Contrast ultrasonographic assessment of cerebral perfusion in patients undergoing decompressive craniectomy for traumatic brain injury

PETER HEPNER, M.B., CH.B., DILANTHA B. ELLEGALA, M.D., MARCEL DURIEUX, M.D., JOHN A. JANE SR., M.D., PH.D., AND JONATHAN R. LINDBERG, M.D.

Cardiovascular Division, and Departments of Neurological Surgery and Anesthesiology, University of Virginia Health System, Charlottesville, Virginia; and Department of Neurosurgery, Auckland City Hospital, Auckland, New Zealand

Object. The aims of this study were to determine whether contrast-enhanced ultrasonography (CEU) could be used for noninvasive evaluation of cerebral perfusion in patients with traumatic brain injury (TBI) and to assess the effect of decompressive surgery on cerebral perfusion as measured by CEU.

Methods. Contrast-enhanced ultrasonography with intravenous administration of a microbubble contrast agent was performed in six patients with TBI undergoing decompressive craniectomy. Contrast-enhanced ultrasonography was performed through a bur hole before craniectomy and through the calvarial defect immediately after craniectomy and on postoperative Days 1 and 2. For the latter two studies, patients were placed in the recumbent position and at a 35° incline to investigate changes in perfusion produced by modulation of intracranial pressure (ICP). Cerebral microvascular blood flow increased by almost threefold immediately after craniectomy, from a mean of 7.5 ± 6.9 (standard deviation [SD]) to 20.9 ± 11.6 (p < 0.05), and further improved on postoperative Day 1 (mean 37.1 ± 13.9 [SD], p < 0.05), compared with postcraniectomy microvascular blood flow) without subsequent change on Day 2. The change in microvascular perfusion correlated inversely with the initial ICP (p < 0.01), indicating less recovery of flow when preoperative ICP was markedly elevated. On postoperative Days 1 and 2, head-of-bed elevation produced an increase in microvascular perfusion on CEU (mean 37 ± 11 compared with 51 ± 20, p < 0.05) and a small decrease in ICP (mean 16 ± 5 mm Hg compared with 12 ± 4 mm Hg, p < 0.05). In patients with parenchymal hematoma, CEU provided spatial information on perfusion abnormalities in the hemorrhagic core and surrounding tissues.

Conclusions. Contrast-enhanced ultrasonography has potential for the intraoperative and bedside assessment of cerebral perfusion in patients with TBI. The technique may be appropriate for evaluating responses to therapies aimed at preventing secondary ischemia and for assessing regional perfusion abnormalities.

KEY WORDS • traumatic brain injury • cerebral perfusion • microvasculature • blood flow • ultrasonography

TRAUMATIC brain injury is divided into primary injury, which occurs at the time of the trauma, and secondary injury or sequelae, including ischemia, cerebral edema, and mass effects from hematoma. It is the secondary insults that modern neurosurgical care is intended to minimize. The detection and prevention of secondary ischemic injury after TBI is currently dependent on measurement and optimization of ICP and CPP. More recent monitoring techniques include measurement of jugular bulb O₂ saturation and brain O₂ and metabolite content, with a view toward the detection and prevention of inadequate CBF and oxygenation. However, these surrogate indices do not directly measure cerebral microvascular blood flow. Although techniques for spatially assessing CBF have been developed for CT and magnetic resonance imaging, they are expensive and complex and are not portable. A noninvasive method for spatially assessing cerebral microvascular blood flow at the bedside would be valuable for monitoring patients, guiding treatment, and evaluating response to therapy.

Contrast-enhanced ultrasonography is a noninvasive perfusion imaging technique that has been used to evaluate microvascular perfusion in the heart, skeletal muscle, and kidneys. This technique relies on ultrasonic detection of intravenously injected gas-filled encapsulated microbubble contrast agents that possess microvascular rheological characteristics similar to those of RBCs. To assess perfusion, microbubbles are infused intravenously and reach a steady state within the microcirculation. Microbubbles are then destroyed by a high-power ultrasonographic pulse and the subsequent rate and extent of microbubble replenishment are used to determine microvascular blood velocity and volume, respectively. Contrast-enhanced ultrasonography has been used to assess microvascular blood flow in...
the brain, and perfusion imaging correlates well with blood flow measurements made by radiolabeled microspheres in animal models.

In this study, we hypothesized that CEU could be used for noninvasive evaluation of cerebral perfusion in patients with TBI and to assess CBF response to therapy. To test our hypothesis, we measured acute changes in microvascular perfusion produced by 1) decompressive craniectomy; and 2) alteration of ICP and CPP from positional changes. A secondary aim was to study whether CEU could be used spatially to assess abnormalities in cerebral perfusion produced by contusion and parenchymal hemorrhage.

