI = F1/FVm)

tions: 1) Is it possible to estimate CPP more accurately? 2) Is it possible to monitor changes in CPP continuously in a noninvasive fashion? 3) When using TCD ultrasonography, what are the factors limiting the accuracy of noninvasive estimation of CPP?

## Clinical Material and Methods

### *Patient Population*

Data were collected from 96 patients suffering from head injury (31 females and 65 males). The patients, whose mean age was 35 years (range 6–75 years) were admitted to the neurointensive care unit at Addenbrooke's Hospital, Cambridge, United Kingdom with a mean Glasgow Coma Scale score of 6 (range 3–12). All patients were sedated with infusions of propofol, fentanyl, and/or midazolam. Muscle relaxation was achieved by using an infusion of atracurium besylate. The patients' lungs were mechanically ventilated with an air–oxygen mixture to maintain adequate oxygenation ($PaO_2 > 12$ kPa) and mild hypocapnia ($PaCO_2$ 35 $\pm$ 5 mm Hg). Intravenous fluids and inotropic support (dopamine, noradrenaline, or adrenaline) were provided as appropriate to achieve and maintain a CPP above 60 mm Hg. Episodes of intracranial hypertension (mean ICP $>$ 25 mm Hg for $\geq$ 15 minutes) were treated according to an accepted protocol that included additional blood pressure increases, hyperventilation, and infusions of mannitol (200 ml of 20% mannitol spread over $\geq$ 20 minutes). Patients in whom bone flaps were removed were excluded. Outcome was assessed 6 months after injury.

### *Monitoring of Patients*

In addition to routine systemic hemodynamic monitoring (ABP, central and pulmonary artery pressures, electrocardiography, and pulse oximetry), ICP and CBFVs were also monitored. The patients' ICP was measured by using a fiberoptic transducer that was inserted intraparenchymally into the right frontal region. Blood pressure was measured directly in the radial artery or the dorsal artery of the foot using a bedside monitor. Cerebral blood FVs were measured daily by transtemporal insonation of the middle cerebral artery (MCA) (20–120 minutes) from the day of admission until discharge or Day 8 after head injury, which was accomplished by using a 2-MHz probe that was supported by a simple rubber strap. The signal of low noise and stable waveform was detected from a depth varying from 4.5 to 5.7 cm, avoiding any section of artery in which the mean FV was above 120 cm/second, indicating the possibility of spasm. This limitation was imposed by the ultrasonograph we used, because it was unable to measure velocity above 200 cm/second.

Signals were monitored during stable ventilatory and nursing periods. Data were excluded during physiotherapy, tracheal suction, and any other nursing maneuvers. The monitoring periods were not related to any particular physiological phenomena and were distributed randomly throughout the day.

### *Data Capture and Calculations*

Analog outputs from the pressure monitors and the TCD unit (maximal frequency envelope) were connected to the analog-to-digital converter that was fitted into a laptop computer. Data were sampled (sampling frequency 50 Hz), digitized (12 bits), and stored on the computer hard disk by using software designed for waveform recording.[21] Digital time series were then processed using software developed in house (by M.C.).

Time-averaged (mean) values of ICP, ABP, CPP (ICPm, ABPm, CPPm, respectively [CPPm = ABPm − ICPm]) were calculated using time integration of waveforms for 5-second intervals. Time-averaged mean, systolic, and diastolic values of FV (FVm, FVs, and FVd, respectively) were calculated after careful spectral filtration to reduce an influence of artifacts and noise and averaged within the same 5-second periods. Digital Fourier analysis[7] was used to evaluate the first harmonic components of arterial pressure (A1) and CBFV (F1) pulse waveforms. Two estimates of CPP were then evaluated: 1) estimate of CPP described by Aaslid, et al.,[1] A1*FVm/F1; and 2) our own formula, ABPm*FVd/FVm.

