Focal cerebral hyperemia after focal head injury in humans: a benign phenomenon?

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Posttraumatic regional alterations in cerebral blood flow (CBF) remain poorly understood. Decreases may be associated with increased intracranial pressure or attributed to the presence of focal lesions such as hematomas and contusions, or occasionally infarction. Posttraumatic flow increases, however, are more difficult to explain. Cerebral hyperemia after trauma has been associated with younger patients and diffuse head injury. It has been seen more frequently between the 2nd and 4th days after trauma and is often considered to be an indicator of poor prognosis, especially when it is late. Most of these studies, however, have used nontomographic measurements. As a result, these studies have been unable to adequately relate focal CBF changes to abnormalities on computerized tomography (CT) scanning and have mainly investigated global CBF, so that limited data were provided on the relationship of focal flow phenomena to focal brain parenchymal structural lesions.

The advent of newer tomography techniques for CBF measurement, such as stable xenon-enhanced CT (XeCT), single-photon emission CT (SPECT), and positron emission tomography (PET), allows the relationship between regional CBF and focal posttraumatic cerebral lesions to be explored. Recent studies using these techniques have provided information about the relationship of injury-induced CBF alterations to surgical mass lesions, CO\textsubscript{2} vasoresponsivity, and outcome. Single-photon emission computerized tomography has been used in a limited number of trauma studies and primarily revealed areas of decreased perfusion. Conversely, hyperemia, and more specifically its relationship to focal brain lesions or areas of edema, has not been sufficiently investigated.

To determine the incidence and significance of focal cerebral hyperemia in patients with focal posttraumatic lesions, we have selected a study population consisting of 53 patients with in situ intraparenchymal or extracerebral focal lesions.
parenchymal mass lesions at the time of CBF mapping. These patients were sufficiently hemodynamically stable to be safely subjected to SPECT scanning. The objectives of the study were twofold: 1) to investigate the relationship between posttraumatic hyperemia and clinical parameters; and 2) to anatomically correlate flow alterations on SPECT with focal brain lesions on CT and MR imaging, to improve our understanding of the pathophysiological mechanisms following head injury and their time course.

Clinical Material and Methods

Blood Flow Mapping

Cerebral blood flow mapping studies were performed via SPECT using technetium-99m (99mTc) hexamethylpropyleneamineoxime (HMPAO) Ceretec (1200 mbq) on 53 patients within 3 weeks of head injury.

Clinical Assessment

The following clinical data were recorded for analysis: age, localizing neurological deficits, pupillary reactivity, Glasgow Coma Scale (GCS) score, duration of traumatic loss of consciousness, and hypotensive or hypoxic episodes. The patients were classified according to the severity of head injury as follows: mild, initial period of unconsciousness for 30 minutes or less and no deterioration from an admission GCS score of 14; moderate, admission GCS 9 to 13 with no deterioration below this range; severe, GCS of less than 9 after resuscitation. Outcome was assessed at 3 months after injury using the Glasgow Outcome Scale.19

Computerized Tomography. Scans were obtained in 6-mm-thick contiguous axial sections immediately after patients’ admission to the neurosurgical unit, at 3-month follow-up evaluation, and as clinically indicated.

Magnetic Resonance Imaging. Imaging was performed with a 0.15-tesla unit, operating at 6.38 MHz. An initial 2-cm-thick spin-echo (SE 200/40 msec) pilot image in the sagittal and coronal plane was used to determine the position of 16 8-mm-thick slices, for a T2-weighted spin-echo sequence (SE 2000/80 msec), and an eight-slice T1-weighted inversion recovery sequence (IR 1660/400/40 msec) was obtained in the axial plane. These examinations were completed on all patients who had undergone SPECT.

The CT and MR analyses were performed within 24 hours of the SPECT study. Patients with hyperemia were serially scanned, and additional late CT and MR studies were performed at a mean period of 3 months after injury. Both T1- and T2-weighted images were performed to demonstrate zones of focal edema.