Clinical Material and Methods

Study Population

This study was approved by both the United States Food and Drug Administration (investigational new drug 69,338) and the Human Investigation Committee at the University of Virginia. Surrogate informed consent was obtained for all patients. Six patients with TBI who were undergoing decompressive craniectomy were included in the study. The enrollment criteria included evidence of TBI on a CT scan, Glasgow Coma Scale score less than 8, and elevated ICP measured by intraparenchymal pressure monitor. Standard neurotrauma care in compliance with the recommendations of the Brain Trauma Foundation’s Guidelines for the Management of Severe Traumatic Brain Injury was initiated at admission. In brief, the standard care included intubation and mechanical ventilation with normocapnia or mild hypocapnia (PCO₂, 35–40 mm Hg), sedation and chemical paralysis (using propofol, midazolam, and fentanyl), and maintenance of normothermia. As a general institutional practice, decompressive craniectomy is performed after mannitol (1-g/kg bolus administered intravenously) has failed to control ICP. All enrolled patients had unsuccessful medical ICP management (persistent elevation of ICP > 20 mm Hg) and underwent surgery for decompressive craniectomy according to institutional practice. Depending on the pattern of edema or presence of underlying hematoma, either unilateral hemicraniectomy or bifrontal decompressive craniectomy as described by Kjellberg and Prieto was performed.

Contrast-Enhanced Ultrasonography

Contrast-enhanced ultrasonography was performed using power-modulation imaging (SONOS 5500; Philips Medical Systems, Bothell, WA), a low-power imaging method that optimizes microbubble signal-to-noise ratio and is nondestructive of microbubble agents. Imaging was performed at a transmission frequency of 1.7 MHz, a mechanical index of 0.2 (—17 to —18 dB), and a pulse-repetition frequency of 2.7 to 2.9 kHz. Background gray-scale was suppressed except at specular borders, and power-gain was optimized and held constant for each patient. Imaging was performed in the sagittal and coronal planes through a bur hole for the initial precranieectomy study and through the calvarial defect at the same site as the bur hole for subsequent studies. For contrast enhancement, a suspension composed of lipid-shelled octafluoropropane microbubbles (Definity; Bristol-Myers Squibb Medical Imaging, Inc., North Billerica, MA) suspended in normal saline solution was infused intravenously at a rate of 0.1 ml/minute. Images were acquired for at least 10 seconds after a two-frame high-power (mechanical index = 0.7) destructive pulse sequence.

Images were analyzed offline. The method used to assess microvascular perfusion is schematically illustrated in Fig. 1. The frame obtained immediately after destruction was selected as background to eliminate signal from large vessels with high-velocity flow. This frame was digitally subtracted from subsequent frames at 1-second intervals. Video intensity was measured from a region of interest placed over the entire brain parenchyma within the field of view, avoiding regions of visually apparent acoustic shadowing. Time versus VI data were fit to the following function: y = A(1 − e−βt), where y is VI at time t, A is the plateau VI reflecting relative microvascular blood volume, and β is the rate constant reflecting the rate of rise of VI or mean RBC velocity. When examining regional perfusion related to hemorrhagic contusions, data were generated from the central nonenhancing core and three concentric regions at 1-cm increments. For comparison, a reference control region located in the contralateral hemisphere at a similar imaging depth was selected from the same imaging plane.

Study Protocol

Baseline CEU measurements were made in the operating room. Mean arterial blood pressure was measured by an arterial catheter, and ICP relative to the foramen of Monro was measured with an intraparenchymal pressure monitor. Cerebral perfusion pressure was determined by subtracting the ICP from the mean arterial pressure. Arterial blood was sampled for measurement of PCO₂. Contrast-enhanced ultrasonography was performed by imaging through the initial single bur hole placed at the Kocher point before craniectomy. All measurements were repeated in the operating room immediately after decompressive craniectomy and on the 1st and 2nd postoperative days, with the probe placed at the same location over the Kocher point. On the postoperative days, studies were performed with the patient in the recumbent position and with the head elevated 35°, in random order. Perfusion imaging of both the ipsilateral hemisphere and the contralateral hemisphere can be performed from a single bur hole by changing the depth of ultrasonographic measurement.

Statistical Analysis

Data were analyzed in RS/1 (Domain Manufacturing Corp., Burlington, MA) and expressed as means ± standard deviations unless stated otherwise. Comparisons between stages were made using repeated-measures analysis of variance. Individual comparisons according to patient position were performed using paired Student t-tests. Correlations were performed using least-squares fit regression analysis or the Spearman rank correlation. Differences were considered significant at a probability value less than 0.05 (two-sided).