The first estimate is based on the SPI (F1/FVm); however, it can also be interpreted as the difference between ABP and critical closing pressure (calculated as ABPm − A1/F1*FVm). The second estimate cannot be related directly to critical closing pressure. A potential disadvantage of both methods is that they are unable to compensate for changes in vascular resistance as long as they do not exert a secondary impact on ABP or ICP. For example, during hyperventilation, vascular resistance decreases and the pulsatility index decreases; therefore, the estimate of Aaslid, et al., increases. Conversely, FVd/FVm decreases with hyperventilation (although generally FVd/FVm is less mobile than F1/FVm), decreasing our estimate of CPP.

### *Statistical Analysis*

Estimates of CPP using both formulas measured CPP (CPPm), ICP (ICPm), ABP (ABPm), and FV (FVm); GPI and SPI were averaged over all examinations made in the same patient. These values were then correlated with CPPm. The Mann–Whitney test was used to compare differences in monitored and predicted parameters in patients with different outcomes.

The modified maximum likelihood estimation method[15]

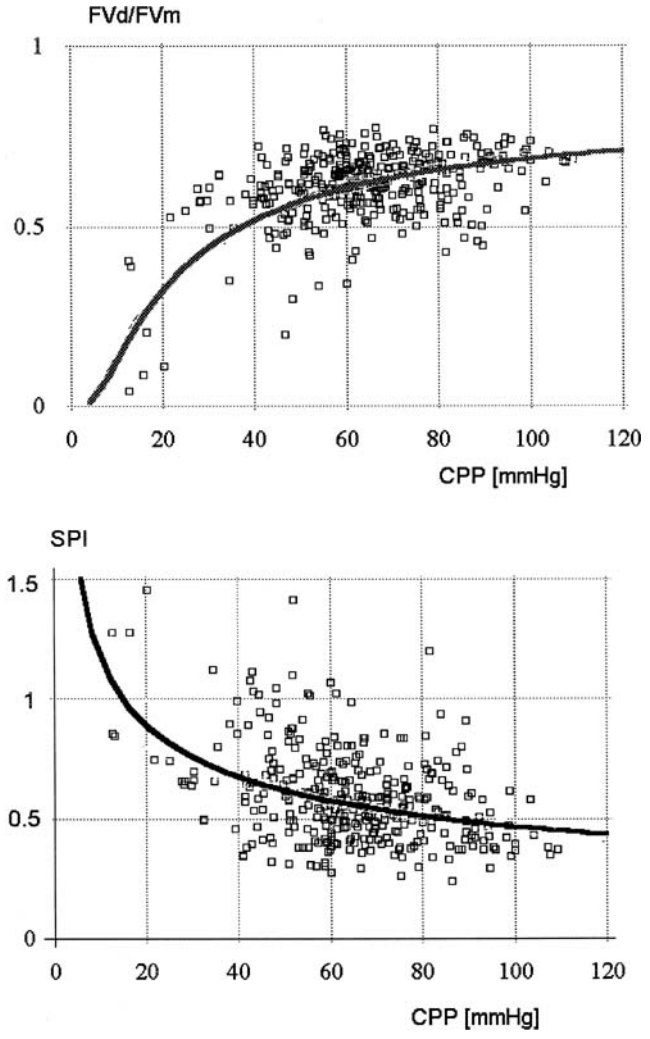


FIG. 1. Composite graphs showing scatterplot of all 421 examinations of the FVd/FVm ratio *(upper)* and SPI *(lower)* compared with CPP in 96 head-injured patients. Modeling curves were calculated using nonlinear regression for data averaged in subsequent patients.

was adopted to minimize error for the CPP estimation. In this method, unknown parameters (constant and multiplicative terms) are estimated to maximize the rate of measurements with an error measuring less than or equal to 15 mm Hg and 10 mm Hg, respectively.

*Sources of Supplies and Equipment*

The fiberoptic transducer used in the experiments was the Camino Direct Pressure Monitor available from Camino Laboratories (San Diego, CA). Blood pressure was measured using the System 800 bedside monitor from S & W Vickers Ltd., Sidcup, United Kingdom). Cerebral blood FVs were measured using the PCDop 842 Doppler Ultrasound Unit, purchased from SciMed, Bristol, United Kingdom). For data capture and calculations, we used the DT 2814 analog-to-digital converter, obtained from Data Translation, Marlboro, MA fitted into a 386SX laptop personal computer. Data were sampled, digitized, and stored using WREC software from W. Zabolotny, Warsaw University of Technology, Poland.

