Relationship of early cerebral blood flow and metabolism to outcome in acute head injury

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Cerebral blood flow (CBF) measurements were obtained acutely in 96 comatose patients with closed head injury, using the intravenous $^{133}$Xe technique. Arteriojugular venous oxygen differences and cerebral metabolic rate for oxygen (CMRO$_2$) were determined in a subgroup of 66 patients. The relationship between each of these variables and outcome at 6 months was analyzed, using the Glasgow Outcome Scale.

The CMRO$_2$ was significantly depressed in patients who subsequently died or remained in a vegetative state, whereas higher values were obtained in patients who later regained consciousness. Although CBF was not predictive of outcome in the total sample, omission of patients with acute hyperemia resulted in a significant relationship that paralleled the metabolic findings. Follow-up studies in the survivors revealed a correlation between CBF and degree of functional recovery, the lowest blood flows being obtained among patients with severe disability.

Age, initial Glasgow Coma Scale score, and occurrence of intracranial hypertension were each found to be predictive of outcome, thus confirming previous reports. When these variables were combined with CMRO$_2$ in a logistic regression analysis, the probability of recovery was correctly predicted in 82% of the cases. The CMRO$_2$ was relatively independent of the other prognostic indicators and, next to age, contributed most to the prediction.

**KEY WORDS** - head injury - outcome - cerebral blood flow - cerebral metabolism

It is now well established that cerebral metabolic rate for oxygen (CMRO$_2$) is significantly reduced in comatose states arising from a variety of causes. Several studies have suggested that the magnitude of the metabolic reduction may serve as a prognostic indicator in patients with acute head injury; that is, patients with CMRO$_2$ values below one-third of normal are less likely to survive than those with higher values. Other reports based on small heterogeneous samples, have been inconclusive with respect to the prognostic value of CMRO$_2$. The purpose of the present study was to clarify this issue by examining the relationship between acute CMRO$_2$ measurements and subsequent outcome in a group of 66 comatose patients with closed head injury.

Attempts to correlate cerebral blood flow (CBF) with outcome following head injury have yielded essentially negative results. Both acutely high CBF (cerebral hyperemia) as well as markedly reduced flow have been found in patients with poor outcome. These findings might be explained by an uncoupling of CBF and metabolism during the acute phase of the illness. To elucidate this issue, the present study examined the relationship between CBF and outcome in 96 patients with severe head injury, in 66 of whom CMRO$_2$ measurements were obtained.

In order to facilitate interpretation of results, three previously established predictors of outcome were included in the analysis. They are: age at time of injury, depth of coma assessed by the Glasgow Coma Scale (GCS), and occurrence of intracranial hypertension. A logistic regression analysis was employed to assess the separate and combined contribution of the several prognostic indicators.

**Clinical Material and Methods**

**Description of Sample**

Regional CBF measurements were performed in 128 comatose patients with closed head injury consecutively admitted to the University of Pennsylvania Head Injury Center. The first measurement was initiated as soon as possible after trauma or emergency surgery, and repeated at regular intervals or whenever a significant
change in neurological status occurred. The CMRO₂ was determined acutely in the majority of patients. In most survivors, follow-up CBF studies were performed at 6 to 12 months postinjury. Informed consent was obtained in all cases in accordance with institutional review board procedures.

Ninety-six patients (75 males and 21 females) were selected for the acute CBF analysis. To be included in the study, at least one CBF measurement had to be performed during coma and within 168 hours of injury. Coma was defined as complete unresponsiveness to verbal commands (Glasgow Motor Scale score ≤ 5).¹⁵ Thirty-two cases were excluded from the study for the following reasons: 12 patients, although comatose, were referred to the hospital later than 168 hours postinjury; nine regained consciousness before a measurement could be initiated; brain death occurred in six cases prior to the first study; and five were undergoing barbiturate therapy, which interfered with the interpretation of results.

