Cerebral Hemodynamics and Metabolism of Severe Diffuse Brain Injury Measured by PET

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Cerebral hemodynamics and metabolism in three patients with severe diffuse brain injury were measured 10 days after onset using PET. In this study, regional cerebral blood flow (rCBF), oxygen extraction fraction (rOEF), cerebral blood volume (rCBV), cerebral metabolic rate for oxygen (rCMRO2), cerebral metabolic rate for glucose (rCMRglc) and cerebral metabolic ratio (rCMRO2/rCMRglc) were measured. The Glasgow Coma Scale scores on admission were 4, 5 and 5, respectively, and CT on admission showed typical findings of diffuse brain injury. As a result, PET revealed misery perfusion and hyperglycolysis in Patient 1 and matching low perfusion and low glucose metabolism in Patients 2 and 3. Although Patient 1 died, Patients 2 and 3 had good recoveries. We speculate that a long-lasting anaerobic state, indicated by a high OEF value and low metabolic ratio, is an important undesirable factor related to the outcome.

Key Words: diffuse brain injury; cerebral blood flow and metabolism; PET

J Nucl Med 1996; 37:1166–1170

Recently, several studies have tried to clarify cerebral hemodynamics and metabolism during the acute phase of brain injury using various methods (*1–4*). It is generally recognized that PET is the most useful method of quantitatively examining cerebral hemodynamics and metabolism in vivo. There have been, however, surprisingly few PET studies of head injury (*5–13*) and most of these studies have been presented as part of a general review of PET. Previous systematic PET studies of head injury (*7,12,13*) examined patients with focal brain injury, but there are no reports of PET findings during the acute phase of severe diffuse brain injury (SDBI). In the present study, we measured cerebral hemodynamics and metabolism in three patients with SDBI 10 days after onset using PET and report the changes in cerebral hemodynamics and metabolism in SDBI in the early stage.

CASE REPORTS

Patients and Methods

The three patients included an 18-yr-old woman, a 25-yr-old woman and a 30-yr-old man who had head injuries caused by traffic accidents. All patients were transferred to the emergency hospital within 15 min after onset of SDBI. All patients were in a deep comatose state with Glasgow Coma Scale (GCS) scores (*14*) on admission of 4, 5 and 5, respectively. However, the GCS score improved to 8 within 3 hr in Patient 2 and 6 within 5 hr in Patient 3 after admission. The GCS of Patient 1 did not improve prior to death. For all patients, CT obtained on admission, revealed typical findings of Diffuse Injury II (Fig. 1) according to the classifications proposed by Marshall et al. (*15*). On admission, respiration patterns for each patient were normal and data from arterial gas analysis showed no remarkable hypoxia. The patients were treated conservatively. PET studies were performed 10 days after injury and follow-up studies were performed 3 mo after injury for Patients