## Results

*Transcranial Doppler Pulse Waveform and CPP*

The FVd/FVm ratio and the SPI (F1/FVm) are crucial for quality CPP estimation. The average relationship between these variables and real CPP found in 96 patients is shown in Fig. 1. Although there was an inverse relationship between the SPI and CPP ($r = 0.47$; $p < 0.001$; 96 patients), the FVd/FVm ratio showed better correlation ($r = 0.65$; $p < 0.0001$; 96 patients, exponential model). This is highlighted in Fig. 1 by the smaller scattering of the measurement points around the modeling curve.

*Estimation of CPP*

The results of regression analysis of CPP compared with estimates of CPP are shown in Fig. 2. A linear predictive model was found to be the most suitable in both cases: $7.72 + 1.14*ABPm*FVd/FVm$; $r = 0.728$; $F = 89$; $p = 0.000001$; 96 patients and $34 + 0.529*A1*FVm/F1$; $r = 0.501$; $F = 26$; $p = 0.00001$; 96 patients.

Our estimator of CPP (eCPP) was associated with better 95% confidence limits for predictors than the estimate of CPP proposed by Aaslid, et al.,[1] (aCPP) ($\pm$ 21 mm Hg and $\pm$ 29 mm Hg, respectively). Both estimators demonstrated a high positive predictive power to detect decreases in real CPP below 60 mm Hg (94% and 84%, respectively). Unfortunately, the negative predictive power in both methods was poor (38% and 36%, respectively).

Further analysis indicated that the maximum likelihood estimators can be evaluated as: $eCPP = ABPm*FVd/FVm + 14$ and $aCPP = A1*FVm/F1 + 15$.

The eCPP was less than 10 mm Hg different from real CPP in 71% of the measurements, whereas only 52% of the aCPP was within 10 mm Hg of real CPP. This difference was significant at $p < 0.0001$ (Fig. 3).

*Accuracy of ICP Estimation*

Using the maximum likelihood method, estimated ICP (eICP) may be predicted as: $eICP = ABPm*(1 - FVd/FVm) - 14$.

The error in estimating ICP by less than 10 mm Hg was achieved in 68% of the measurements. However, it was possible to reduce the error in ICP estimation to less than 5 mm Hg in only 39% of the measurements.

A summary of median values, both measured and estimated in patients with different outcomes, is presented in Table 1. There was no difference between CPPs in patients with favorable and unfavorable outcome, probably signifying the success of the CPP-oriented therapy we use in our center.

*Monitoring of Changes in Real CPP Over Time*

Estimated CPP was highly specific for detecting changes in measured CPP as a result of either increases in ICP (plateau waves) or systemic hypotension.

In six patients with ICP plateau waves, eCPP compared with measured CPP had an average goodness-of-fit coefficient $r^2$ of 0.82. An example is provided in Fig. 4 *upper.*