In the 96 selected patients, age ranged from 15 to 85 years with a mean age of 36 years. The first CBF measurement was performed on the day of injury in 46% of the cases, and within 48 hours in 70%. All but five patients were studied within 96 hours after injury. At the time of the first measurement, the total GCS score averaged 6.2 ± 1.9 (mean ± standard deviation). Intracranial pressure (ICP) was monitored in all but one patient, in 91 by means of a subarachnoid bolt and in four by intraventricular catheter. Thirty-seven patients (34%) underwent brain surgery, 34 of whom had evacuation of mass lesions. Initially, all patients were intubated and mechanically ventilated, oxygen being supplemented as required.

Computed tomography (CT) of the brain was performed in all cases upon hospital admission, and repeated when clinically indicated. Fifty-one patients (53%) had focal findings, consisting of hematomas and/or hemorrhagic contusions, believed to be the principal lesions. The remaining 47% of the patients were classified as having diffuse lesions, based on CT evidence of diffuse cerebral swelling, extensive subarachnoid hemorrhage, or small hemorrhages in the white matter suggestive of diffuse axonal injury.¹⁹

Measurements of CMRO₂ and arteriojugular venous oxygen difference (AVDO₂) were obtained acutely in a subgroup of 66 patients. For technical and logistic reasons, not all patients for whom acute CBF samples were obtained could be studied. Nevertheless, the sub-sample was comparable to the total group in age (mean 34 years, range 15 to 80 years), GCS score (5.9 ± 1.6), percentage undergoing brain surgery (33% of cases), and type of CT lesion (59% focal, 41% diffuse).

Sixty-nine patients who recovered consciousness were selected for follow-up CBF analysis. This group consisted of 49 survivors from the acute sample, plus 20 patients who did not qualify for inclusion in the acute study because of delayed hospital admission, early emergence from coma, or interfering barbiturate therapy. Since most patients had more than one follow-up study, a separate analysis could be performed of "early" and "late" CBF measurements, defined as the first and last examinations after regaining consciousness. In patients with only one follow-up examination, studies performed less than 2 months postinjury were classified as "early," while those conducted after this time were classified as "late." In accordance with these definitions, 59 patients had early studies, averaging 28 days postinjury (range 2 to 126 days), and 62 patients had late studies, averaging 193 days (range 12 to 417 days).

**CBF and CMRO₂ Measurements**

Regional CBF was measured by the intravenous ¹³³Xe technique,²³,²⁵ either at the bedside in the intensive care unit or in the CBF laboratory. Clearance curves were recorded for 15 minutes from 16 extracranial detectors, eight over each hemisphere. An average of 4.5 measurements were made per patient, totaling 522 examinations. Analysis of the clearance curves was performed by a two-compartment deconvolution from which a mean CBF estimate, CBF₁₅, was obtained.²⁶ This parameter is based on a modified height-over-area method, where the clearance curves are integrated to 15 minutes in order to minimize extracerebral contamination. All blood flow values were CO₂-corrected to 34 mm Hg, the mean pCO₂ for the acute studies. In accordance with previous findings on 41 of the patients, a correction factor of 3% CBF change per mm Hg pCO₂ was employed, as follows:

\[
\text{CBF}_{15}(\text{corr}) = \text{CBF}_{15} / (1 + 0.03*(p\text{CO}_2 - 34)).
\]

When possible, CO₂ corrections were minimized by selecting normocapnic studies in patients with multiple determinations.

In the subgroup with CMRO₂ measurements, catheters were inserted into a peripheral artery and internal (usually right) jugular vein. In contrast to the arterial line, which was inserted for routine patient management, jugular catheterization was not attempted if the patient was physiologically unstable or otherwise considered to be at risk. Arterial and venous blood samples were simultaneously drawn during the CBF study, from which differences in oxygen content (AVDO₂) were determined.²⁴ The CMRO₂ was calculated according to the Fick equation seventeen as the product of the AVDO₂ and uncorrected CBF₁₅, averaged over all 16 regions. Although mean regional CBF is not strictly comparable to global AVDO₂, the calculated CMRO₂'s are in good agreement with those obtained by the Kety-Schmidt method.¹⁷