Single-Photon Emission Computerized Tomography. The SPECT studies were performed by means of a head-dedicated imager. Twenty-one of the 53 patients were studied more than once, 24 hours to 3 months apart. In a subgroup of individuals with large acute hematomas, the initial blood flow studies were performed with the hematomas in situ as follows: in 12 patients, 99mTc HMPAO was injected as soon as the hematoma was diagnosed by CT scan and before craniotomy. Immediately after hematoma evacuation, the SPECT scanning was performed. The first-pass binding characteristics of 99mTc HMPAO retain it in the cerebral tissue with virtually no redistribution for approximately 5 to 6 hours, in proportion to blood flow passing through the brain at the time of injection.1 The SPECT studies thus represent the blood flow distribution with the hematoma in situ, even when they are obtained after the hematoma has been removed.18

Because of uncertainties about the mathematical modeling of 99mTc HMPAO uptake and back diffusion from the brain, CBF was not calculated from the tomography images.1 Analysis of SPECT images was performed by measuring regional 99mTc HMPAO uptake and comparing this with 99mTc HMPAO uptake in the medial occipital cortex when studied with the patient’s eyes closed. In over 140 posttraumatic SPECT scans, the occipital cortex was the region found to be least affected after head injury. Regional hyperemia was recorded when 99mTc HMPAO uptake in the area of interest exceeded mean uptake in the occipital cortex.

Conclusions about the size of the ischemic or hyper-
Hyperemia after head injury

Emic areas should be drawn with caution because of partial volume effects (resolution of the SPECT imager ± 0.8 cm). Brian uptake of $^{99m}$Tc HMPAO is dependent on, and thus closely correlated with, regional CBF. \(^{12,33}\) This has been demonstrated for corrected $^{99m}$Tc HMPAO, regional CBF, and xenon-133; \(^{2,15,16}\) PET oxygen-15, \(^{16}\) and regional CBF \(^{14C}\)-iodoantipyrine data. \(^{7}\) Although "hyperfixation phenomenon" for $^{99m}$Tc HMPAO has been reported in subacute ischemic stroke, there is little support of this finding in other pathological conditions. \(^{46}\) Conversely, $^{99m}$Tc HMPAO SPECT has been shown to generally underestimate high flow when compared with PET. \(^{17}\) and xenon-133 CBF. \(^{48}\)

Results

Distribution and Time Course of Focal Hyperemia

Hyperemic areas were found in 20 (38%) of 53 patients. They were commonest in patients with focal contusions and intracerebral hematomas. The hyperemic regions were always directly adjacent to zones of profound ischemia surrounding contusions or intracerebral hematomas and affected both gray and white matter (Figs. 1–4). The hyperemic zone never exceeded 15% of the hemisphere volume; foci of low flow were surrounded by multiple hyperemic areas in many patients. Hyperemia was always seen in tissue of normal density, as judged by CT or MR imaging, and was never seen within the contusion itself, the low-density "edematous" CT zone, or within tissue that on MR imaging appeared to have high T2-weighted signal intensity, indicating edema (Figs. 1–4). In all hyperemic patients who were serially scanned, the hyperemia had disappeared by the 2nd week after injury; however, in one patient minimal hyperemia was probably present 3 weeks after injury. Late CT or MR studies were performed in 14 of 20 patients with hyperemia, and in all of these, the previously hyperemic tissue appeared structurally normal.

Distribution and Time Course of Hypoperfusion

In every contusion greater than approximately 1.5 cm in diameter that was revealed on CT or MR imaging, a zone of profoundly reduced CBF was seen on SPECT at the site of the lesion, and in the surrounding brain tissue (Figs. 1–4). All contusions demonstrated edema as a zone of T2-weighted signal on MR images or a zone of lucency on CT, and all were accompanied by a focal zone of low CBF on SPECT. Larger contusions demonstrated zones of reduced CBF that were larger than the T2-weighted (hemorrhagic) lesion on MR image, but no larger than the T2-weighted MR imaged lesion corresponding to edematous brain. This zone of reduced CBF persisted for months in many cases, but in most of the patients scanned late, the ischemic zone became smaller with time. In two individuals the ischemic zone appeared larger when SPECT scanning was performed 3 months after injury. These findings are reported in more detail elsewhere. \(^{9}\)

Clinical Features in Patients With Hyperemia

The mean age of patients with hyperemia was 53 years and of patients without hyperemia it was 52 years. There was no significant difference in the frequency of hyperemia in different age groups. Hemiparesis was present in four with hyperemia (20%) and in four without (12%) (Table 1). Four (20%) of 20 patients with hyperemia had an episode of hypoxia or hypotension. Among the patients without hyperemia, 12% had such episodes.

Among the hyperemic patients, the lowest GCS score on admission to the neurosurgical unit was 5 and the highest was 13. Four (20%) of 20 patients with hyperemia, and five (15%) of 33 patients without hyperemia were comatose on admission (GCS score of 9 or less). Among the patients without hyperemia, the lowest GCS score on the day of the SPECT study was 5 and the highest 14. At the time of SPECT, the range of GCS scores was 3 to 14 in the patients without hyperemia.