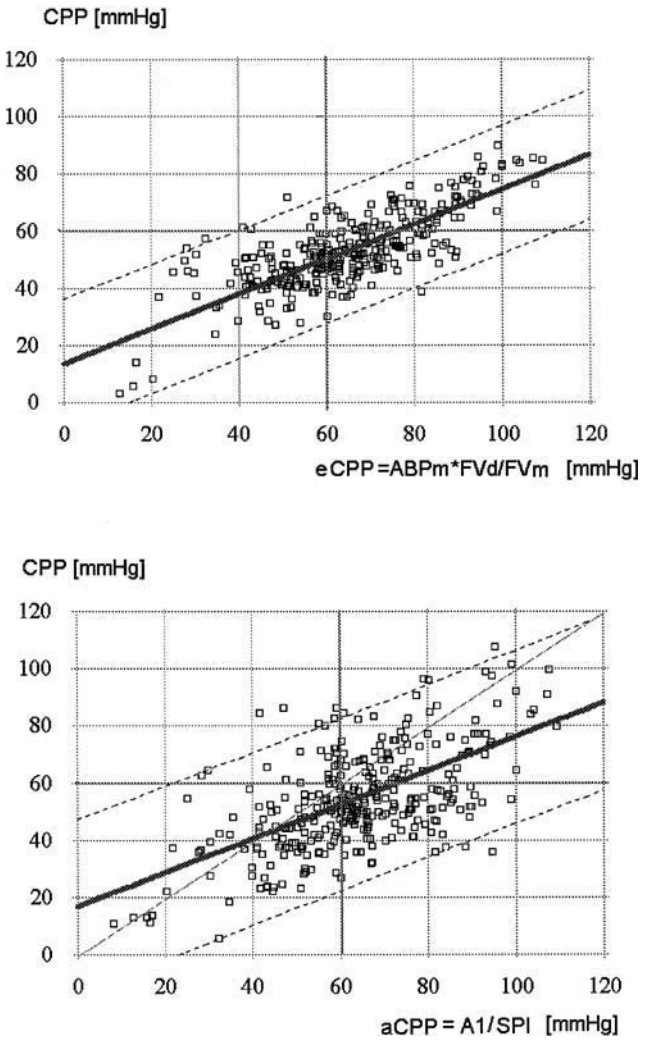


FIG. 2. Graphs. *Upper:* Relationship between our estimator of CPP (eCPP) and real CPP. *Lower:* Relationship between the estimator of CPP proposed in Aaslid, et al., (aCPP) and real CPP. The pa-rameters of the linear regression models are described in text. *Dashed lines* signify 95% confidence limits for predictors calculated by using averaged values for 96 patients.

Furthermore, the eCPP was very sensitive for detecting decreases in ABP below 70 mm Hg (in 10 patients) with an average goodness-of-fit coefficient $r^2$ of 0.92 (Fig. 4 *center*). The B waves (observed in seven patients) in ICP and ABP, which affect real CPP, can also be detected by the eCPP (Fig. 4 *lower*).

Five or more daily examinations were performed in 41 patients. Day-by-day variations in measured CPP that was 15 mm Hg or greater (25 patients) were reflected by variations in eCPP with a goodness-of-fit coefficient $r^2$ of 0.71 (see example in Fig. 5).

### *Confounding Factors*

Changes in cerebrovascular resistance, such as that produced by variations in $PaCO_2$, may disturb CPP estimation. Although an increase in arterial $CO_2$ tension (from mild hypocapnia to normocapnia) decreased the measured CPP (increasing ICP on average by 5 mm Hg in four patients), it often resulted in a slight increase in eCPP (mainly because of an increase in the FVd/FVm factor due to vasodilation).

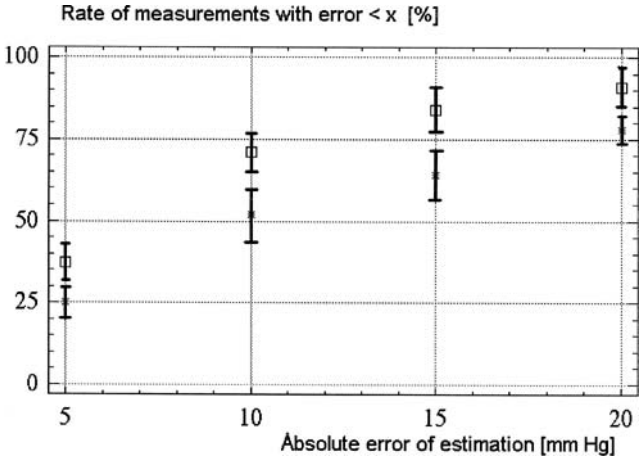


FIG. 3. Graph depicting the rate of error in CPP estimation (mean values and 95% confidence limits) plotted against value of error (*open squares* = our method, *asterisks* = method described by Aaslid, et al.

Similarly, in patients with artery stenosis or proximal spasm (three patients), CPP was overestimated ipsilateral to the stenosis (average side-to-side difference 11 mm Hg). Possible proximal vasospasm may also be one confounding factor. However, an error in CPP estimation was not related to the evidence of subarachnoid blood visible on computerized tomography scanning or to mean FV increased above 80 cm/second. On the other hand, one should bear in mind that our equipment was not able to pick up blood velocities within the range normally observed in severe vasospasm (that is, FVs $>$ 200 cm/second).

