Non-invasive assessment of cerebral perfusion pressure in brain injured patients with moderate intracranial hypertension

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Background. A non-invasive estimation of cerebral perfusion pressure (CPP) using transcranial Doppler sonography was assessed in brain-injured patients by comparing conventional measurements of CPP (difference between mean arterial pressure and intracranial pressure) (CPPm) with the difference between APmean and the critical closing pressure of the cerebral circulation (CPPe).

Methods. Twenty adults with bilateral and diffuse brain injuries were included in the study. CPPe was estimated using a formula combining the phasic values of flow velocities and arterial pressure. In group A (n=10) the comparison was repeatedly performed under stable conditions. In group B (n=10) the comparison was performed during a CO2 reactivity test. Covariance analysis was used to assess the relationships.

Results. In group A, CPPe and CPPm were correlated (slope, 0.76; intercept, +10.9; 95% CI, –3.5 to +25.4). During the increase in intracranial pressure (group B) (+1.9 (SD 1.5) mm Hg per mm Hg of \( P_{eCO2} \)) the relationship persisted (slope, 0.55; intercept, +32.6; 95% CI, +16.3 to +48.9) but the discrepancy between the two variables increased as reflected by the increase in bias and variability.

Conclusion. Non-invasive estimation of CPP can be used for brain monitoring of head-injured patients, but the accuracy of the method may depend on the level of intracranial hypertension.

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epidural space pressure, which is an accessible estimate of ICP.13
Thus the aim of the present prospective study was to
assess the adequacy of the latter formula for the care of
brain-injured patients, monitored by an intracerebral sensor,
in both a stable state and during a rapid change in cerebro-
vascular tone following a deliberate change in arterial blood
carbon dioxide pressure (\( P_{\text{aCO}_2} \)) as previously reported in
healthy volunteers, pregnant women and brain-injured patients.7 14 15

Methods

Study population
Adult traumatic brain-injured patients who had been
admitted to the surgical intensive care unit with post-
resuscitation Glasgow Coma Scale (GCS) scores \( \leq 8 \) were
considered for inclusion. Recruitment was considered after
the resuscitation period if the cerebral injuries were diffuse
and bilateral according to the Marshall system at the second
cranial computed tomography performed on day 2 or 3.16
The study was approved by the local ethics committee and
informed consent was obtained from the next of kin. The
study was approved by the local ethics committee and
informed consent was obtained from the next of kin. The

care of the patients was directed by the existing protocols
and was not modified by the study.17 Patients were sedated
and their lungs were mechanically ventilated with a minute
ventilation adjusted to maintain \( P_{\text{aCO}_2} \) between 35 and
40 mm Hg. No patient needed an \( F_{\text{I/O}_2} \) >60% and/or a PEEP >5 cm H₂O. The arterial to end-tidal difference
in \( P_{\text{aCO}_2} \) was below 10 mm Hg in all patients.

Clinical and haemodynamic data
The Injury Severity Score (ISS)²⁸ and the Simplified Acute
Physiological Score (SAPS II)¹⁹ were calculated to assess
the magnitude of the trauma and its general consequences.
An Abbreviated Injury Score for the cephalic region
(AIShead) ≥3 corresponded to a significant brain injury.
The AP was measured through a radial catheter
(Summit®, Baxter, 78310 Maurepas, France), and the
ICP was measured through an intraparenchymal catheter
(Neuronmonitor-MicroSensor kit®, Codman, 92290 Chatenay-
Malabry, France) inserted in the right cerebral hemisphere.
The ‘measured’ CPP (CPPm), calculated as the arithmetic
difference between mean AP and mean ICP, was continu-
ously displayed on a monitor (Merlin 1006A®, Hewlett
Packard, 91400 Les Ulis, France). A 2 MHz pulsed trans-
cranial Doppler probe (HP Sonos 5500®, Hewlett Packard,
91400 Les Ulis, France) was used to examine the M1 portion
(first 2 cm after branching from the circle of Willis) of the
MCA. On average, the Doppler examination was completed
within 10 min. The systolic, diastolic and mean MCA
velocities were recorded. Measurements were performed
bilaterally and a minimum of five waveforms were averaged
for each measurement. The ‘estimated’ CPP (CPPe) was
calculated using the following formula:
\[
\text{CPPe} = \left( \frac{\text{v}_{\text{mean}}}{\text{v}_{\text{mean}-\text{v}_{\text{diast}}}} \right) \times (\text{AP}_{\text{mean}} - \text{AP}_{\text{diast}})
\]
where \( v_{\text{mean}} \) and \( v_{\text{diast}} \) are the mean and diastolic MCA
velocities, respectively, and \( \text{AP}_{\text{mean}} \) and \( \text{AP}_{\text{diast}} \) are the
mean and diastolic APs, respectively. A resistance–area
product (RAP=\( \text{AP}_{\text{mean}}/\text{v}_{\text{mean}} \)), was used to calculate the
cerebral flow index CFI=CPPe/RI, which was expressed
in cm s⁻¹.²⁰