Relationship of Hyperemia to Severity of Head Injury

The percentage of patients who suffered a head injury with no loss of consciousness or with only a brief loss was significantly higher among hyperemic patients than in patients without hyperemia (twice as high, p < 0.05) (Table 2). Among patients with hyperemia, seven (35%) had suffered a mild head injury compared to nine (27%) of patients without hyperemia. The percentage of patients who had more severe head injury was higher among patients without hyperemia, 10 (30%) of 33 whereas in the hyperemic group there were four (20%) of 20 (Table 3).

X-Ray, CT, and MR Findings

There were no significant differences in the frequency of skull fracture among the hyperemic and nonhyperemic group. Fifteen (75%) of 20 patients with hyperemia had a skull fracture; in the majority of these cases (80%), the hyperemic zone was homolateral to the fracture (Table 4). Hyperemia was most frequently seen in patients with contusions and intracerebral hematomas (17 of 38; 45%), and acute extradural hematomas (two of five; 40%); in one, it was present \textit{ab initio} at the margin of the tissue, which was compressed by the extradural hematoma. In the second patient, hyperemia developed 24 hours after removal of the extradural hematoma and was most marked in the contralateral frontal region (Fig. 2). A zone of reduced CBF was seen immediately underlying the extradural hematoma in all five patients, but this was mild even when the extradural hematoma was large. Among the seven individuals with acute subdural hematomas, only one showed hyperemia. In this patient a small contusion was also present underlying the subdural hematoma. In two of these acute subdural hematoma patients, a marked and extensive zone of blood flow reduction was present under the hematoma.

No consistent MR pattern was noted in relation to hyperemia. Hyperemia always occurred within tissue that had a normal appearance on CT or MR. In all patients with focal contusions or intracerebral hematomas, large zones of high-signal intensity were seen on T2-weighted images, suggesting cerebral edema in relation to these focal lesions.

Patient Outcome

Outcome was slightly better in patients with hyperemia than in those without (Table 5). Five patients were lost to...
Of those remaining, one unconscious patient with hyperemia adjacent to a contusion died (mortality 5.5%), and two (11%) remained severely disabled (one subdural, one contusion). Fifteen (83%) of the 18 hyperemic patients achieved a good outcome or minimal disability at follow up. Among the patients without hyperemia, 23 (77%) of 30 had a favorable result; four (13%) remained severely disabled, and three (10%) died. Patients with hyperemia had lower mortality (5%) compared with patients without hyperemia (10%), but the difference did not reach statistical significance (Table 5).
Discussion

Time Course, Clinical Features, and Outcome

This study demonstrated that focal intracranial injury is frequently accompanied by a transient zone of focal cerebral hyperemia that does not appear to be associated with harmful effects on clinical condition and outcome. Furthermore, our CBF mapping studies suggested that a much wider spectrum of trauma-related cerebral hyperperfusion exists than has been previously recognized. Post-traumatic cerebral hyperemia has been portrayed as a transient inhomogeneous global phenomenon seen after removal of intracranial hematomas or diffuse injury; it is chiefly seen in younger patients and is associated with poor prognosis, particularly when it is late, with only 8% of hyperemic patients having a favorable outcome.

We, however, focused on a different facet of the hyperemic phenomenon and investigated patients with focal intraparenchymal and extracerebral mass lesions who were predominantly posttraumatic hyperemia because focal high flows did not affect outcome and persisted for up to 2 weeks after trauma.

In other reports, the mean CBF had usually increased to “relative hyperemia” within 24 hours after injury, with in 72 hours most patients were hyperemic, but those examined more than 96 hours after injury showed little evidence of hyperemia. Recent tomography studies have demonstrated that hyperemia occurs after 24 hours, within 3 to 7 days, and most frequently between the 2nd and 4th days after trauma. In contrast to our results, most previous studies suggested that hyperemia is usually associated with a low GCS score with the exception of the most severely injured patients (GCS score 3), who did not show hyperemia.