It should be emphasized that the patients were relatively stable physiologically, being aggressively treated for both intracranial and systemic disorders. Studies were not performed during agonal stages of illness, or at times of extreme physiological perturbation. Although intracranial hypertension (ICP > 20 mm Hg) developed in approximately half of the patients, ICP was under reasonable control during the studies (max-
imum 30 mm Hg), and adequate perfusion pressure was maintained. Except for one patient in whom studies could only be carried out during hyperventilation, cerebral AVDO₂ did not exceed 10 vol%, suggesting that there was little ongoing global ischemia. This does not, of course, rule out regional cerebral ischemia that might go undetected by the AVDO₂ method of measurement.

Assessment of Outcome

A Glasgow Outcome Scale score¹⁴ was assigned to each patient at 6 months postinjury. This scale consists of five categories: died within 6 months (Dead); persistent vegetative state (PVS); severe disability (SD); moderate disability (MD); and good recovery (GR). For purposes of statistical analysis, the Dead and PVS categories were combined, since only three PVS patients were in the sample. The outcome ratings were made independently by two observers, one without any knowledge of the CBF or CMRO₂ findings. Disagreements in three cases were resolved by a third observer after careful review of the data.

Results

Acute Analysis

Chi-squared tests were performed on variables previously known to affect outcome. Significant relationships were obtained for each of the three variables examined: age, GCS score, and ICP. As shown in Table 1, age is an important determinant of outcome following severe head injury. Recovery of consciousness (SD/MD/GR) in teenage patients was almost three times higher than for patients above age 40 years.

Table 2 reveals that recovery from head injury is related to depth of coma as assessed by the GCS. Whereas death and PVS occurred in 79% of patients with a GCS score of 3 or 4, they were found in only 26% of those with a GCS score of 7 to 9. As expected, outcome following head injury was significantly related to acute intracranial hypertension. Table 3 indicates that an elevated ICP, defined as pressures exceeding 20 mm Hg on more than one occasion, was associated with a greater incidence of death and PVS.

A two-way analysis of variance was performed to assess the relationship between CMRO₂ and outcome. Figure 1 presents the results of this analysis, which was statistically significant (F = 4.34, p < 0.008). The higher metabolism in cases with improved outcome could not be accounted for by differences in elapsed time between injury and CMRO₂ measurement (F = 0.50, p < 0.68).
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A similar analysis of variance for CBF and outcome, presented in Fig. 2, demonstrated no significant relationship (F = 0.76, p < 0.52). It should be noted that 52 of the patients had acute hyperemia, defined as blood flows within or above the normal limit for waking subjects. Since CBF and metabolism are likely to be uncoupled in such patients, this lack of relationship is not surprising. However, when the hyperemic patients were removed from the sample, leaving 44 cases with reduced flow (Fig. 2), a significant correlation with outcome emerged that paralleled the metabolic findings (F = 3.0, p < 0.042).

Figure 3 presents the relationship between AVDO₂ and outcome. The AVDO₂ values were corrected to a mean pCO₂ of 34 mm Hg by dividing CMRO₂ by the corresponding CO₂-corrected CBF₁₅. Although an overall analysis of variance yielded a significant F-ratio, subsidiary t-tests revealed that the only reliable difference was between SD/MD/GR and Dead/PVS. Whereas most patients who regained consciousness had AVDO₂ levels above 5.0 vol%, those who died or remained in PVS had significantly lower values (t = 3.37, p < 0.002).

In order to optimize prediction of outcome, a multiple regression analysis was performed in which age, GCS score, ICP, and CMRO₂ were entered as independent variables. Due to the noncontinuous nature of outcome, a logistic regression model was employed as follows:\(^6\)₃₇

\[
\ln \frac{P}{1-P} = \beta_0 + \beta_1 x_1 = U,
\]

where P is the probability of recovery (SD/MD/GR), \(x_i\) the predictor variables, and \(\beta_i\) the corresponding weighting coefficients. In this analysis, the predictor variables were chosen to be dichotomous; that is, a value of +1 was assigned if they equaled or exceeded the median, and −1 if they were below the median. The only exception was ICP, where the generally accepted upper limit of normal was employed.