Study procedure
In the first group of 10 patients (group A), the values of CPPe
and CPPm were compared during the clinical course. Eight
to ten pairs of values were obtained from each patient. Hae-
modynamic stability was defined by limited changes (±20%) in
ICP, an unchanged dosage of norepinephrine infusion and
no need for additional volume loading or mannitol therapy
during the preceding 24 h period.
Following this first part of the study, the values of CPPe
and CPPm were recorded in a second group of 10 patients
(group B) before and after the routine assessment of cerebral
carbon dioxide vascular reactivity.²¹ A deliberate increase in
\( P_{\text{aCO}_2} \) was induced by a 20% reduction in tidal volume while
maintaining the ventilatory frequency. The test was com-
pleted when \( P_{\text{aCO}_2} \) reached a plateau or was interrupted if
CPPm decreased <40 mm Hg through an increase in ICP.
Arterial and jugular venous (if available) blood samples
were obtained before and after the test for arterial and
venous (\( S_{\text{vjo}} \)) blood gas analysis.

Data analysis
Results are expressed as mean (SD). A covariance analysis
was used to assess the linear regression between CPPe
and CPPm from each side of the head in group A patients. CPPm
was considered as the independent variable. The analysis
was performed using the routine lm function from S-Plus.²² Two
fixed effects (the slope and the intercept) were considered. A
random effect with mean zero and variance \( \sigma^2 \) was added to
each of the two fixed effects to model inter-individual varia-
bility, and the significance of this random effect in the model
was tested. The goodness of fit was assessed using the log-
restricted likelihood. Fitted values of the two fixed-effect
parameters are reported with a 95% CI calculated as \( \pm 2\sigma \),
where \( \sigma \) is the random effect error. The bias in prediction
was calculated as the mean error
\[
\text{ME} = \frac{1}{N} \sum_{i=1}^{N} (\text{CPPe} - \text{CPPm}).
\]
Similarly, the precision of the prediction was calculated as
the root mean square error
\[
\text{RMSE} = \sqrt{\frac{1}{N} \sum_{i=1}^{N} (\text{CPPe} - \text{CPPm})^2}.
\]
The clinical and biological variables reported before and
after the assessment of vascular reactivity in group B were

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compared using Student’s t-test for paired data after a check for normality by a Shapiro–Wilk test. The same analytical method as in group A was used in group B to compare CPPe and CPPm before and after CO₂ vascular reactivity assessment, despite the fact that only two values were available for each patient. The bias (ME) and precision (RMSE) of the prediction were also calculated before and after the vascular reactivity test for both sides. An analysis of residuals was performed and shown graphically.

Results

Repeated estimation of CPP during the clinical course of group A patients

This estimation was performed in 10 patients (33 (21–57) yr) who had suffered severe trauma (ISS=30 (SD 14)), including brain injury (median GCS=6 (3–8)), with moderate intracranial hypertension (ICP=28 (10) mm Hg), and associated with significant physiological consequences (SAPS II=37±6, ICU mortality=10%) (Table 1).

