Focal ischemia due to traumatic contusions documented by stable xenon-CT and ultrastructural studies

MARC L. SCHRÖDER, M.D., J. PAUL MUIZELAAR, M.D., PH.D., M. ROSS BULLOCK, M.D., PH.D., JACKSON B. SALVANT, M.D., AND JOHN T. POVLISHOCK, PH.D.

Division of Neurosurgery, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia

A traumatic cerebral contusion causes a zone of perifocal neuronal necrosis, the cause of which is not known; the surgical management of these lesions remains controversial. To determine the pathophysiological mechanisms responsible for brain damage after contusions, the authors performed cerebral blood flow (CBF) mapping studies and related these to change in local cerebral blood volume (CBV) and ultrastructure. In 11 severely head injured patients with contusion, CBF and CBV were measured in pericontusional areas using stable xenon-computerized tomography (CT). These studies demonstrated a profound reduction in perilesional CBF (mean 17.5 ± 4 ml/100 g/min), which was always accompanied by a zone of edema defined by CT density measurements. Mean CBV in these regions was 2.3 ± 0.4 ml/100 g, a reduction to approximately one-half the value of 4.8 ml/100 g found in the nonedematous regions, and to approximately 35% of the value of 6.0 ml/100 g found in normal volunteers. Ultrastructural analysis of the pericontusional tissue, taken at surgery in four patients with high intracranial pressure showed glial swelling with narrowing of the microvascular lumina due to massive podocytic process swelling. Additionally, some suggestion of vascular occlusion due to erythrocyte and leukocyte stasis was seen. These data support the conclusion that microvascular compromise by compression and/or occlusion is a major event associated with profound perilesional hypoperfusion, which is a uniform finding within edematous pericontusional tissue.

KEY WORDS • cerebral contusion • cerebral blood flow • cerebral blood volume • cerebral edema • ultrastructure • microvasculature
Blood flow studies that have used intracarotid xenon-133 and external collimated detectors have provided evidence that contusions may be associated with reduced cerebral blood flow (CBF)\textsuperscript{18,21}. However, interpretation of the results of the xenon 133 technique is uncertain in the presence of focal damage, because the technique is notomographic and is degraded by the “look-through phenomenon,” unknown diffusion coefficients ($\lambda$), fast tissue peaks, and other factors, so that conclusions about regional (r)CBF changes cannot be accurately drawn. We have, therefore, studied rCBF with an accurate, quantitative tomodographic method in parallel with structural CT. Our aim was to test the hypothesis that rCBF is reduced adjacent to focal intraparenchymal traumatic lesions to an extent sufficient to cause ischemic neuronal necrosis. We also report regional cerebral blood volume (rCBV) and ultrastructural data suggesting that microvascular compression and occlusion may explain these CBF findings.

**Clinical Material and Methods**

These studies were performed at the Medical College of Virginia, Richmond, Virginia and were approved by the Institutional Review Board and the local Committee on the Conduct of Human Research.

**Patient Selection and Study Protocol**

Eleven patients with a severe closed head injury (Glasgow Coma Scale\textsuperscript{55} score $\leq 8$ or a motor score $\leq 5$) harboring a cerebral contusion more than 2 cm in size were analyzed for this study. Clinical features are shown in Table 1. On admission to the emergency room, patients were immediately intubated, hemodynamically stabilized, and resuscitated when necessary. The initial diagnostic head CT scan was immediately followed by a stable xenon-CT assessment of CBF. In addition, a CBV measurement was obtained whenever possible. In one patient a coexisting subdural hematoma requiring surgical removal was present, and in this patient the CBF study was performed before the craniotomy. In four cases a CBF/CBV study was repeated between the 2nd and 4th days.

**Determination of Pericontusional CBF**

All CBF studies were executed on a CT scanner equipped with a stable xenon gas delivery system and a matching CBF software package, which has been described elsewhere\textsuperscript{23}. Blood flow determinations were made at three CT planes, each 5 mm in thickness. In normal volunteers the mean value for CBF is $55 \pm 6$ ml/100 g/min\textsuperscript{22}. To compute CBF in pericontusional zones, a region of interest was drawn freehand on the diagnostic CT scan around all contiguous low-density zones adjacent to the contusion (Fig. 1 left). The mean CT density in Hounsfield units (HU) was calculated for the low-density area, as well as for an adjacent brain region of normal density on the contralateral side. This template was then superimposed on the computerized blood flow map and CBF was calculated in the respective “edematous” and normal brain areas (Fig. 1 right).

