Cerebral arteriovenous oxygen difference as an estimate of cerebral blood flow in comatose patients

CLAUDIA S. ROBERTSON, M.D., RAJ K. NARAYAN, M.D., ZIYA L. GOKASLAN, M.D., RAJESH PAHWA, M.D., ROBERT G. GROSSMAN, M.D., PEDRO CARAM, JR., M.D., AND ELIZABETH ALLEN, R.N.

Department of Neurosurgery, Baylor College of Medicine, Houston, Texas

The hypothesis that cerebral arteriovenous difference of oxygen content (AVDO₂) can be used to predict cerebral blood flow (CBF) was tested in patients who were comatose due to head injury, subarachnoid hemorrhage, or cerebrovascular disease. In 51 patients CBF was measured daily for 3 to 5 days, and in 49 patients CBF was measured every 8 hours for 5 to 10 days after injury. In the latter group of patients, when a low CBF (< 0.2 ml/gm/min) or an increased level of cerebral lactate production (CMRL) was encountered, therapy was instituted to increase CBF, and measurements of CBF, AVDO₂, and arteriovenous difference of lactate content (AVDL) were repeated. When data from all patients were analyzed, including those with cerebral ischemia and those without, AVDO₂ had only a modest correlation with CBF (r = -0.24 in 578 measurements, p < 0.01). When patients with ischemia, indicated by an increased CMRL, were excluded from the analysis, CBF and AVDO₂ had a much improved correlation (r = -0.74 in 313 measurements, p < 0.01). Most patients with a very low CBF would have been misclassified as having a normal or increased CBF based on the AVDO₂ alone. However, when measurements of AVDO₂ were supplemented with AVDL, four distinct CBF patterns could be distinguished. Patients with an ischemia/infarction pattern typically had a lactate-oxygen index (LOI = -AVDL/AVDO₂) of 0.08 or greater and a variable AVDO₂. The three nonischemic CBF patterns had an LOI of less than 0.08, and could be classified according to the AVDO₂. Patients with a normal CBF (mean 0.42 ± 0.12 ml/gm/min) had an AVDO₂ between 1.3 and 3.0 μmol/ml. A CBF pattern of hyperemia (mean 0.53 ± 0.18 ml/gm/min) was characterized by an AVDO₂ of less than 1.3 μmol/ml. A compensated hypoperfusion CBF pattern (mean 0.23 ± 0.07 ml/gm/min) was identified by an AVDO₂ of more than 3.0 μmol/ml. These studies suggest that reliable estimates of CBF may be made from AVDO₂ and AVDL measurements, which can be easily obtained in the intensive care unit.

KEY WORDS: cerebral metabolism, head injury, cerebral blood flow, arteriovenous oxygen difference, lactate-oxygen index, arteriovenous lactate difference.

In normal individuals, cerebral blood flow (CBF) is closely coupled to and regulated by the cerebral metabolic rate of oxygen (CMRO₂), which is calculated, by the Fick equation, from the product of the arterial-jugular venous oxygen difference (AVDO₂) and the CBF (CMRO₂ = AVDO₂ × CBF). Local CBF is increased or decreased depending on the tissue metabolic requirements. In certain altered physiological states, such as during seizures, changes in brain temperature, and anesthesia, CBF remains coupled to the CMRO₂. If the CMRO₂ is decreased, by anesthesia for example, then CBF will also decrease since requirements for metabolic substrates are less. If the CMRO₂ is increased, for example by fever, then CBF will also increase. Because the ratio between CMRO₂ and CBF does not change if these parameters are normally coupled, the cerebral AVDO₂ remains constant.

In patients in coma due to trauma or metabolic encephalopathy, CMRO₂ is typically reduced from a normal value of 1.5 μmol/gm/min to between 0.6 and 1.2 μmol/gm/min. If CBF remains coupled to CMRO₂, then CBF will also be reduced. Normal coupling of CBF is retained in only 45% of comatose head-injured patients, however; in most of these patients, the CBF regulatory mechanisms are abnormal and, rather than being coupled to CMRO₂, CBF is increased or decreased independently of the reduced CMRO₂. In this situation, the ratio between CMRO₂ and CBF will vary. As CBF changes occur, measurements of the reciprocal changes in AVDO₂ might serve as an indicator of CBF adequacy. A normal AVDO₂ would suggest that CBF is normally coupled to CMRO₂, a decreased AVDO₂ would indicate that CBF is excessive for cerebral metabolic requirements, and an elevated
Cerebral arteriovenous oxygen difference in estimating CBF

![Diagram](image)

**Fig. 1.** Relationship between arteriovenous oxygen difference (AVDO\(_2\)) and cerebral blood flow (CBF). If a coupled change in cerebral metabolic rate of oxygen (CMRO\(_2\)) and CBF occurs, then AVDO\(_2\) remains unchanged and the relationship between CBF and AVDO\(_2\) shifts to a new CMRO\(_2\) curve (horizontal arrows). If CMRO\(_2\) remains constant, then changes in AVDO\(_2\) reflect uncoupled changes in CBF (curved arrows).