Table 4 shows the cutoff values for each of the variables and the resulting regression equation. All four variables contributed significantly to the prediction of outcome as determined by stepwise logistic regression. The magnitude of the coefficients in the equation indicates that, when combined, age had the greatest effect, CMRO₂ and GCS score slightly less, and ICP the least effect on the prediction.

Based on the equations shown in Table 4, the probability of recovery at 6 months was calculated for each

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TABLE 4  
Prediction of outcome by logistic regression analysis*  

<table>
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| age: | -1 for age ≤ 30 yrs CMRO₂: -1 for CMRO₂ ≤ 1.5  
+1 for age > 30 yrs +1 for CMRO₂ > 1.5  
| GCS: | -1 for GCS ≤ 5  
+1 for GCS > 5  
| ICP: | -1 for ICP ≤ 20  
+1 for ICP > 20  
| multiple regression equation:‡ |  
| U = -1.090 *age + 0.9021 *CMRO₂ + 0.8633 *GCS - 0.6917 *ICP + 0.1410  
| probability of recovery (SD/MD/GR): | \(P = \frac{\exp(U)}{1 + \exp(U)}\)  

* GCS = Glasgow Coma Scale score; CMRO₂ = cerebral metabolic rate for oxygen (in ml/100 gm/min); ICP = intracranial pressure (in mm Hg); SD = severe disability; MD = moderate disability; GR = good recovery.

**Significance of improvement in chi-squared analysis with stepwise regression: p < 0.0001 for CMRO₂, p < 0.003 for GCS, p < 0.008 for age, p < 0.049 for ICP.  

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patient. Figure 4 presents the frequency distribution of these probabilities, plotted separately for the Dead/PVS and recovered (SD/MD/GR) groups. Using a threshold probability of 0.50, outcome was correctly predicted in 82% of the cases, with a sensitivity of 83% and a specificity of 81%.

Follow-Up Analysis

Because of the invasiveness of the procedure, CMRO₂ data were not obtained in conscious patients. Follow-up CBF data, which are presumably coupled with metabolism, were analyzed in relation to outcome. Patients were grouped into three categories according to the degree of recovery (SD, MD, and GR). Figure 5 presents the CBF results for "early" and "late" follow-up studies. An analysis of variance revealed significantly different levels of flow for the three outcome categories in both samples. The late studies, however, showed a more pronounced increase in blood flow with improved outcome (F = 10.45, p < 0.0001).

Discussion

Following the suggestion of Shalit, et al., that CMRO₂ values below 1.4 ml/100 gm/min in pathological coma are incompatible with regaining consciousness, a number of studies have examined the relationship between CMRO₂ and outcome. Some reports, based on small and/or etiologically heterogeneous samples, were unable to establish a clear relationship. In contrast, Tabaddor and coworkers reported a significant association between acute CMRO₂ and survival in 28 head-injured patients, while Hass obtained similar findings in 42 cases.

The present study confirms and extends the latter observations. Specifically, the results showed a significant depression of acute CMRO₂ among patients with unfavorable outcomes (Dead and PVS) relative to the higher values obtained among patients who subsequently regained consciousness (Fig. 1). In the latter group, CMRO₂ increased with the degree of functional recovery.

In agreement with previous findings, no relationship was obtained between outcome and acute CBF measurements in the total sample, which included patients with normal and supernormal flows (hyperemia) as well as reduced flows. Noting the heterogeneity of CBF in the acute phase, Overgaard and Tweed observed that extreme values (both very high and very low) were associated with a poor prognosis. It is not surprising, therefore, that the mean level of such heterogeneous flows bears little relationship to outcome.