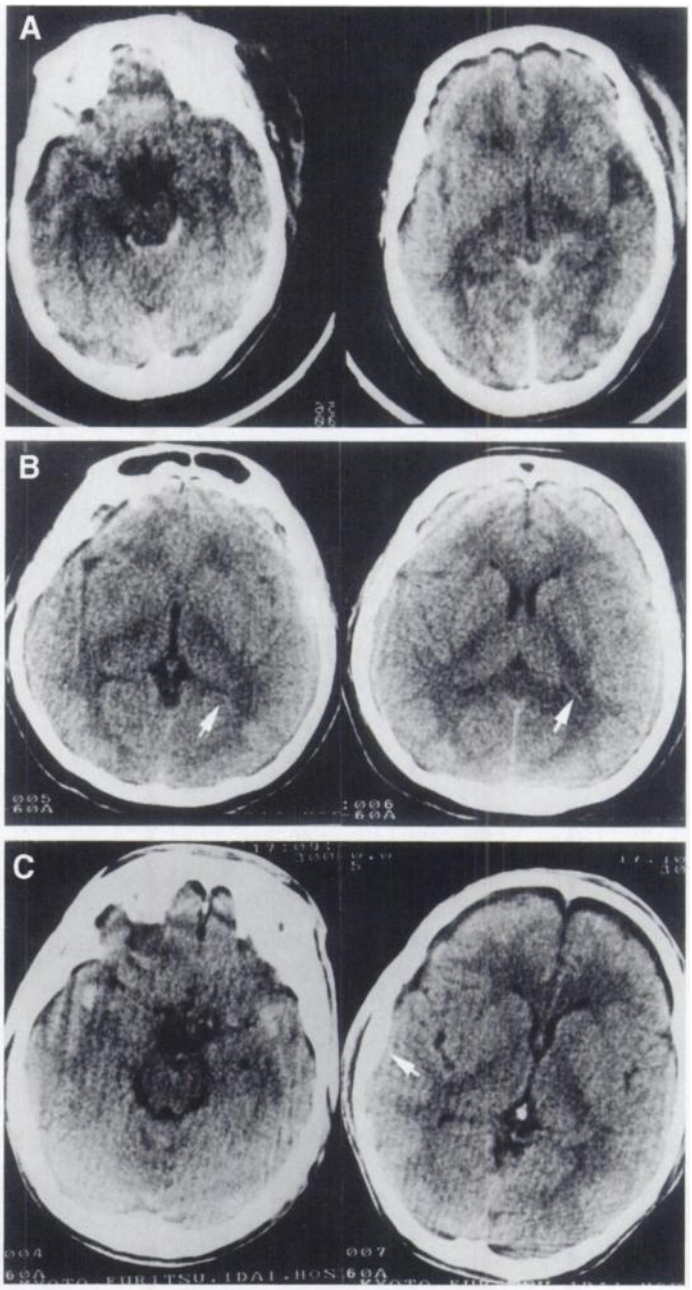

FIGURE 1. (A) Admission CT image of Patient 1 depicts traumatic subarachnoid hemorrhage in the ambient cistern, quadrigeminal cistern and cerebral contusion in the right temporal lobe. (B) Admission CT scan of Patient 2 demonstrates intraventricular hemorrhage in the left lateral ventricle (arrows). (C) Admission CT scan of Patient 3 shows small hemorrhagic lesions in the bi-temporal lobes and small epidural hematoma in the temporal region (arrow).

Received Mar. 29, 1995; revision accepted Oct. 8, 1995.
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TABLE 1
Results of Arterial Gas Analysis on PET Studies

Patient no.	PaO_2 (mmHg)	$PacO_2$ (mmHg)	pH	SaO_2 (%)	Hb (g/dl)
1	81.0	42.0	7.53	96.9	7.9
2					
Study 1	91.1	39.5	7.41	97.0	12.0
Study 2	104.9	38.2	7.39	97.8	11.3
3	87.3	39.0	7.42	96.8	11.0

2 and 3. GCS scores on the day of the first PET study were 4, 14 and 10, respectively, and GCS scores on the day of the follow-up PET studies were 15 (Patient 2) and 14 (Patient 3).

PET scans were obtained with a scanner that has an image resolution of 8 mm FWHM and a slice thickness of 11–13 mm FWHM. Tomographic planes were established 1.5 cm apart, 3.0, 4.5, 6.0 cm above and parallel to the orbitomeatal line. These planes were set parallel those in the CT studies. Arterial oxygen saturation (SaO_2) was derived from measured arterial oxygen tension (PaO_2) using the equation of Hill (*16*). Total arterial oxygen content (CaO_2) was then calculated as 1.39 × hemoglobin (Hb) concentration × SaO_2 + 0.0031 × PaO_2.

Regional cerebral blood flow (rCBF), oxygen extraction fraction (rOEF) and regional metabolic rate of oxygen ($rCMRO_2$) were measured using a ^{15}O-labeled gas steady-state technique as described by Frackowiak et al. (*17*). Regional cerebral blood volume was measured after bolus inhalation of ^{15}O-labeled carbon monoxide gas as described by Phelps et al. (*18*). Steady state was obtained by continuous inhalation of 0.1–0.4 GBq/min $C^{15}O_2$ and $^{15}O_2$ gas, and dose of $C^{15}O$ bolus inhalation was 0.8–4 GBq. In each study, we corrected for overestimation of rOEF and $rCMRO_2$ by CBV according to the method by Lammertsma et al. (*18*). In each patient, regional metabolic rates of glucose (rCMRglc) were also measured after bolus injection of ^{18}F-labeled 2-deoxy-D-glucose (^{18}FDG) (3.7 MBq/kg) immediately after the ^{15}O-gas studies. rCMRglc was estimated by the formula of Hutchins et al. (*20*) using the lumped constant and rate constants described by Phelps et al. (*21*). We calculated the metabolic ratio ($rCMRO_2$/rCMRglc) in each patient as the index of the balance between oxygen metabolism and glucose metabolism. Circular regions of interest (ROIs) in the gray matter contained 188 mm^2 (47 pixels) and were 16 mm in diameter, whereas the white matter ROIs contained 116 mm^2 (29 pixels) and were 12 mm in diameter.