Results

Demographic and Clinical Data

The clinical data for the patients enrolled in the study are shown in Table 1. The study population included five fe-
male patients and one male patient, with a median age of 27 years (range 17–50 years). The mean time from trauma to surgery was 11 ± 6 hours (median 9 hours). All patients except one were involved in a motor vehicle accident. Neurological status improved rapidly in four patients, all of whom were able to follow verbal commands by Day 3 after decompressive craniectomy, and improved more slowly in one other patient. In the remaining patient neurological status remained poor by Day 3 postinjury, and the patient died after supportive care was withdrawn.

### Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>median age (yrs)</td>
<td>27</td>
</tr>
<tr>
<td>male/female ratio</td>
<td>1:5</td>
</tr>
<tr>
<td>mean time to surgery (hrs)</td>
<td>11 ± 6</td>
</tr>
<tr>
<td>mean Injury Severity Score</td>
<td>0.24 ± 0.13</td>
</tr>
<tr>
<td>mean Glasgow Coma Scale score</td>
<td>4.3 ± 1.5</td>
</tr>
<tr>
<td>no. of patients w/ clinical condition</td>
<td>3</td>
</tr>
<tr>
<td>hyperlipidemia</td>
<td>3</td>
</tr>
<tr>
<td>history of hypertension</td>
<td>0</td>
</tr>
<tr>
<td>diabetes mellitus</td>
<td>0</td>
</tr>
<tr>
<td>cerebrovascular disease</td>
<td>0</td>
</tr>
</tbody>
</table>

**Effect of Decompressive Cranectomy on Cerebral Perfusion**

Mean arterial blood pressure, ICP, CPP, and PCO2 measurements immediately before, immediately after, and on postoperative Days 1 and 2 after decompressive craniectomy are shown in Table 2. Cranectomy produced an acute decrease in ICP of approximately 20 mm Hg that persisted over the first 2 postoperative days. The drop in ICP resulted in an increase in the CPP acutely after craniectomy. The patients were mildly hypocapnic in the operating room as a result of hyperventilation deemed necessary for treatment of elevated ICP before craniectomy.

Decompressive craniectomy resulted in an acute threefold improvement in cerebral microvascular blood flow measured by CEU, due largely to an improvement in microvascular blood volume (Fig. 2). Microvascular blood flow and volume further improved by almost twofold between the immediate postcraniectomy study and postoperative Day 1, without subsequent change on Day 2. Contrast-enhanced ultrasonography images demonstrating sequential improvement in cerebral perfusion after decompressive craniectomy are shown in Fig. 3. In this example, there was a marked, acute improvement in perfusion immediately after craniectomy. Most of the improvement occurred because of an increase in microvascular blood volume, indicated by an increase in the plateau VI obtained after complete contrast replenishment of the sector. Although the study was not
powered to explore the prognostic value of CEU, the one patient who did not experience neurological recovery had the lowest value of perfusion evaluated with CEU on postoperative Day 2, despite having an ICP less than 10 mm Hg.

No relation was found between the absolute value of microvascular blood flow evaluated with CEU and the absolute ICP ($r = 0.02, p = 0.61$). There was, however, a significant inverse relation between the change in ICP and the change in microvascular blood flow after craniectomy (Fig. 4 left). This seemingly paradoxical relationship indicated that flow recovery was less likely when preoperative ICP was extremely elevated, a concept that is further supported by the significant negative relation between the initial ICP and subsequent change in microvascular blood flow (Fig. 4 right). No significant relation was found between CPP and any blood flow parameters. There was no relation between the injury severity score and any of the perfusion parameters.

**Influence of Position on Microvascular Perfusion**

Head-of-bed elevation to an incline of 35° was performed on postoperative Days 1 and 2. Data from both days were grouped for analysis. Compared with the recumbent position, head-of-bed elevation produced a small but significant decrease in ICP and a substantial (> 30%) increase in microvascular blood flow measured by CEU. Cerebral perfusion pressure did not significantly change with position (Table 3).

**Spatial Assessment of Perfusion in Patients With Hematoma**

A discrete parenchymal hematoma was identified on the CT scans of the head in three patients. Figure 5 shows an example of hypoperfusion in the region of a hematoma with incrementally greater perfusion with increasing distance from the central core. In all three patients with hematoma, microvascular blood flow was essentially absent in the region of the hematoma and increased with radial distance from the hematoma (Fig. 6). Microvascular blood flow in tissue immediately adjacent to the hematoma tended to be lower than in normal tissue, consistent with mass effect and compression of vasculature, whereas flow adjacent to this area tended to be greater than in normal tissue further removed, consistent with hyperemia of the border zone.