As shown in Figure 1, a significant correlation was found between CPPe and CPPm. The slope of the regression line was similar between patients; no random effect (inter-individual variability) associated with the slope was found for either the right or the left side (Table 2 and Fig. 2). The intercept of the regression line was significantly different from zero and was associated with a significant random effect for both the right and the left sides, demonstrating a significant inter-individual variability. The bias (ME is −7.1 mm Hg and −5.0 mm Hg) and the precision of prediction (RMSE is 18.1 mm Hg and 19.1 mm Hg) were similar for the right and left sides.

Estimation of CPP during the assessment of cerebral carbon dioxide vascular reactivity (group B)

This estimation was performed in a second similar group of 10 patients (33 (23–50) yr) who had suffered severe trauma (ISS=34 (12)), including brain injury (median GCS=5 (3–8)), with moderate intracranial hypertension (ICP=24 (12) mm Hg) and associated with significant physiological consequences (SAPS II=47 (8), ICU mortality 20%) (Table 1). Following the reduction of tidal volume, $P_{E_{CO2}}$ reached a plateau in 24 (10) min (Table 3). A 15% increase in $P_{E_{CO2}}$ was associated with a 10% increase in $P_{a_{CO2}}$ and a 12% decrease in $P_{a_{o2}}$. An increase in measured ICP (1.9 (1.5) mm Hg per mm Hg of $P_{E_{CO2}}$) was observed in each patient. There was a trend towards an increase in CFI, with a significant 4% increase in $S_{v_j}$ (Table 3).

As in group A, a significant correlation was found between CPPe and CPPm values and the slope of the regression line was similar between patients without significant

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Table 1 Clinical characteristics of the patients. AIShead, Abbreviated Injury Score for the cephalic region; ISS, Injury Severity Score; Ped., pedestrian; Traf., traffic accident

<table>
<thead>
<tr>
<th></th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Trauma</th>
<th>ISS</th>
<th>AIShead</th>
<th>GCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>F</td>
<td>50</td>
<td>Ped.</td>
<td>50</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>A2</td>
<td>M</td>
<td>21</td>
<td>Fall</td>
<td>16</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>A3</td>
<td>M</td>
<td>25</td>
<td>Traf.</td>
<td>32</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>A4</td>
<td>M</td>
<td>23</td>
<td>Traf.</td>
<td>48</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>A5</td>
<td>F</td>
<td>57</td>
<td>Traf.</td>
<td>18</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>A6</td>
<td>M</td>
<td>45</td>
<td>Traf.</td>
<td>36</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>A7</td>
<td>M</td>
<td>32</td>
<td>Fall</td>
<td>28</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>A8</td>
<td>M</td>
<td>26</td>
<td>Traf.</td>
<td>20</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>A9</td>
<td>M</td>
<td>38</td>
<td>Traf.</td>
<td>32</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>A10</td>
<td>M</td>
<td>22</td>
<td>Traf.</td>
<td>18</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>B1</td>
<td>M</td>
<td>23</td>
<td>Traf.</td>
<td>17</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>B2</td>
<td>M</td>
<td>27</td>
<td>Traf.</td>
<td>36</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>B3</td>
<td>M</td>
<td>30</td>
<td>Traf.</td>
<td>36</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>B4</td>
<td>M</td>
<td>23</td>
<td>Fall</td>
<td>16</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>B5</td>
<td>F</td>
<td>23</td>
<td>Traf.</td>
<td>41</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>B6</td>
<td>F</td>
<td>50</td>
<td>Ped.</td>
<td>34</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>B7</td>
<td>M</td>
<td>50</td>
<td>Fall</td>
<td>36</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>B8</td>
<td>M</td>
<td>38</td>
<td>Traf.</td>
<td>50</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>B9</td>
<td>M</td>
<td>40</td>
<td>Traf.</td>
<td>50</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>B10</td>
<td>M</td>
<td>24</td>
<td>Ped.</td>
<td>21</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 2 Typical values of slope and intercept in group A and group B patients. The 95% CI of the intercept was calculated using the random effect. *Numbers in parentheses are the coefficient of variation of the estimates of fixed effects