When hyperemic patients were removed from the sample, leaving only those with reduced flow (Fig. 2), a significant relationship was found between CBF and outcome that paralleled the metabolic findings. This result might be anticipated from a previous study from our group, which showed normal coupling between CBF and CMRO₂ in patients with reduced flow, and uncoupling in patients with acute hyperemia. Further studies have indicated that blood flow is related to outcome by virtue of its coupling with metabolism rather than because of some intrinsic relationship. A similar interpretation can be made for the correlation between CBF and functional recovery in the follow-up studies (Fig. 5), it being reasonable to assume that metabolism is a major determinant of blood flow in conscious patients.

The AVDO₂ findings in Fig. 3 can be interpreted in terms of the balance between blood flow and metabolism, expressed by the equation: AVDO₂ = CMRO₂/CBF. Patients with the poorest outcome (Dead/PVS) had significantly lower AVDO₂, averaging 4.1 vol%. This value, which is well below the projected normal
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range of 5.0 to 9.8 vol% for a PaCO$_2$ of 34 mm Hg, suggests that blood flow exceeded the metabolic need in a number of cases; that is, there was a relative hyperemia. Indeed, 23 of 31 patients who died or remained in PVS had AVDO$_2$ values in the hyperemic range (< 5 vol%), in contrast to only 13 of 35 patients who recovered (SD/MD/GR). The apparent adverse effect of hyperemia could relate to its association with brain swelling and intracranial hypertension.

It should be noted that the AVDO$_2$ results are based on CO$_2$-corrected values, obtained by dividing CMRO$_2$ (which is uncorrected) by the CO$_2$-corrected CBF. The AVDO$_2$ correction assumes that metabolism remains constant as pCO$_2$ varies, and that an accurate CBF correction was employed. Constancy of CMRO$_2$ is a reasonable assumption, except in cases with severe ischemia where alteration of CBF may induce metabolic changes. As noted above, all patients were physiologically stable at the time of the studies, so that global cerebral ischemia seems unlikely. The CBF correction is an approximation based on the mean CO$_2$ responsiveness of 41 patients in the series, and thus may differ from the actual reactivity of a given patient. In spite of these limitations, a correction for CO$_2$ was deemed necessary in order to control unwanted variations in CBF and AVDO$_2$ that would otherwise obscure their relationship to outcome.

Tables 1, 2, and 3 confirm previous reports on the relationship of outcome to age, GCS score, and ICP in patients with severe head injury. When combined with measurements of CMRO$_2$ in a logistic regression analysis (Table 4), each variable was found to contribute significantly to the prediction of outcome. Of particular interest is the contribution of CMRO$_2$, which yielded the greatest improvement in goodness of fit, and had the second highest coefficient in the regression equation. The four predictors were relatively independent, as revealed by the low intercorrelation between coefficients, the highest being $0.35$ between age and GCS score, and $-0.27$ between CMRO$_2$ and ICP. Taken together, the four variables correctly predicted recovery in 82% of the cases (Fig. 4).

Prognostic indicators not included in the above analysis are morphological variables derived from the CT scan. A high incidence of unfavorable outcomes has been reported in association with subdural hematoma, compression of basal cisterns, and diffuse axonal injury. The possibility arises that the observed correlation between CMRO$_2$ and outcome is related to the type and location of the brain lesion. Analysis of the CT findings failed to show any relationship between CMRO$_2$ and the presence or absence of either subdural hematoma or diffuse axonal injury, which were found in 26 and 22 of the patients, respectively. On the other hand, 26 patients with compressed or absent basal cisterns had a significantly lower CMRO$_2$ than the 40 patients without such signs ($1.39 \pm 0.46$ vs. $1.60 \pm 0.49$ ml/100 gm/min; $t = 1.70$, $p < 0.047$, one-tailed test). Whether the lower metabolism is due to diffuse cerebral

injury or disruption of ascending brain-stem influences can only be speculated.

Another potentially important factor that this study was unable to address is the occurrence of early hypoxic-ischemic episodes, which have been found to be predictive of a poor outcome. As suggested by studies following cardiac arrest, such insults could have a marked effect on CBF and metabolism. It remains for future research to determine whether early posttraumatic hypoxia or ischemia contributes to a depressed CMRO$_2$ and its correlation with outcome.

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