TABLE 2
Regional Data of PET Parameters 10 Days after Injury in Patient 1

	rCBF	rOEF	$rCMRO_2$	rCMRglc	Metabolic ratio ($rCMRO_2$/rCMRglc)
Normal value of gray matter	43 ± 7 ml/100 g/min	0.42 ± 0.08	3.3 ± 0.5 ml/100 g/min	7.0 ± 0.8 mg/100 g/min	
Rt. frontal	33	0.78	2.5	8.4	0.30
Lt. frontal	34	0.62	2.4	8.6	0.28
Rt. temporal	35	0.71	2.6	8.9	0.29
Lt. temporal	37	0.81	2.3	9.2	0.25
Rt. occipital	34	0.77	2.5	8.3	0.30
Lt. occipital	37	0.65	2.5	8.1	0.31
Rt. parietal	30	0.78	2.5	8.3	0.31
Lt. parietal	31	0.74	2.4	8.5	0.28
Average	34	0.73	2.5	8.5	0.29
Normal value of white matter	25 ± 4 ml/100 g/min	0.44 ± 0.06	2.0 ± 0.3 ml/100 g/min	4.9 ± 0.8 mg/100 g/min	
Rt. white matter	20	0.58	1.2	6.7	0.18
Lt. white matter	22	0.58	1.4	6.3	0.22
Average	21	0.58	1.3	6.5	0.20

TABLE 3
Regional Data of PET Parameters 10 Days after Injury in Patient 2

	rCBF	rOEF	$rCMRO_2$	rCMRglc	Metabolic ratio ($rCMRO_2$/rCMRglc)
Normal value of gray matter	43 ± 7 ml/100 g/min	0.42 ± 0.08	3.3 ± 0.5 ml/100 g/min	7.0 ± 0.8 mg/100 g/min	
Rt. frontal	41	0.40	2.7	6.9	0.39
Lt. frontal	40	0.40	2.5	6.7	0.37
Rt. temporal	45	0.39	2.8	6.5	0.43
Lt. temporal	41	0.41	2.7	6.5	0.42
Rt. occipital	40	0.42	2.6	6.5	0.40
Lt. occipital	36	0.45	2.6	6.6	0.39
Rt. parietal	37	0.45	2.7	6.3	0.43
Lt. parietal	35	0.44	2.6	6.3	0.43
Average	39	0.42	2.7	6.5	0.41
Normal value of white matter	25 ± 4 ml/100 g/min	0.44 ± 0.06	2.0 ± 0.3 ml/100 g/min	4.9 ± 0.8 mg/100 g/min	
Rt. white matter	22	0.44	1.5	4.7	0.32
Lt. white matter	22	0.39	1.4	4.5	0.31
Average	22	0.42	1.5	4.6	0.32

TABLE 4
Regional Data of PET Parameters 10 Days after Injury in Patient 3

	rCBF	rOEF	$rCMRO_2$	rCMRglc	Metabolic ratio ($rCMRO_2$/rCMRglc)
Normal value of gray matter	43 ± 7 ml/100 g/min	0.42 ± 0.08	3.3 ± 0.5 ml/100 g/min	7.0 ± 0.8 mg/100 g/min	
Rt. frontal	39	0.38	2.3	4.3	0.54
Lt. frontal	39	0.40	2.3	4.2	0.55
Rt. temporal	48	0.38	2.7	4.6	0.59
Lt. temporal	36	0.43	2.3	4.6	0.50
Rt. occipital	38	0.39	2.2	4.1	0.54
Lt. occipital	37	0.38	2.1	4.2	0.50
Rt. parietal	37	0.39	2.2	4.3	0.51
Lt. parietal	38	0.40	2.1	4.0	0.53
Average	39	0.40	2.3	4.3	0.53
Normal value of white matter	25 ± 4 ml/100 g/min	0.44 ± 0.06	2.0 ± 0.3 ml/100 g/min	4.9 ± 0.8 mg/100 g/min	
Rt. white matter	24	0.37	1.3	3.2	0.41
Lt. white matter	24	0.37	1.3	3.1	0.42
Average	24	0.37	1.3	3.2	0.42