**Discussion**

A method capable of accurately assessing cerebral microvascular blood flow in the operating room or at the bedside would be valuable in the treatment of patients with TBI. Such a technique could be used to determine severity of hypoperfusion, to evaluate adequacy of interventions to improve microvascular blood flow, to monitor for second-

**TABLE 2**

<table>
<thead>
<tr>
<th>Measure (mm Hg)</th>
<th>Precraniectomy</th>
<th>Postcraniectomy</th>
<th>Postop Day 1</th>
<th>Postop Day 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP</td>
<td>89 ± 16</td>
<td>90 ± 17</td>
<td>95 ± 16</td>
<td>95 ± 30</td>
</tr>
<tr>
<td>ICP</td>
<td>35 ± 8</td>
<td>12 ± 6†</td>
<td>17 ± 4†</td>
<td>15 ± 6†</td>
</tr>
<tr>
<td>CPP</td>
<td>55 ± 21</td>
<td>78 ± 16†</td>
<td>78 ± 18†</td>
<td>86 ± 31†‡</td>
</tr>
<tr>
<td>PCO$_2$</td>
<td>32 ± 5</td>
<td>32 ± 5</td>
<td>36 ± 5</td>
<td>36 ± 4</td>
</tr>
</tbody>
</table>

* MAP = mean arterial pressure.  
† $p < 0.05$, compared with precraniectomy.  
‡ $p = 0.05$, compared with postcraniectomy.
Fig. 3. Contrast-enhanced ultrasonographic images obtained in the parasagittal plane after a high-power destructive pulse sequence (upper) and graph showing corresponding time versus VI curves in a patient before decompressive craniectomy, immediately after craniectomy, and on postoperative Day 1 (lower). Perfusion is markedly improved immediately after craniectomy and further improved by Day 1, largely because of an increase in microvascular blood volume (plateau VI).

Fig. 4. Graphs depicting the relationship between reduction in ICP after craniectomy and change in microvascular perfusion over all postoperative studies (left) and the relationship between initial ICP and change in microvascular perfusion over all postoperative studies (right). MBF = microvascular blood flow.
ary ischemic injury, and possibly to determine prognosis. Although ICP and CPP measurements provide prognostic value in patients with TBI,\textsuperscript{12,17,18} they do not directly measure temporal changes in CBF that occur during secondary injury, thereby limiting somewhat their utility in the detection of inadequate cerebral perfusion. Accordingly, it has been suggested that individualized management in each case should be based not only on ICP and CT findings but also on serial assessment of regional\textsuperscript{19} and global CBF.\textsuperscript{18}

Although methods for evaluating cerebral perfusion have been put into clinical use in contemporary neurosurgical practice, most have substantial limitations. Methods that rely on CT, magnetic resonance, and PET imaging are expensive, require patient transport with its attendant risks, and are poorly suited for intraoperative applications and frequent monitoring. Measurement of Xe clearance, thermal diffusion, and arteriovenous nitrous oxide gradients can be performed at the bedside,\textsuperscript{15,21} but these methods are limited in assessment of the entire brain or regional perfusion abnormalities.\textsuperscript{2} Transcranial Doppler ultrasonography can be used to evaluate the status of large vessels but not microvascular flow.

In this pilot study, we have demonstrated that CEU can be used temporally and spatially to assess cerebral perfusion in patients with severe TBI. Contrast-enhanced ultrasonography was used to quantify changes in blood flow produced by decompressive craniectomy, to assess blood flow alterations related to patient position and ICP, and to evaluate spatial heterogeneity of flow produced by parenchymal hematoma. This noninvasive imaging technique has several practical advantages, making it ideal for clinical application. It is portable, relatively inexpensive, and provides information almost immediately to the clinician. It is also rapid, requiring approximately 5 minutes to perform, and therefore can be used to assess perfusion with high temporal resolution and evaluate the effects of an acute intervention. Contrast-enhanced ultrasonography also provides a direct measure of microvascular blood flow independent of vascular permeability owing to the use of microbubble contrast agents that are not diffusible and that have microvascular behavior similar to that of RBCs.\textsuperscript{16} In the current study, quantitative techniques were used that were originally developed to assess myocardial perfusion\textsuperscript{28} and have been validated for quantifying cerebral perfusion.\textsuperscript{22} This method allows for the separate evaluation of microvascular blood volume and velocity and has been applied to assess stroke-related regional cerebral perfusion abnormalities using transtemporal bone windows\textsuperscript{8,14} and to assess flow abnormalities associated with gliomas in animal models.\textsuperscript{6} The image analysis protocols used to assess relative capillary perfusion and its components have been validated in comparison with analyses using radiolabeled microspheres and capillary xanthine oxidase activity in animal studies and in comparison with PET imaging in patients.\textsuperscript{5,23,27,29}