Location of Hyperemic Foci

We studied the location of the hyperemic zones, comparing coaxially aligned CT and MR imaging and the SPECT CBF study; this technique had not been used previously for trauma. It was demonstrated via CT and MR imaging that hyperemia occurs only in normal tissue (both

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Relationship of hyperemia to neurological findings in focal head injury patients*</th>
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</thead>
<tbody>
<tr>
<td>Factor</td>
<td>Hyperemia</td>
</tr>
<tr>
<td>coma (GCS &lt;9)</td>
<td>4</td>
</tr>
<tr>
<td>hemiparesis</td>
<td>4</td>
</tr>
<tr>
<td>fixed dilated pupil</td>
<td>2</td>
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* GCS = Glasgow Coma Scale

FIG. 3. Studies in a 19-year-old man who was the victim of an assault. He had a left temporal depressed fracture and was dysphasic with a right hemiparesis on admission to the neurosurgical unit. Left: A $T_2$-weighted magnetic resonance (MR) image showing a contusion underlying the fracture. Center: A single-photon emission computerized tomography (SPECT) study showing the associated hypoperfusion and hyperemia medial and lateral to the contusion. Right: The association is not seen on follow-up SPECT at 6 months.

TABLE 2 | Relationship of hyperemia to duration of initial loss of consciousness (LOC) in head-injured patients
<table>
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<tr>
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</thead>
<tbody>
<tr>
<td>Duration of LOC*</td>
<td>No. of Cases (%)</td>
<td>Hyperemia (%)</td>
<td>No Hyperemia (%)</td>
</tr>
<tr>
<td>no LOC</td>
<td>15 (28)</td>
<td>5 (25)</td>
<td>10 (36)</td>
</tr>
<tr>
<td>&lt;30 min</td>
<td>18 (34)</td>
<td>11 (55)</td>
<td>7 (21)</td>
</tr>
<tr>
<td>30 min–3 hrs</td>
<td>6 (11)</td>
<td>0</td>
<td>6 (18)</td>
</tr>
<tr>
<td>3 hrs–6 hrs</td>
<td>2 (4)</td>
<td>0</td>
<td>2 (6)</td>
</tr>
<tr>
<td>&gt;6 hrs</td>
<td>12 (23)</td>
<td>4 (20)</td>
<td>8 (25)</td>
</tr>
<tr>
<td>total cases</td>
<td>53</td>
<td>20</td>
<td>33</td>
</tr>
</tbody>
</table>

* $p < 0.05$ (Sidak test) comparison between hyperemic and nonhyperemic patients (groups with no LOC or LOC for less than 30 minutes have been combined).
white and gray matter) directly adjacent to focal mass lesions (Figs. 1–4). Other researchers have also found focally increased CBF, both adjacent to regions of cortical contusion and laceration and globally in the hemisphere underlying a subdural hematoma. However, in contrast to our study, hyperemia was related to high intracranial pressure and diffuse swelling on CT.

Delayed persistent hyperemia, in particular, was observed postoperatively in patients with surgical hematomas, and it has been associated with marked alterations of CO₂vasore sponsivity. The discrepancy between the apparently more severe consequences of global hyperemia reported in previous studies and this report is probably explained by the preponderance of severe head injury patients in previous studies, in contrast to ours in which only 18% of patients were in coma.

Mechanisms of Hyperemia

The incidence, pathophysiological significance, and clinical relevance of hyperemia following head injury are not yet understood. High CBF during coma in patients with suppressed metabolism suggests an uncoupling of the two variables. Absolute and relative hyperemia have been described after trauma but no correlation between CBF and metabolism has been clearly established in hyperemic patients. In studies that showed a significant association between hyperemia and increased intracranial pressure, 35% of hyperemic patients had normal pressure. Moreover, serial studies of posttraumatic CBF have shown that with time, it may range widely from hypo- to hyperperfusion.

A direct association has been demonstrated between cerebrospinal fluid lactic acidosis and a form of posttraumatic cerebral hyperemia, which has been attributed to a decrease in vasomotor tone or "metabolic" vasodilatation. This may result in increased blood volume, elevated intracranial pressure, disruption of the blood-brain barrier, vasogenic edema formation, and red cell diapedesis and extravasation following surges of systemic arterial hypertension.

None of our cases manifested these features. Furthermore, our focal CBF increases are in contrast to the brief, transient postischemic reperfusion hyperemic phenomenon seen in animal models following severe focal or global ischemia; this form of reperfusion affects the previously ischemic tissue only and per-

<table>
<thead>
<tr>
<th>Severity of Injury</th>
<th>No. of Cases (%)</th>
<th>Hyperemia (%)</th>
<th>No. Hyperemia (%)</th>
</tr>
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<tbody>
<tr>
<td>mild</td>
<td>16 (30)</td>
<td>7 (35)</td>
<td>9 (27)</td>
</tr>
<tr>
<td>moderate</td>
<td>23 (43)</td>
<td>9 (45)</td>
<td>14 (43)</td>
</tr>
<tr>
<td>severe</td>
<td>14 (27)</td>
<td>4 (20)</td>
<td>10 (30)</td>
</tr>
<tr>
<td>total cases</td>
<td>53</td>
<td>20</td>
<td>33</td>
</tr>
</tbody>
</table>