As a control, the corresponding brain regions were investigated by the same method in seven healthy adult volunteers, aged 20–64 yr (37.4 ± 15.6), who had been previously studied in our department (*22*).

RESULTS

The arterial gas and Hb values in each patient's PET study are shown in Table 1. In all patients, the raw rCBF, rOEF, $rCMRO_2$, rCMRglc values and metabolic ratios were similar throughout the gray and white matter. This was illustrated by the average values of the bilateral frontal, temporal, occipital and parietal gray matter as well as the white matter of the centrum semiovale shown in Tables 2, 3 and 4. The average values of the seven normal volunteers are also shown.

As shown in Table 2 and Figure 2, the rOEF in Patient 1 was extremely high and the metabolic ratio was 0.29 ml O2/mg glc in the gray matter and 0.20 ml O2/mg glc in the white matter. These findings indicated anaerobic glycolysis. The patient's clinical condition did not improve after admission and she died 12 days after the injury.

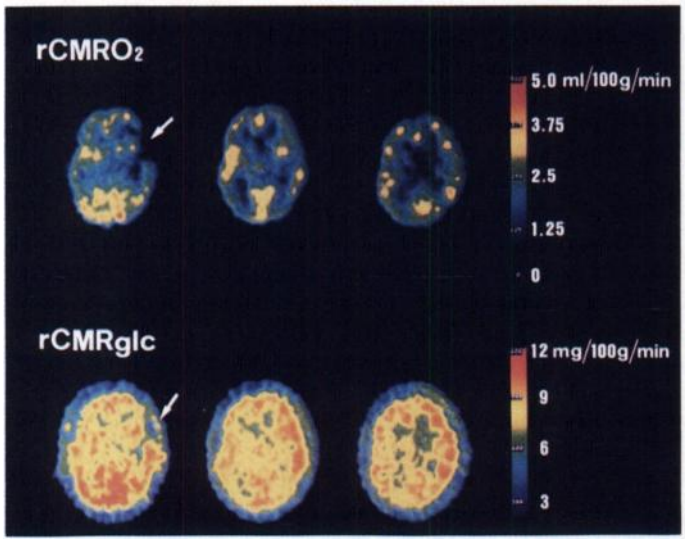

FIGURE 2. PET images show $rCMRO_2$ (upper) and rCMRglc (lower) in Patient 1. Three tomographic planes are shown. Images show remarkable decrease in $rCMRO_2$ and an increase in rCMRglc. The absence of the radioactive portion (arrows) seen on the $rCMRO_2$ and rCMRglc images represents normal left Sylvian fissure.

In Patients 2 and 3, PET findings demonstrated matching low perfusion and low metabolism as shown in Tables 3 and 4. The metabolic ratios were 0.40 and 0.53 ml O_2/mg glc in the cortex and 0.32 and 0.41 ml O2/mg glc in the white matter, respectively. The outcome in each case was good recovery according to Glasgow Outcome Scale (*23*) 6 mo after injury. Follow-up PET studies performed 3 mo after injury showed normal findings on all parameters in Patient 2 (Table 5). In Patient 3, only rCMRglc was studied and the results were within normal limits (Table 6). CT scans obtained at the same time as the PET study did not reveal any abnormal findings.

DISCUSSION

Anaerobic glycolysis in the brain is a well-known phenomenon in cases of ischemic brain damage (*24*) and in malignant brain tumors (*25*). It is also well known that the lactate level in cerebrospinal fluid (CSF) increases after head injury, and the level of CSF lactate may indicate the severity of cerebral injury and therefore have some prognostic value (*26,27*). Recently, some studies demonstrated anaerobic glycolysis in severe traumatic brain injury by showing that the intracranial temperature is higher than the bladder temperature (*4,28*). These reports, however, suggest that anaerobic glycolysis after head injury could be determined indirectly.