TABLE 1

*Median values and significance levels of differences (Mann–Whitney test) for measured and estimated (maximum likelihood method) values obtained in patients with favorable and unfavorable outcomes**

| Factor | Favorable Outcome | Unfavorable Outcome | p Value |
|---|---|---|---|
| measured | | | |
| ABP (mm Hg) | 80 | 84 | <0.052, NS |
| ICP (mm Hg) | 15 | 20 | <0.008 |
| CPP (mm Hg) | 63 | 61 | NS |
| FVd/FVm ratio | 0.64 | 0.60 | <0.03 |
| pulsatility index | 1.01 | 1.17 | <0.01 |
| estimated (mm Hg) | | | |
| CPP: eCPP | 64 | 63 | NS |
| CPP: aCPP | 67 | 67 | NS |
| ICP: eICP | 15 | 20 | <0.005 |
| ICP: aICP | 13 | 18 | <0.047 |
| absolute error of eCPP (mm Hg) | 5.19 | 8.17 | <0.022 |
| absolute error of aCPP (mm Hg) | 10.8 | 8 | NS |

* NS = not significant.

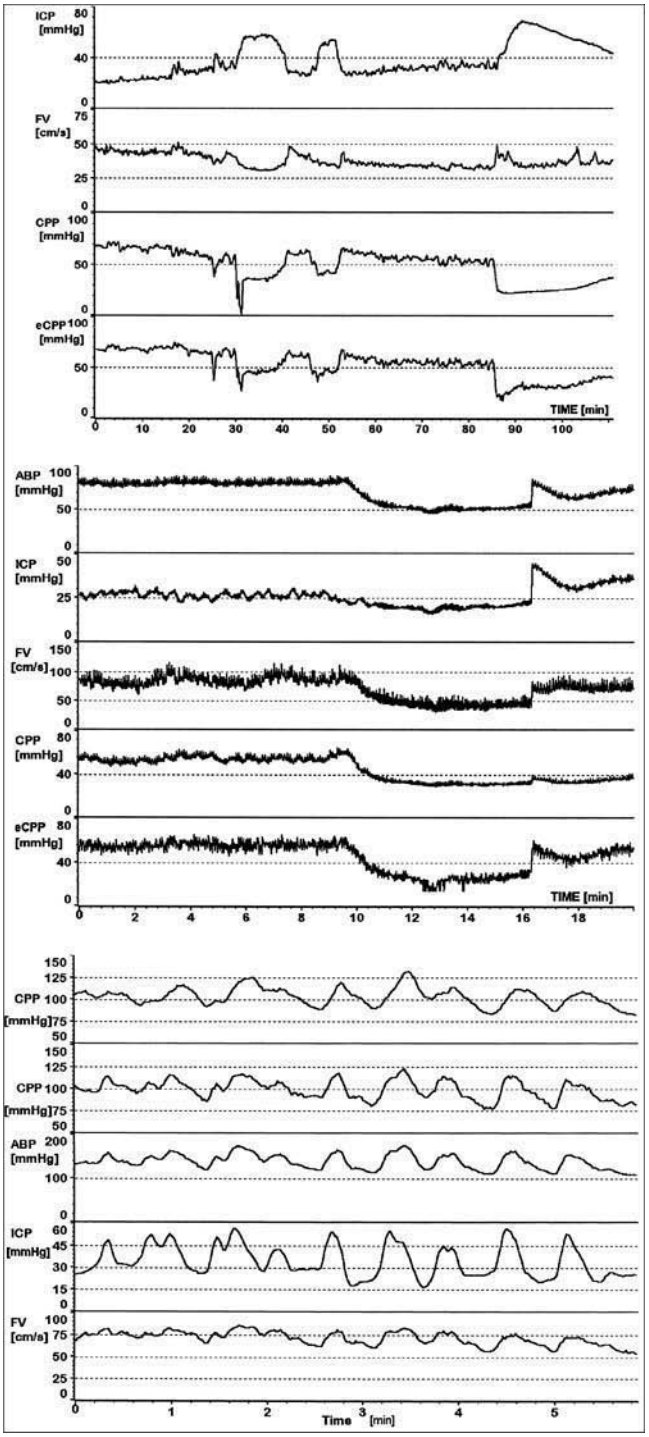


FIG. 4. Traces displaying continuous monitoring of ABP, ICP, CBFV, real CPP, and eCPP during plateau waves *(upper)* during an episode of arterial hypotension due to short discontinuation of infusion of dopamine *(center)*, and in the case of deep B waves of ICP *(lower)*.

## Discussion

A noninvasive CPP estimation will be advantageous to those caring for patients with head injuries, especially in centers where neurosurgical expertise is not immediately available. Patients in whom no surgical intervention is warranted at the time of admission may benefit, but some measure of CPP is required without the risks and costs of invasive ICP monitoring. Furthermore, noninvasive estimation of CPP will provide a measure of CPP in patients at risk from cerebral ischemia during nonneurosurgical procedures, such as liver transplantation, in whom coagulation abnormalities prevent insertion of ICP monitoring devices.

Many attempts have been made to find an "estimator" for CPP;[1,10] however, there is no currently available method accurate enough to be clinically useful. In this study, we attempted to highlight the benefits of our CPP estimation method, which although limited in its ability to predict CPP as a number is able to provide a reasonable detection of changes in real CPP over time. Both the rate of achieving an absolute error below 15 mm Hg and a positive predictive power to detect CPP below 60 