**Determination of Pericontusional CBV**

In seven patients we measured rCBV in the pericontusional low-density areas and compared the values to the corresponding contralateral side. Cerebral blood volume was calculated according to the central volume principle\textsuperscript{23}, which entails computing by dynamic CT scanning the mean transit time (MTT) through the brain tissue of an intravenous 50-ml bolus of iodine contrast medium directly following the CBF study. Cerebral blood volume was computed according to the equation $\text{CBV} = \text{CBF} \times \text{MTT}$. To define CBV in the pericontusional regions, we superimposed the identical template, as described above, on the contrast-enhanced dynamic CT scan taken from the same plane. In normal volunteers mean CBV is $6.0 \pm 0.4$ ml/100 g\textsuperscript{23}.
Brain tissue was obtained for the purpose of electron microscopic assessment in four patients who underwent craniotomy for evacuation of focal contusions that were significant space-occupying lesions. All tissue was harvested from brain regions with documented low CBF and CBV surrounding the evacuated contusion. The specimens were immediately transferred to a fixative composed of 2% paraformaldehyde and 2.5% glutaraldehyde for 48 to 72 hours. During fixation, the tissue was divided into smaller portions to improve fixative penetration. After fixation, specimens were washed in buffer and immersed in 1% OsO₄ for 1 hour. The specimens were then dehydrated in ascending concentrations of ethyl alcohol and propylene oxide and embedded in resin.* The plastic-embedded material was sectioned on an ultramicrotome. Thick sections were cut for light microscopic evaluation, and thin sections were prepared for electron microscopic evaluations. In addition to this pericontusional tissue, control tissue was harvested from the margins of resection in a patient undergoing temporal lobectomy for seizures, and this was processed in the same fashion. This tissue was used as control material to address the concern that the tissue-processing protocols used could induce persistent artifactual change.

Statistical Analysis

Because the data were not normally distributed, the significance of the differences in CBF and CT density in the pericontusional and normal areas was tested using the Spearman’s rank test. Cerebral blood volume differences were tested using the Wilcoxon matched paired rank test. A p value of less than 0.05 was considered significant.

Results

The mean CT density numbers in the pericontusional and normal areas taken from the diagnostic CT scan and stable xenon-CT assessment of CBF were compared for 11 patients, together with the corresponding mean CBF and CBV values. The difference in HU between the “edematous” pericontusional (45 ± 4.8) and normal (54 ± 4.3) areas in the same patient was highly significant (p < 0.001). Flow values in the pericontusional areas were less than half the values seen in the normal density areas (p < 0.01). Most of the areas adjacent to contusions had CBF values below the threshold for ischemic damage (CBF ≤ 20 ml/100 g/min) (Fig. 2). Cerebral blood flow values for edematous pericontusional areas and areas showing no edema were 17.5 ± 4.0 (range 9.5 to 28.5) and 39.9 ± 11.2 ml/100 g/min, respectively. Values in normal volunteers were 55 ± 6 ml/100 g/min. A significant difference was also found between CBV in the pericontusional areas and in normal brain: 2.3 ± 0.4 ml/100 g compared to 4.6 ± 0.8 ml/100 g (p < 0.001), a decrease of 50% in the pericontusional zones. The mean value in normal volunteers was 6.0 ± 0.4 ml/100 g. The correlation between CBV and CBV in the “low-density” pericontusional areas was almost significant (p = 0.058).

Cerebral Blood Flow Changes Over Time

Within the edematous pericontusional tissue, a trend was seen for the CT density (in HU) to decrease over time when the interval between injury and CT scan was plotted (Fig. 3). No clear trends were seen when the relationship between pericontusional CBV, pericontusional CBF, and time were similarly plotted. No tendency for delayed reperfusion of the pericontusional ischemic zones was seen.

Ultrastructural Vascular Changes

All tissue samples showed excellent ultrastructural detail with preservation of neural, glial, and vascular elements. In some foci the brain parenchyma appeared relatively normal, with only modest glial swelling dispersed among otherwise normal neuronal elements. The majority of samples, however, showed evidence of overt cellular change, the most conspicuous being the presence of pronounced glial swelling (Fig. 4 upper). This swelling was typically found in perivascular loci that revealed distended, electron-lucent glial foot processes. Frequently, the adjacent vascular lumina were narrowed (Fig. 4 upper right).