In their PET studies, Baron et al. (*24*) found that a depressed metabolic ratio was associated with increased OEF pointing to protracted tissue hypoxia as the trigger for anaerobic glycolysis. In the present study, the results of arterial gas analysis in Patient 1 suggest that tissue hypoxia might not be a cause of anaerobic glycolysis as previously suggested (*3,29*).

In experimental studies of cerebral concussion, Duckrow et al. (*30*) and Yang et al. (*31*) noted that an elevated lactate level in the cortex was immediately shown after cortical concussion. They speculated that elevation of the lactate level is not a consequence of ischemia and hypoxia but may depend on derangement of brain energy metabolism in the absence of substrate limitation. Their findings support the observation that anaerobic glycolysis, as seen in our Patient 1, might not depend on the hypoxic state but on the magnitude of cerebral cell damage. Recently, elevation of local rCMRglc as well as elevated lactate levels after experimental cerebral concussion in

TABLE 5
Regional Data of PET Parameters 3 Months after Injury in Patient 2

	rCBF	rOEF	$rCMRO_2$	rCMRglc	Metabolic ratio ($rCMRO_2$/rCMRglc)
Normal value of gray matter	43 ± 7 ml/100 g/min	0.42 ± 0.08	3.3 ± 0.5 ml/100 g/min	7.0 ± 0.8 mg/100 g/min	
Rt. frontal	46	0.40	2.9	7.1	0.41
Lt. frontal	44	0.40	2.9	6.9	0.42
Rt. temporal	48	0.43	3.2	6.9	0.46
Lt. temporal	48	0.45	3.2	6.6	0.49
Rt. occipital	43	0.46	3.0	7.6	0.40
Lt. occipital	40	0.48	2.9	7.5	0.39
Rt. parietal	45	0.48	3.4	7.1	0.48
Lt. parietal	41	0.49	3.1	7.0	0.44
Average	44	0.45	3.1	7.1	0.44
Normal value of white matter	25 ± 4 ml/100 g/min	0.44 ± 0.06	2.0 ± 0.3 ml/100 g/min	4.9 ± 0.8 mg/100 g/min	
Rt. white matter	25	0.40	1.6	5.0	0.32
Lt. white matter	24	0.40	1.6	4.9	0.33
Average	25	0.40	1.6	5.0	0.33

TABLE 6
Regional Data of PET Parameters 3 Months after Injury in Patient 3

	rCMRglc
Normal value of gray matter	7.0 ± 0.8 mg/100 g/min
Rt. frontal	7.1
Lt. frontal	6.9
Rt. temporal	6.9
Lt. temporal	6.6
Rt. occipital	7.6
Lt. occipital	7.5
Rt. parietal	7.1
Lt. parietal	7.0
Average	7.1
Normal value of white matter	4.9 ± 0.8 mg/100 g/min
Rt. white matter	5.0
Lt. white matter	4.9
Average	5.0

the rat using [^{14}C]deoxyglucose autoradiography have been reported (*32,33*). Kawamata et al. (*33*) speculated that excitatory amino acid-activated ion channels were involved in the post-traumatic increase in glucose utilization, which reflects the energy demand of cells required to drive pumping mechanisms against an ionic perturbation seen immediately after the concussive injury. These reports suggest that anaerobic glycolysis would be observed not only in Patient 1 but also in Patients 2 and 3 in the early phase after the injury. Such a state, however, was not maintained for a long period in Patients 2 and 3.

It was reported that the poor outcome of SDBI patients is well correlated to low $rCMRO_2$ values during the acute phase (*34,35*). According to the present data, a low $rCMRO_2$ value is thought to be a necessary condition but not a necessary and sufficient indicator of poor outcome in these patients because Patients 2 and 3 in this present report had low $rCMRO_2$ values similar to that in Patient 1. Significant findings from PET studies in Patient 1 were that rCBF was the lowest, while rOEF and rCMRglc were the highest, compared with those values in the other two patients. In the present study, although the number of patients was limited to three, we speculate that a long-lasting state of anaerobic glycolysis is an important factor in the poor outcome of SDBI patients.