AVDO\(_2\) would indicate a decreased CBF. Figure 1 illustrates the nonlinear relationship between CBF and AVDO\(_2\) that would be expected in normal and pathophysiological conditions; a series of curves is displayed, each described by the formula: AVDO\(_2\) = CMRO\(_2\)/CBF. Each individual curve defines the relationship between AVDO\(_2\) and CBF that would occur if CMRO\(_2\) were held constant at a particular value and CBF were varied. The brain extracts oxygen more completely than most tissues, and the normal cerebral AVDO\(_2\), shown by the horizontal dashed lines in Fig. 1, is 1.8 to 3.9 \(\mu\)mol/ml.\(^6\) If a coupled change in CMRO\(_2\) and CBF occurs, then AVDO\(_2\) remains unchanged, and the relationship between CBF and AVDO\(_2\) simply shifts to a new CMRO\(_2\) curve, as illustrated by the horizontal arrows. Assuming that CMRO\(_2\) remains constant, changes in AVDO\(_2\) (curved arrows) reflect uncoupled variations in CBF. A low AVDO\(_2\) suggests that CBF is elevated relative to cerebral metabolic requirements, while an increased AVDO\(_2\) suggests that CBF is low. This hypothesis is of particular interest, because technology has become available to monitor cerebral AVDO\(_2\) continuously.\(^*\) Such continuous monitoring of CBF adequacy may allow early identification and treatment of secondary ischemic injury.

Two conditions are obviously required for this hypothesis to be valid: CMRO\(_2\) must be relatively constant and in the expected range; alternatively, if CMRO\(_2\) does change, there must be a marker that CMRO\(_2\) has moved out of the expected range. Previous studies have shown that when a head injury is accompanied by cerebral infarction, the first condition may not be true.\(^{12}\) In such cases, CMRO\(_2\) is typically less than 0.6 \(\mu\)mol/gm/min in the presence of ischemic injury. However, these studies also showed that the characteristic elevation of cerebral lactate production may provide a satisfactory marker of the presence of significant cerebral ischemia, and therefore that CMRO\(_2\) may not be in the expected range.

The purpose of the present study was to assess the value of AVDO\(_2\) in predicting CBF and, in particular, in identifying patients with a low CBF.

**Clinical Material and Methods**

**Patient Population and Management**

From April 1, 1983, to March 31, 1986, 51 patients who were admitted to Ben Taub General Hospital in coma (Glasgow Coma Scale score \(\leq 8\)) secondary to a head injury had measurements of CBF, CMRO\(_2\), and cerebral metabolic rate of lactate (CMRL) performed at least once a day for 3 to 5 days after injury. In the subsequent 22-month period, an additional 49 patients admitted in coma due to head injury, subarachnoid hemorrhage, or cerebrovascular disease had these parameters measured every 8 hours for the first 5 to 10 days after injury. The demographic characteristics of both groups of patients are shown in Table 1.

All head-injured patients were treated by a standard protocol that emphasized early surgical evacuation of intracranial hematomas, controlled ventilation, and monitoring of intracranial pressure. Patients with subarachnoid hemorrhage were also treated by a standard protocol that included early clipping of aneurysms, with postoperative hypervolemic therapy guided by monitoring pulmonary wedge pressure. Routine medications included phenytoin, morphine for sedation, and antibiotics. Intracranial pressures greater than 20 mm Hg were treated with hyperventilation (pCO\(_2\) 25 to 30 mm Hg), cerebrospinal fluid drainage, sedation and paralysis, mannitol, and (if necessary) barbiturates. Because of the marked effect of barbiturates on cerebral metabolism, CBF measurements obtained while patients were in barbiturate coma are not included in this analysis.