Although not all microvessels were affected equally, similar changes were observed throughout the tissue samples. Erythrocytes and leukocytes were frequently observed within the vascular lumina (Fig. 4 lower left); however, platelet activation and thrombosis were not observed in the specimens studied to date. Despite the occurrence of this dramatic perivascular swelling and the apparent narrowing of the vascular lumina, the endothelium appeared intact and adjacent tight interendothelial junctions were unaltered. The endothelial cells were closely adherent to the underlying basal lamina. In some endothelial cells, occasional swelling of mitochondria and organelles was detected, but these changes were modest.

* Medcast resin obtained from Ted Pella, Inc., Redding, California.
given the overall magnitude of the related glial swelling and vascular compression.

In contrast to the perivascular and vascular changes seen in the material harvested adjacent to contusions, the control tissue did not show comparable changes. In the control tissue, the perivascular glia appeared normal with no evidence of swelling (Fig. 4 lower right). Similarly, although the vascular lumina did show red blood cell packing, no evidence of occlusion due to leukocytic plugging was found (Fig. 4 lower right). This suggests that the changes associated with contusion were not artifactually induced by the preparative procedures.

Discussion

These studies of CBF with stable xenon-CT clearly demonstrate profound reductions in blood flow surrounding focal cerebral contusions. Both the CBV data and the microvessel morphology studies support the concept that microvascular compromise, via compression and/or leukocytic occlusion, seems to be the major factor causing perilesional hypoperfusion in this study. This result accords with previous ultrastructural morphology studies in human and animal models of focal contusion.10–12,14,38,54 This study also demonstrates a close relationship between the occurrence of pericontusional edema and rCBF. Whenever edema is present, as measured by CT density in HU or T1-weighted signal on MR imaging, rCBF is low: usually close to the threshold value for development of edema, as shown by Bell, et al., in primates (≤ 19 ml/100 g/min). Values of CT density below ± 50 HU and zones of abnormal attenuation on MR imaging have been shown to be linearly related to the development of edema, as measured by microgravimetry.13 Moreover, these studies have shown that the hypoperfused edematous zones do not reperfuse significantly with the passage of time, in contrast to, for example, either nonhemorrhagic infarction as seen in human middle cerebral artery occlusion54 or the global changes in CBF after severe head injury.47,48

Mechanical Deformation and Ion Flux

Mechanical deformation of neuronal tissue causes massive ion flux, leading to K+ efflux into the extracellular fluid and consequently to astrocytic swelling.16,48 Our recent microdialysis studies have also shown a 10- to 15-fold increase in glutamate and aspartate release lasting up to 4 days in the extracellular fluid adjacent to human focal contusions.44 This may exacerbate ion flux and astrocyte swelling by opening glutamate-gated ion channels.42 Glutamate antagonist drugs, such as CGS19755, have been shown to lower ICP in head-injured humans, and this may be due to an effect on astrocyte swelling.37,53

J. Neurosurg. / Volume 82 / June, 1995

Fig. 3. Scatterplot showing change in computerized tomography (CT) density of pericontusional tissue with time after contusional injury. A trend was seen for the CT density (in Hounsfield units (HU)) to decrease over time when the interval between injury and CT scan was plotted (p = 0.3, r = 0.25).

Fig. 4. Electron micrographs. Uranyl acetate, lead, and nitrate. Upper Left: A tissue sample harvested from a pericontusional area demonstrating prominent glial swelling (asterisk). Note that one microvessel in the field (V) is encompassed by a swollen and disrupted astrocytic process. Original magnification, × 6000. Upper Right: Prominent perivascular glial swelling is again seen. Note the presence of numerous expanded and disrupted astrocytic foot processes (asterisk) that surround this compressed vessel displaying luminal narrowing. Original magnification, × 6000. Lower Left: Dramatic perivascular glial swelling is again demonstrated, associated in this case with a vessel whose lumen is occluded by a circulating leukocyte and a red blood cell. Original magnification, × 6000. Lower Right: Control tissue revealing a microvessel surrounded by numerous glial end feet. Note that the glial cells and their foot processes (asterisk) display normal detail, with no evidence of swelling. Original magnification, × 9000.
Mechanisms of Injury Propagation

Mechanical injury of neural or vascular tissue, at both the core and the periphery of the contusion, may result in a series of events that include 1) release of free ions from extravasated erythrocytes, catalyzing the Haber–Weiss reaction; 2) endothelial activation with up-regulation of transferrin receptors and surface adhesion proteins; 3) augmentation of the arachidonic acid cascade with concomitant release of leukotrienes, prostaglandins, and free radicals; and 4) activation of platelets and leukocytes with release of cytokines. These changes, either individually or in combination, can alter vascular–leukocyte interactions, promoting adhesions. Leukocyte adhesion to the vascular wall induces focal sites of occlusion and ischemia. The probable efficacy and rapidity of onset of free radical scavengers in improving ICP add further support for this supposition. The importance of leukocyte–vascular interactions has led us to initiate a clinical trial investigating the effect of anti-CD11b monoclonal antibodies against leukotrienes in trauma patients.