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right side</td>
<td>Left side</td>
</tr>
<tr>
<td>Slope*</td>
<td>0.76 (11%)</td>
<td>0.65 (14%)</td>
</tr>
<tr>
<td>Intercept*</td>
<td>10.9 (66%)</td>
<td>20.7 (39%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>−3.5 to +25.2</td>
<td>+2.2 to +39.2</td>
</tr>
</tbody>
</table>
inter-individual variability (Table 2). A random effect was only present for the intercept. The analysis of residuals demonstrated an increase in the discrepancy between CPPe and CPPm values during the acute change in ICP (Fig. 3). The bias (ME is 8.1 mm Hg versus 2.8 mm Hg for the right side, and 9.8 mm Hg versus 1.1 mm Hg for the left side) and the precision of prediction (RMSE is 13.6 mm Hg versus 8.2 mm Hg for the right side, and 15.2 mm Hg versus 7.6 mm Hg for the left side) increased during the change in ICP. The critical closing pressure was calculated before and during hypoventilation (CPPe–APmean) and compared with ICP. In contrast with a constant increase in ICP during hypercapnia, critical closing pressure increased in five patients (+7.2 (6.4) mm Hg) and decreased in the others (–9.6 (8.8) mm Hg).

Discussion

The quality of functional outcome for brain-injured patients depends on the severity of the secondary brain damage.5 These newly developed injuries are mainly of ischaemic origin because of a prolonged imbalance of global and regional cerebral perfusion.23 Because CPP represents the physiological variable defining the driving pressure which generates the cerebral blood flow and supplies the cerebral structures with oxygen and nutrients,24 a deliberate increase in CPP is a main objective of the management of brain-injured patients.1–3 This objective can be achieved by an increase in AP and/or a decrease in ICP. However, it is more difficult to influence ICP than AP.5 Moreover, direct measurement of ICP may be impossible for technical reasons in non-specialized units25 and for safety reasons in patients with coagulopathy,26 27 and the validity of the measurement is questionable after a craniotomy.28 On the other hand, a deliberate and systematic increase in mean AP may be proposed, but this systemic hypertension could be deleterious if a major autoregulatory impairment of cerebral blood flow exists.29 Thus a non-invasive estimation of ICP or at least of CPP, the difference between AP and effective downstream pressure, would appear to be a valuable tool for

![Image](https://academic.oup.com/bja/article-abstract/94/2/216/255273/2216256273)

**Fig 2** Individual relationship between ‘estimated’ and ‘measured’ cerebral perfusion pressure in group A patients (10 patients, 89 measurements). The common slope (0.76) is represented by the broken line. The intercept (95% CI) is indicated in the lower part of the figure. Reported data were collected using the right MCA velocities for the estimation.

**Table 3** Cardiovascular and biological parameters before and after the reduction of tidal volume (V T) in group B patients. *P<0.05 vs before V T decrease

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before V T decrease</th>
<th>After V T decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>V T (ml)</td>
<td>648 (41)</td>
<td>518 (35)</td>
</tr>
<tr>
<td>Ventilatory frequency (bpm)</td>
<td>16 (2)</td>
<td>16 (2)</td>
</tr>
<tr>
<td>Delay between measurements (min)</td>
<td>–</td>
<td>24 (10)</td>
</tr>
<tr>
<td>Systolic AP (mm Hg)</td>
<td>144 (12)</td>
<td>148 (21)</td>
</tr>
<tr>
<td>Diastolic AP (mm Hg)</td>
<td>75 (6)</td>
<td>78 (9)</td>
</tr>
<tr>
<td>Mean AP (mm Hg)</td>
<td>98 (4)</td>
<td>102 (9)</td>
</tr>
<tr>
<td>Heart rate (beats min⁻¹)</td>
<td>75 (16)</td>
<td>78 (16)</td>
</tr>
<tr>
<td>Pao₂ (torr)</td>
<td>134 (34)</td>
<td>118 (18)*</td>
</tr>
<tr>
<td>Paco₂ (torr)</td>
<td>40 (5)</td>
<td>44 (5)*</td>
</tr>
<tr>
<td>PTCO₂ (torr)</td>
<td>33 (5)</td>
<td>38 (4)*</td>
</tr>
<tr>
<td>ΔP(a–E)CO₂ (torr)</td>
<td>6 (3)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Sao₂ (%)</td>
<td>97 (1)</td>
<td>97 (1)</td>
</tr>
<tr>
<td>SvjO₂ (%)</td>
<td>73 (4)</td>
<td>76 (5)*</td>
</tr>
<tr>
<td>Measurement depth (mm)</td>
<td>53 (5)</td>
<td>52 (4)</td>
</tr>
<tr>
<td>MCA systolic velocity (cm s⁻¹)</td>
<td>133 (18)</td>
<td>149 (45)</td>
</tr>
<tr>
<td>MCA diastolic velocity (cm s⁻¹)</td>
<td>56 (18)</td>
<td>62 (23)</td>
</tr>
<tr>
<td>MCA mean velocity (cm s⁻¹)</td>
<td>85 (21)</td>
<td>95 (40)</td>
</tr>
<tr>
<td>Measured ICP (mm Hg)</td>
<td>28 (10)</td>
<td>38 (12)*</td>
</tr>
<tr>
<td>Measured CPP (mm Hg)</td>
<td>70 (9)</td>
<td>63 (9)</td>
</tr>
<tr>
<td>Estimated CPP (mm Hg)</td>
<td>67 (10)</td>
<td>71 (15)</td>
</tr>
<tr>
<td>Critical closing pressure (mm Hg)</td>
<td>31 (10)</td>
<td>30 (18)</td>
</tr>
<tr>
<td>Estimated CFI (cm s⁻¹)</td>
<td>57 (14)</td>
<td>68 (29)</td>
</tr>
</tbody>
</table>