mm Hg proved to be high. The method may be used as a noninvasive alarm in continuous monitoring of patients after mild and moderate head injury. Both the value of estimated CPP below 60 mm Hg and a decrease in CPP seen over time should stand as a warning of cerebral hypoperfusion, whereas a stable value of predicted CPP above 60 mm Hg does not necessarily indicate good cerebral hemodynamic reserve.

Contrary to the method proposed by Aaslid, et al.,[1] our formula has no elegant physiological or hemodynamic interpretation; it is purely based on the authors' 6 years of clinical experience. We may summarize that for the range of higher CPPs ($>$ 70 mm Hg) changes in ABP mainly contribute to variations seen in CPP, whereas for the range of low CPPs the high ICP (best detected by decreasing the FVd/FVm factor [Fig. 1]) is a stronger contributer to variations in cerebral perfusion. Therefore, the combination (multiplication) of the mean ABP and nonlinear CPP-dependent FVd/FVm factor produces our formula. The method has a lower saturation level of 14 mm Hg when FVd disappears. In clinical practice, this phenomenon in itself should warn us of a deeply inadequate level of cerebral perfusion and trigger an immediate attempt to recover a normal pattern of CBF in basal arteries.

### *Noninvasive Monitoring of the Time-Dependent Changes in CPP*

The most important advantage of using our noninvasive CPP estimator is the ability to detect fluctuations in real CPP over time. We were reliably able to detect changes in CPP that were induced by episodes of intracranial hypertension, arterial hypotension, and arterial hypertension. However, we must emphasize that moderate nonvasogenic fluctuations in ICP (10 mm Hg) are not reliably detected because these changes may not induce sufficient hemodynamic stress to change the FV waveform. On the other hand, vasogenic waves in ICP (5–10 mm Hg) are readily detected by using our estimator.

### *Accuracy of CPP Estimation*

By using our formula, we were able to estimate CPP more accurately than by using the previously proposed method.[1] Estimation error was less than 10 mm Hg and 15 mm Hg, respectively, in 71% and 84% of the measurements (421 patients) compared with 52% and 64%