In the first group of patients, the presence of cerebral ischemia was identified retrospectively by the development of an infarction on computerized tomography as described in a previous study.\(^2\) It became evident that focal cerebral ischemia could be identified in the presence of a normal global CBF by an elevated cerebral lactate production, so in the second group of patients cerebral ischemia was defined as a CBF of 0.2 ml/gm/min or below or a CMRL of \(-0.06\) \(\mu\)mol/gm/min or less. When changes characteristic of cerebral ischemia were found, treatments intended to increase CBF were undertaken. Treatments varied from patient to patient, but included allowing pCO\(_2\) to increase to 35 mm Hg, institution of hypervolemic hemodilution, and/or induction of hypertension by dopamine administration.

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\(^*\) Monitoring system manufactured by Oximetrix, Inc., Mountain View, California.
The results of treatment were followed with repeated measurements of CBF, CMRO$_2$, and CMRL. Treatment was considered successful if an increase in CMRO$_2$ accompanied the improvement of CBF.

Cerebral Blood Flow

Cerebral blood flow was measured by the Kety-Schmidt technique, using N$_2$O as the indicator. A total of 578 individual CBF measurements were obtained, 174 in the first group of 51 patients and 404 in the second group of 49 patients. A No. 18 Teflon catheter was inserted percutaneously into the internal jugular vein and positioned so that the tip was in the jugular bulb. The catheter was placed on the side of the most severe injury, or on the right side if the injury was diffuse. The correct position of the catheter tip was confirmed by an x-ray study. A No. 20 catheter was placed in the radial artery. Ten percent N$_2$O was introduced into the patient's inspired gases in a stepwise fashion, and 10 timed samples of arterial and jugular venous blood were anaerobically collected during the first 15 minutes of N$_2$O saturation. The N$_2$O concentration was measured in the blood samples on an infrared analyzer† using an extraction system modified from that described by Swedlow and Lewis. The CBF was calculated from curves fit to the measured N$_2$O concentrations and integrated to 15 minutes (CBF-15) and to infinity. The coefficient of variation of repeated CBF measurements was 3%. The CBF values are reported uncorrected for pCO$_2$. Mean CBF measured by this method in a normal adult population is 0.5 ml/gm/min.

<table>
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<th>Group 2</th>
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<td>15</td>
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<td>34</td>
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<tr>
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<tr>
<td>severe disability/vegetative</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td>dead</td>
<td>13</td>
<td>14</td>
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</table>

*Group 1 patients were admitted between April 1, 1983, and March 31, 1986; Group 2 patients were admitted between April 1, 1986, and January 31, 1988.

Cerebral Metabolism

Arterial and jugular venous blood samples were obtained simultaneously with measurement of CBF for determination of blood gases, oxygen saturation, hemoglobin, and lactate concentration. The blood gases were measured on a Corning 165/2 or 170 blood gas analyzer and the hemoglobin and oxygen saturation on an IL-282 co-oximeter. Whole-blood lactate concentrations were measured by an enzymatic method or with a lactate analyzer.§

The CMRO$_2$ and CMRL values were calculated by multiplying the CBF-15 by the AVDO$_2$ and the arterial-jugular venous difference of lactate (AVDL), respectively. As a measure of the ratio of the amount of glucose metabolized anaerobically to the amount metabolized aerobically, the lactate-oxygen index (LOI) was calculated by the formula, LOI = -AVDL/AVDO$_2$. Although it does not accurately reflect the stoichiometry of glucose metabolism, the LOI is a simple calculation that does not require measurement of CBF or arterial-venous difference of glucose. The LOI value is normally less than 0.03. If CBF is decreased but cerebral oxygen consumption is maintained by increased extraction of oxygen, both AVDO$_2$ and AVDL will be increased and the LOI ratio will be unchanged. However, if increased oxygen extraction cannot compensate for the reduced CBF, then cerebral oxygen consumption will decrease, cerebral lactate production will increase, and the ratio LOI will be increased. In a previously reported series of patients, a LOI of 0.08 or more accurately predicted increased cerebral lactate production.

By the conventions used in this study, CMRO$_2$ is a positive number, since there is always a net consumption of oxygen by the brain. In a normal adult, mean CMRO$_2$ is 1.5 μmol/gm/min. The CMRL can be a positive or negative number, depending on whether there is a net uptake or excretion of lactate by the brain. Normally, there is a small but measurable cerebral lactate production (mean CMRL = -0.02 μmol/gm/min). Elevated production of lactate by the brain is indicated by a more negative CMRL and by an increased LOI.