### TABLE 3

<table>
<thead>
<tr>
<th>Factor</th>
<th>No. of Cases</th>
<th>Hyperemia</th>
<th>No. Hyperemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>x-ray film</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>skull fracture</td>
<td>32</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>CT scan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no structural abnormality</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>extradural hematoma</td>
<td>5</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>subdural hematoma</td>
<td>7</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>intracerebral hematoma</td>
<td>15</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>parenchymal contusion</td>
<td>23</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>total cases</td>
<td>85</td>
<td>35</td>
<td>50</td>
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Hyperemia after head injury

TABLE 5

<table>
<thead>
<tr>
<th>Outcome*</th>
<th>No. of Cases†</th>
<th>Hyperemia</th>
<th>No Hyperemia</th>
</tr>
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<tbody>
<tr>
<td>Favorable</td>
<td>38</td>
<td>15 (83%)</td>
<td>23 (77%)</td>
</tr>
<tr>
<td>Good result</td>
<td>18</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>Minimal disability</td>
<td>20</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Poor</td>
<td>10</td>
<td>3 (17%)</td>
<td>7 (23%)</td>
</tr>
<tr>
<td>Severe disability</td>
<td>6</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Death</td>
<td>4</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Total cases</td>
<td>48</td>
<td>18</td>
<td>30</td>
</tr>
</tbody>
</table>

* Outcome defined by Glasgow Outcome Scale® score.
† Five patients were lost to follow up, two with hyperemia and three without hyperemia.

It is possible that these findings may represent one end of a spectrum. A “malignant” form of hyperemia may occur as long as the ischemic event, usually minutes or hours.

Disorders of Vasomotor Control

Selective impairment of vasomotor reactivity (defective pressure autoregulation with preserved CO2 reactivity) has been described as “dissociated vasoparalysis”; it is, however, fairly short-lived and vasoreactivity returns within a couple of hours. Release of perivascular neuropeptides has been implicated in global CBF increases associated with acute severe hypertension, seizures, and fluid percussion head injury.

Endothelial factors may play an important role as defense mechanisms when perfusion is locally compromised because of trauma. Inhibition of locally produced angiotensin II leads to a selective dilation of large cerebral arteries. Endothelium-dependent relaxing factor can influence basal tone and responses of large cerebral arteries and has been implicated in cerebral and systemic vascular relaxation and hyperemia as a defense mechanism against ischemia, but little is known of its action in trauma.

Local Metabolic Factors

Our previous studies demonstrated that ionic flux (efﬂux of K+, changes in Na+ of up to 40 meq in extracellular fluid) and a 10-fold sustained efﬂux of excitatory amino acids occur in pericontusional regions, and last up to several days following human focal injury. We therefore speculate that the sustained, apparently benign, focal hyperemic zones in these individuals may be secondary to increased metabolic demands or to release of metabolic mediators of vascular tone such as H+, adenosine diphosphate, and CO2. This hypothesis accords with the increases in focal cerebral glucose use, which have been demonstrated in several trauma models. In these areas, metabolism may be primarily directed at normalization of ionic homeostasis secondary to increased ionophore permeability, which may last for days after trauma.

Conclusions

We postulate that there are two distinctly different pathophysiological patterns of hyperemia, although it is possible that these findings may represent one end of a spectrum. A “malignant” form of hyperemia may occur that is associated with diffuse brain swelling, low level of consciousness, increased intracranial pressure, and poor outcome. It may be more common in younger patients, become a global phenomenon more frequently, and be associated with increased morbidity and mortality.

A “benign” form of hyperemia has also been demonstrated that is focal and persistent and has minimal effect on intracranial pressure and level of consciousness. This focal hyperemia did not occur in tissue subjected to subthreshold ischemia sufficient to cause infarction, which was shown by the absence of late CT or MR evidence of structural abnormality. It was associated with better outcome in common with another recent study.

The two forms of hyperemia are not mutually exclusive. In the early posttraumatic period (1–4 days posttrauma), this benign hyperemia may represent an “early” or “arrested” form of the global hyperemia described by other researchers. An understanding of the factors involved in the evolution of benign to malignant hyperemia could lead to development of therapeutic strategies for controlling high intracranial pressure. Functional imaging in combination with anatomical imaging, as used in this study, may allow valuable information to be gathered and characteristic patterns of alterations in flow and metabolism to be identified that are clinically relevant and helpful in the management of head-injured patients.

References


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283