**Fig 3** Analysis of residuals. Differences between ‘estimated’ and ‘measured’ cerebral perfusion pressure in group B patients recorded before (white circle) and during (grey circle) an acute reduction of tidal volume. The two biases are represented by a broken line with the respective values indicated by circles: open circles, before acute reduction of tidal volume; grey circles, during acute reduction of tidal volume. Reported data were collected using the right MCA velocities for the estimation.
the management of brain-injured patients according to international guidelines.30–32

The transcranial Doppler probe, which is a major component of multimodal neurological monitoring, allows non-invasive assessment of cerebral perfusion.1,6 The determination of effective downstream pressure using the zero-flow pressure derived from the cerebral pressure–flow velocity relationships,7–9 or the critical closing pressure derived from Fourier analysis of the first harmonics of velocity and pressure waveforms,10,11 requires a rather complex computerized method. A formula originally proposed by Aaslid in 1986 (see Belfort et al.13) was modified to use areas under pulsatile amplitudes rather than under the first harmonics. The mean velocity was defined as the area under the entire velocity waveform curve and the pulsatile component, directly related to the CPP, was the difference between the mean and diastolic areas of the velocity waveform. The equation was further simplified to allow the simple use of velocity measurements without requiring a fast Fourier transformation. This method was applied in pregnant women by estimating the ICP through a puncture in the epidural space13 and was used for physiological and pharmacological studies.14,15 The present results obtained in brain-injured patients using intraparenchymal measurement of ICP demonstrated a higher bias (−7.1 versus 0.28 mm Hg) compared with a zero-flow pressure study. The increased difference between CPPe and CPPm, i.e. between the critical closing pressure and ICP in the absence of changes in AP, was previously demonstrated in patients with moderate intracranial hypertension.7–9

The difference between AP_mean and critical closing pressure is frequently considered as the ‘real’ cerebral perfusion pressure, because it represents the sum of tissue pressure, vasomotor tone and backward venous pressure. The apparent discrepancy between CPPe and CPPm disappears in patients with severe intracranial hypertension when ICP exceeds the critical closing pressure at the arteriolar level and represents the outflow pressure of the proximal Starling resistor.7

Within the limits of these preliminary data, especially the small number of selected patients, a bilateral and continuous measurement of MCA velocities automatically linked to a continuous and invasive, or intermittent and non-invasive, measurement of AP may have potential benefit for the assessment of CPP when it is neither practical nor safe to measure ICP directly in the cerebral circulation of trauma patients. This is particularly true during the surgical treatment of extracranial injuries in patients with severe head trauma where adequate brain monitoring has been demonstrated to allow the prevention of the deleterious consequences of intraoperative hypotension.14

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