In this study, CEU was performed in patients with severe TBI undergoing emergent decompressive craniectomy for evidence of persistently elevated ICP, most of whom also had evidence of high-risk features on CT scans, such as cisternal effacement, midline shift, intracerebral hemorrhage, or subarachnoid hemorrhage. Previous studies using CT perfusion imaging have demonstrated that surgical intervention can substantially improve CBF in these patients.\textsuperscript{31} Using CEU, we were able to determine that microvascular blood flow increased an average of fivefold over the 3-day study period. The ability to perform CEU in the operating suite, minutes before and after craniectomy, allowed assessment of the immediate effects of decompress-

\begin{table}[h]
\centering
\caption{Mean ICP and hemodynamic measurements in six patients with TBI according to patient position}  
\begin{tabular}{lcc}
\hline
 & Recumbent & 35° Incline \\
\hline
ICP (mm Hg) & 16 $\pm$ 5 & 12 $\pm$ 4* \\
CPP (mm Hg) & 82 $\pm$ 23 & 84 $\pm$ 20 \\
MAP (mm Hg) & 95 $\pm$ 23 & 96 $\pm$ 19 \\
MBF ($A \times B$) & 37 $\pm$ 11 & 51 $\pm$ 20* \\
\hline
\end{tabular}
\textsuperscript{*} p < 0.05, compared with recumbent (paired Student t-test).
\end{table}

\fig{5}{Computerized tomography scan obtained in a patient with a focal hemorrhage (left) and CEU performed in the same patient on postoperative Day 1 (right). The CEU image demonstrates a central region of hypoperfusion (arrow), and microvascular blood flow appears to increase with radial distance from the hematoma.
we found that cerebral perfusion
0.05, compared with the cen-
Some clinicians have ad-
Contrast-enhanced ultrasonography per-
Although the study was underpow-
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SEM) microvascular blood
and serves to explain why changes in microvascular
blood flow were proportionally greater than changes in ICP.
Regional assessment of perfusion is also an important
consideration in patients with parenchymal hematoma.
Studies using CT or PET imaging have demonstrated mark-
edly reduced perfusion at the central core of a focal con-
tusion with gradual improvement with radial distance
from the center.\textsuperscript{20,26} Contrast-enhanced ultrasonography per-
formed in the current study revealed a similar pattern of
abnormal perfusion and a peripheral rim of relative hyper-
emia. We believe that the ability to serially assess perfusion
with CEU could be valuable for characterizing how region-
al flow abnormalities associated with contusion are affected
by interventions aimed at improving global flow and ICP.
There are several limitations of this study. First, a small
number of patients were enrolled, although we believe that
our results justify a larger and more comprehensive study.
Second, imaging was performed through a craniectomy de-
fect or bur hole. We did not test the ability to image through
a temporal or other bone window because our aim was to
keep the acoustic power as low as possible given the pau-
city of information on safety of cerebral CEU using high-
power imaging. Third, we did not include a control group
with a similar degree of TBI who did not undergo craniec-
tomy, because ultimate determination of the most appropri-
ate therapy was not the primary aim of the study. Another
technical limitation is that relative perfusion rather than ab-
solute perfusion was measured. Although a constant infu-
sion rate for contrast was used for each patient, differences
in microbubble volume of distribution or clearance rate at
the different study intervals may have influenced the mea-
surement of microvascular blood volume. Additional non-
standard monitoring techniques were not used to validate
CEU, but future studies will likely include such compar-
isons.

**Conclusions**

Contrast-enhanced ultrasonography can be used at the
bedside to assess cerebral perfusion in patients with TBI.
The technique has many advantages, including portabil-
ity, capacity for rapid data acquisition, and widespread
availability of imaging hardware. Our results indicate that
changes in CBF that occur immediately after decompress-
ive craniectomy or secondary to positional changes can be
detected by CEU and that CEU is sensitive enough to detect
regional changes in blood flow in the traumatized brain.
Larger studies evaluating whether information provided by
CEU can be used to guide therapy or to predict long-term
outcomes will be needed to establish the role of this tech-
nique in contemporary neurosurgical care.

**References**

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