Statistical Analysis

All summary data are expressed as the mean ± standard deviation. For the 578 measurements of CBF, the relationship between AVDO$_2$ and CBF was analyzed by nonlinear regression analysis. For the patients who were identified as having developed cerebral ischemia, the CBF, CMRO$_2$, and CMRL measured before and after treatment of the ischemia were compared by a paired t-test. A p value of < 0.05 was considered significant.

† Infrared N$_2$O analyzer manufactured by Vital Signs, Inc., East Rutherford, New Jersey.

‡ Blood gas analyzers manufactured by Ciba Corning Diagnostics Corp., Medfield, Massachusetts; co-oximeter manufactured by Instrumentation Laboratories, Lexington, Massachusetts.

§ YSI-23L lactate analyzer manufactured by Yellow Springs Instruments, Yellow Springs, Ohio.
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Results

When all 578 of the CBF measurements obtained in the 100 patients were examined, the expected nonlinear relationship between CBF and AVDO₂ was found to be present (Fig. 2), but with a correlation coefficient of only −0.24 (p < 0.01). Most (72%) of the CMRO₂ values fell between 0.6 and 1.2 μmol/gm/min, which was the expected range for patients with severe head injury. However, 112 (25%) of the CMRO₂ values were less than 0.6 μmol/gm/min. Only 12 (3%) of the values were over 1.2 μmol/gm/min. The patients with a very low CBF (≤ 0.2 ml/gm/min) could not be identified by an elevated AVDO₂ since their values ranged from 0.45 to 5.44 μmol/ml. Most patients with a CBF of 0.2 ml/gm/min or less would have been misclassified as having a normal or increased CBF if only the AVDO₂ had been known.

When CBF measurements that were accompanied by an LOI of 0.08 or greater, indicating elevated cerebral lactate production, were excluded from the analysis, the correlation between CBF and AVDO₂ was significantly improved (r = −0.74 in 313 measurements, p < 0.01). As shown in Fig. 3, most of the patients with very low CMRO₂ values were eliminated by identifying elevated cerebral lactate production. In addition, the remaining patients without cerebral ischemia could be divided into three CBF categories by the level of their AVDO₂. All of the patients with a CBF of 0.2 ml/gm/min or less had an AVDO₂ over 3.0 μmol/ml. All of the patients with a very elevated CBF (> 0.8 ml/gm/min) had an AVDO₂ of less than 1.3 μmol/ml. Most patients with a CBF of 0.2 ml/gm/min or less would have been misclassified as having a normal or increased CBF if only the AVDO₂ had been known.

From these data, a classification of CBF abnormalities was developed based on measurements of AVDO₂ and AVDL. The mean values for CBF and CMRO₂ in each CBF category are listed in Table 2. Patients with the ischemia/infarction CBF pattern, identifiable by an LOI of 0.08 or more and a variable AVDO₂, had a mean CBF of 0.388 ± 0.200 ml/gm/min and a mean CMRO₂ of 0.49 ± 0.30 μmol/gm/min. Patients without ischemia, identifiable by an LOI of less than 0.08, had a mean CMRO₂ of 0.82 ± 0.21 μmol/gm/min regardless of the level of the CBF. Patients with an AVDO₂ of less than 1.3 μmol/ml had an elevated or hyperemic CBF (mean 0.529 ± 0.181 ml/gm/min). Patients with an AVDO₂ between 1.3 and 3.0 μmol/ml had a normal CBF (mean 0.416 ± 0.124 ml/gm/min). Patients with an AVDO₂ greater than 3.0 μmol/ml had a normal or increased CBF (mean 0.515 ± 0.130 ml/gm/min).

TABLE 2
Classification of CBF abnormalities from AVDO₂ and AVDL *

<table>
<thead>
<tr>
<th>Classification</th>
<th>AVDO₂ (μmol/ml)</th>
<th>LOI</th>
<th>CBF (ml/gm/min)</th>
<th>CMRO₂ (μmol/gm/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>nonischemic patterns</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hyperemia</td>
<td>&lt; 1.3</td>
<td></td>
<td>0.529 ± 0.181</td>
<td>0.87 ± 0.08</td>
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<td>normal CBF</td>
<td>1.3-3.0</td>
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<td>0.416 ± 0.124</td>
<td>0.82 ± 0.22</td>
</tr>
<tr>
<td>compensated hypoperfusion</td>
<td>&gt; 3.0</td>
<td></td>
<td>0.234 ± 0.069</td>
<td>0.84 ± 0.18</td>
</tr>
<tr>
<td>ischemia/infarction</td>
<td>variable</td>
<td>≥ 0.08</td>
<td>0.338 ± 0.200</td>
<td>0.49 ± 0.30</td>
</tr>
</tbody>
</table>

* CBF = cerebral blood flow; AVDO₂ = arteriovenous oxygen difference; AVDL = arterial-jugular venous difference of lactate; LOI = lactate-oxygen index; CMRO₂ = cerebral metabolic rate of oxygen.