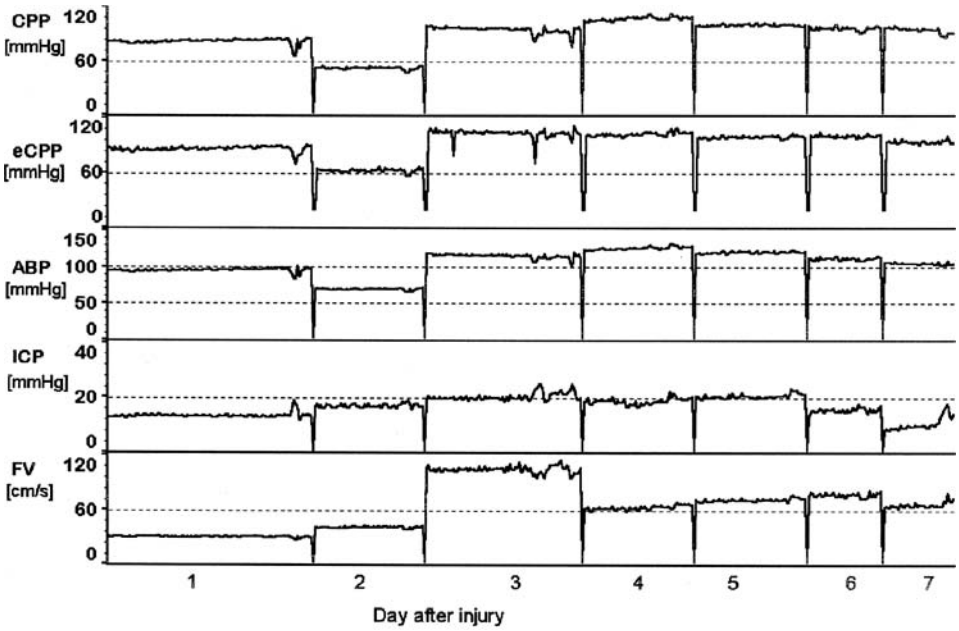


FIG. 5. Day-by-day recording of real CPP, eCPP, ABP, ICP, and CBFV.

achieved using an alternative formula[13] (rates significantly different at $p < 0.001$). Average absolute error (Table 1) was approximately 6.5 mm Hg, which may be considered by a majority of neurointensive care physicians as acceptably low. Apart from knowing CPP as a number, the most important clinical application of the method is to monitor relative changes in CPP over time. Ultrasound probes, once mounted, may be easily kept in position over a longer period. A decrease in the estimated CPP measured over time should trigger either appropriate therapy or introduction of direct ICP monitoring.

Another interesting possibility is to assess the left–right side difference between bilaterally estimated CPP. Such a project is in progress and we hope to present these results soon.

*Assessment of ICP*

Because of their low accuracy, many methods available for the noninvasive measurement of ICP have not been adopted in clinical practice. Although the tympanic membrane displacement[17] and TCD pulsatility index[16] are useful for the assessment of shunt patency in patients with hydrocephalus, it is not possible to obtain an accurate ICP measurement by using either method. The transfontanelle pressure method of ICP measurement is useful in newborns and infants; however, there have been doubts about whether it can measure ICP accurately.[13] The less invasive epidural catheters used for ICP measurement are prone to both case- and time-dependent errors.[10]

Our method of ICP estimation is not radically better than previously described algorithms based on TCD waveform analysis.[1,10] Theoretically, the noninvasive estimation of CPP suffers from the same degree of inaccuracy as the noninvasive assessment of ICP. However, because ICP is much lower than CPP, a 10-mm Hg error is unacceptable in estimating ICP, whereas this degree of error seems to be satisfactorily low for CPP estimation. Furthermore, in many situations (such as head injury with midline shift), the circulation of cerebrospinal fluid is disturbed to such an extent that real intraparenchymal pressure may be unevenly distributed within the brain. Therefore, "real ICP" observed with intraparenchymal transducers may be different from the one affecting dynamics of blood FV in the MCA,[20] and, hence, estimated using the TCD waveform.

## Conclusions

We have reported a new method for noninvasive assessment of CPP. This CPP estimator can predict real CPP with an error margin of less than 10 mm Hg over 70% of the time. This is of potential benefit for continuous monitoring of changes in real CPP over time in situations in which direct measurement of CPP is not readily available.

### Acknowledgment

Drs. Czosnyka and Smielewski are on leave from Warsaw University of Technology, Warsaw, Poland.

### Disclosure

An application has been filed by the authors to patent the method of noninvasive assessment of CPP described in this article.

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