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EDITORIAL

Metabolic Consequences of Acute Brain Trauma: Is There a Role for PET?

Brain injury following head trauma is a serious central nervous system disorder that affects several hundred thousand individuals in the United States every year. Appropriate assessments of the degree of damage caused is essential in initiating the required therapies and determining prognosis.

Over the past two decades, we have witnessed many significant developments in the diagnosis and management of patients with head injury. The introduction of a single and reproducible grading system, the Glascow Coma Scale (GCS), was a major step toward categorizing patients with regard to the severity of injury sustained (*1*). The utilization of x-ray computed tomography in the early 1970s and MRI in the 1980s also made immeasurable contribution to the detection and characterization of a variety of lesions caused by head trauma (*2,3*). Despite such important advances, however, much needs to be accomplished to understand the underlying pathophysiologic and metabolic alteration that accompany two major injuries to the brain: ischemic cell damage and diffuse axonal injury (DAI). Ischemic cell damage occurs in over 90% of patients who succumb to head injury (*4*). In many victims of head injury with postmortem ischemic or hypoxic lesions, no predisposing disorders are found prior to death. Diffuse axional injury is probably the basic pathological damage in head injury (*5*). This injury occurs as a result of stretching and tearing of axons in the white matter of the cerebral hemisphere and the brainstem.

In addition, it has been demonstrated that brain injury results in a series of molecular events that lead to accumulation of toxic products which eventually result in ischemia—reperfusion type of injury (*6–8*). This is considered the underlying mechanism for ischemia noted with various insults to the brain, including trauma or subarachnoid hemorrhage and stroke (*9*). Although postmortem studies have revealed clear evidence for focal and global ischemia in patients with head trauma, no convincing clinical evidence for such a complication following head injury has been demonstrated by researchers (*10–15*). Most ischemic changes have been observed in the "frontoparietal" watershed areas. These changes were noted in patients who were severely injured (*16*). Most head trauma investigators believe that ischemia plays a distinct role in the clinical outcome of patient with head trauma.

A powerful methodology which has allowed investigation of hemodynamic and metabolic changes in the brain is the noninvasive measurement of absolute cerebral blood flow (CBF) and some metabolic parameters following the intravenous administration or inhalation of ^{133}Xe (*17*). Utilizing this powerful technique, the relationship among CBF, cerebral metabolic rate for oxygen (O_2) utilization ($CMRO_2$) and the level of consciousness have been elucidated (*14, 15*). With this technique, a measurement of only limited brain tissue sample is made utilizing detectors which are placed over the skull. Metabolic rates for oxygen ($CMRO_2$) can be calculated by measuring arterio-jugular O_2 difference and multiplying by the average CBF estimates from the detectors selected for this purpose (*15*). Obviously, this technique provides information about superficial structures of predetermined sites in the brain. In spite of these shortcomings, much knowledge has been gained by studying patients with acute head injury. It has been noted that $CMRO_2$ is consistently depressed in head-injured comatose patients and whose magnitude is correlated well with GCS (*15*). However, an interesting observation has been made when CBF and $CMRO_2$ were compared in such patients. In about half of the patients, CBF and $CMRO_2$ are coupled, as seen in normal states. In the remainder, an uncoupling of blood flow and metabolism is clearly demonstrated. In these patients, relative hyperemia is detected despite significantly reduced $CMRO_2$. In other words, CBF exceeds the metabolic requirements of the tissue perfused. In patients with hyperemia, there is a high incidence of increased intracranial hypertension. In spite of its major contributions to the understanding of hemodynamic and metabolic consequences of head injury, the ^{133}Xe CBF technique cannot demonstrate evidence for cerebral ischemia in this disorder.

The use of regional functional imaging techniques such as SPECT, PET (*18*), nuclear magnetic resonance (NMR) (*19,20*) spectroscopy and stable xenon x-ray CT (*21,22*) has provided a unique opportunity to visualize and quantify several important physiologic and metabolic parameters that are considered important in head injury.

Received Dec. 12, 1995; revision accepted Dec. 28, 1995.

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