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FIG. 2. Correlation between arteriovenous oxygen difference (AVDO₂) and cerebral blood flow (CBF) in 100 comatose patients with and without cerebral ischemia (r = −0.24 in 578 measurements, p < 0.01).

FIG. 3. Correlation between arteriovenous oxygen difference (AVDO₂) and cerebral blood flow (CBF) in 55 comatose patients without cerebral ischemia (r = −0.74 in 313 measurements, p < 0.01).
FIG. 4. Findings in a patient with a transient episode of hyperemia.  
Left: Graphs showing changes in cerebral blood flow (CBF) and arteriovenous oxygen difference (AVDO₂) over time after injury. On Day 2, CBF increased with no change in the cerebral metabolic oxygen rate (CMRO₂).  
Right: The relationship between AVDO₂ and CBF is shown for each CBF measurement. All of the points fall close to the 0.9-μmol/gm/min CMRO₂ curve. The increase in CBF on Day 2 is easily identifiable by the decrease in AVDO₂.

an AVDO₂ of more than 3.0 μmol/ml had a low CBF (mean 0.234 ± 0.069 ml/gm/min). Because this last category of patients did not have elevated cerebral lactate production or a CMRO₂ of less than 0.6 μmol/gm/min, this CBF pattern was called "compensated hypoperfusion" rather than ischemia.

Because of the shape of the CMRO₂ curves, AVDO₂ was more sensitive for identifying patients with a low CBF. Small changes in CBF were associated with large changes in AVDO₂ when CBF was low. There was considerable overlap in AVDO₂ values between patients with a normal CBF and those with hyperemia. Nevertheless, increases in CBF in individual patients could be distinguished by changes in AVDO₂. An example of findings in a patient with a temporal lobe contusion who developed a transient period of hyperemia is shown in Fig. 4. During the time that the CBF was elevated, the CMRO₂ was unchanged, and the CBF abnormality was evident from a decrease in AVDO₂.

Eleven (22%) of the 49 patients who were evaluated for ischemia prospectively were found to have the characteristic changes of compensated hypoperfusion: decreased CBF and AVDO₂ greater than 3.0 μmol/ml, but a normal LOI. Their CBF averaged 0.221 ± 0.038 ml/gm/min. One of the patients who had intracranial hypertension being managed with mechanical hyperventilation developed an ischemia/infarction CBF pattern after having an initially normal CBF. In one of the patients, the ischemia was due to severe intracranial hypertension that developed 24 hours after evacuation of a traumatic intracerebral hematoma. A second patient developed ischemia due to vasospasm 72 hours after a subarachnoid hemorrhage. The other two patients developed cerebral ischemia 2 to 3 days after closed head injury. Regardless of the etiology, all four patients changed from a pattern of normal CBF, with a normal AVDO₂ and a normal cerebral lactate production, to a pattern of infarction (Fig. 6) between the routine CBF measurements (approximately 8 hours). The CBF dropped from 0.342 ± 0.035 to 0.214 ± 0.042 ml/gm/min, CMRO₂ decreased from 0.76 ± 0.09 to 0.18 ± 0.13 μmol/gm/min, and cerebral lactate production increased from −0.020 ± 0.017 to −0.042 ± 0.007 μmol/gm/min. The AVDO₂ decreased from 2.23 ± 0.36 to 0.81 ± 0.54 μmol/ml, which, if interpreted alone, might suggest that CBF had increased. However, the LOI dramatically increased, from 0.03 ± 0.02 to 0.36 ± 0.29, indicating the presence of ischemia/infarction, and that AVDO₂ would not accurately reflect CBF. In each case, a lateral skull x-ray film documented that the venous catheter remained in the jugular bulb; however, it cannot be ruled out that, with the drop in CBF, increased extracerebral contamination of the jugular venous blood might have accounted for the increase in venous oxygen saturation.
Cerebral arteriovenous oxygen difference in estimating CBF