Conclusions

These studies have several implications for the care of the focally brain injured patient. First, resection of focally contused brain tissue that is causing major mass effect, clinical deterioration, or high ICP should be performed without hesitation, even in “evocative” brain areas, because such tissue is already infarcted and nonviable. It is true that there are no good methods to assist the surgeon in defining the volume of pericontusional tissue that needs to be removed, but our finding of a zone of densely ischemic but noncontused tissue, extending about 1 cm around in the contusion core, provides a margin of safety during contusion removal.

Second, these studies provide an adequate explanation for the delayed enlargement or secondary swelling that is so frequently seen in focal contusions. Our previous studies have shown that the blood–brain barrier remains closed to “marker” molecules, such as technetium-99m (Pertechnetate) and gadolinium diethylenetriamine pentaacetic acid, in at least one-third of patients with focal contusions, and that in patients in whom it does not, this is unusual in the first 2 to 3 days of a Marmarou, personal communication, 1993. It is not necessary to invoke a “vasogenic” edema component to explain pericontusional swelling; it may occur due to progressive cytotoxic (ischemic) edema during the first 2 to 3 days. Third, we have previously shown similar profound CBF reductions in certain patients with acute subdural hematoma and hemispheric brain swelling when these studies were performed within the first few hours after injury. Most of these patients with large volumes of hypoperfused brain either died or remained severely disabled. The mechanisms that cause hypoperfusion and low-density zones on CT or “T1 edema” on MR imaging, which we have shown in this study, may therefore affect larger areas of brain in more severely injured patients who usually die due to brain swelling.

Further studies in these focally injured patients as well as in animal models should be directed at identification of the factors that lead to astrocytic swelling and polymorphonuclear leukocyte activation. Several hypotheses can be advanced to explain these events, identify their mechanisms, and then ameliorate them with drugs specifically designed to block the mechanisms. As noted above, some of these studies have already been initiated (tirilazad to prevent lipid peroxidation, dismucet as an oxygen radical scavenger, LY303932 to ameliorate leukocyte–vascular interactions, and GCS19755 as a glutamate antagonist).

References

Focal ischemia due to contusions


Manuscript received January 10, 1994. Accepted in final form September 21, 1994.

This work was supported by Grants No. 5RO1NS29412–03 and NS19469 from the National Institutes of Health, Bethesda, Maryland, and the Lind Lawrence Fund, Richmond, Virginia.

Address reprint requests to: J. Paul Muizelaar, M.D., Ph.D., Neurological Surgery Department, University Health Center, 4201 St. Antoine 6E, Detroit, Michigan 48201.
TABLE 1

Clinical characteristics of the patients with contusions assessed with stable xenon-CT scan*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>11</td>
</tr>
<tr>
<td>no. of CBF studies</td>
<td>19</td>
</tr>
<tr>
<td>mean age, yrs (range in yrs)</td>
<td>34 (17–63)</td>
</tr>
<tr>
<td>sex (M/F)</td>
<td>10:1</td>
</tr>
<tr>
<td>mean GCS score (range)</td>
<td>5 (3–8)</td>
</tr>
<tr>
<td>time of study (range in hrs postinjury)</td>
<td>80 (2–204)</td>
</tr>
<tr>
<td>ICP (range) mm Hg</td>
<td>19.8 (10–34)</td>
</tr>
<tr>
<td>MABP (range) mm Hg</td>
<td>104 (86–142)</td>
</tr>
<tr>
<td>cause of injury</td>
<td></td>
</tr>
<tr>
<td>4 MVA</td>
<td></td>
</tr>
<tr>
<td>2 fall</td>
<td></td>
</tr>
<tr>
<td>4 assault</td>
<td></td>
</tr>
<tr>
<td>1 other</td>
<td></td>
</tr>
<tr>
<td>area of pericontusional “edematous”</td>
<td>8.8 ± 6.7</td>
</tr>
<tr>
<td>regions on each CT (cm²)</td>
<td></td>
</tr>
</tbody>
</table>

* CT = computerized tomography; CBF = cerebral blood flow; GCS = Glasgow Coma Scale; ICP = intracranial pressure; MABP = mean arterial blood pressure; MVA = motor vehicle accident.