Ten (20%) of the 49 patients evaluated for ischemia prospectively had an ischemic pattern on the initial CBF measurement or developed cerebral ischemia during their subsequent hospital course. In two patients in whom the cerebral ischemia was due to intractable intracranial hypertension, it was not possible to follow treatment of the ischemia with CBF measurements, because they died despite aggressive treatment. In the remaining eight patients, nine separate episodes of treatment of cerebral ischemia were documented with CBF measurements before and after treatment. The treatments that were examined included increasing pCO₂ to 35 mm Hg (three patients), hypervolemic hemodilution (five patients), and dopamine-induced hypertension (one patient). In all nine cases, CBF increased with treatment from 0.163 ± 0.038 to 0.303 ± 0.107 ml/gm/min. With five of the episodes of ischemia, an increase in CMRO₂ accompanied the increase in CBF, from a mean value of 0.26 ± 0.17 to 0.68 ± 0.14 μmol/gm/min (Fig. 7 upper). In four patients,

Fig. 5. Summary of treatment of compensated hypoperfusion in 11 patients. Left: Graphs showing the mean values for cerebral blood flow (CBF) and cerebral metabolic oxygen rate (CMRO₂) before and after treatment. The CBF increased with treatment, while CMRO₂ remained unchanged. Right: The relationship between CBF and the arteriovenous oxygen difference (AVDO₂) is shown before and after treatment for the individual patients. The changes in CBF did not alter cerebral metabolism and were accompanied by reciprocal changes in AVDO₂.

Fig. 6. Findings during the development of cerebral ischemia in four patients who initially had a normal cerebral blood flow (CBF). Left: Graphs showing the mean values for CBF and cerebral metabolic oxygen rate (CMRO₂). Over a period of 8 hours, CBF and CMRO₂ decreased, while cerebral lactate production increased from −0.020 to −0.042 μmol/gm/min. Right: The relationship between CBF and the arteriovenous oxygen difference (AVDO₂) is shown for the individual patients. As the CBF decreased, the AVDO₂ also decreased.
FIG. 7. Treatment of cerebral ischemia in nine patients. When cerebral blood flow (CBF) increased, cerebral metabolic oxygen rate (CMRO₂) increased in five patients (upper) and remained unchanged in four (lower). * Left: Graphs showing the mean CBF and CMRO₂ values before and after treatment. When an increase in CBF improved CMRO₂, cerebral lactate production decreased (upper pair). When the ischemic changes were irreversible, CMRO₂ and cerebral metabolic lactate rate were unchanged by treatment (lower pair). Right: The relationship between CBF and the arteriovenous oxygen difference (AVDO₂) is shown for the individual patients. The changes in AVDO₂ as CBF increased were variable and not predictive of whether or not CMRO₂ was improved.

CMRO₂ remained unchanged, although CBF was increased by the therapy (Fig. 7 lower). The change in AVDO₂ was quite variable, and it was not possible to determine from the changes in AVDO₂ whether CMRO₂ was improved or not. However, the LOI decreased in the five episodes of cerebral ischemia where treatment resulted in an increase in CMRO₂, and, in contrast, increased in the four patients in whom CMRO₂ remained unchanged. Both of the patients whose CMRO₂ did not change with treatment eventually died of their neurological injury. In the four patients in whom the improvement in CMRO₂ was sustained for the remainder of the CBF monitoring, the LOI decreased to less than 0.08, clearly into the nonischemic range, while in the patient in whom the improvements in cerebral metabolism were transient despite continued treatment, the LOI decreased only from 0.45 to 0.13.

Discussion

From the data presented in this study, the model shown in Fig. 8 was developed. The model is based on the hypothesis, which was confirmed in this study, that in the absence of ischemia, CMRO₂ is relatively constant in the comatose patient, typically ranging from 0.6 to 1.2 μmol/gm/min, and CBF may vary independently of CMRO₂. In these patients without ischemia, AVDO₂ and CBF have the relationship represented by the constant CMRO₂ curves. If CBF is in excess of cerebral metabolic requirements, AVDO₂ will be de-
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![Graph](image)

FIG. 8. Model diagramming the relationship between cerebral blood flow (CBF) and cerebral metabolism in comatose patients. In the absence of cerebral ischemia, the arteriovenous oxygen difference (AVDO₂) and CBF have the relationship illustrated by the solid curve, with cerebral metabolic rate of oxygen (CMRO₂) averaging 0.9 μmol/gm/min. In the presence of cerebral ischemia/infarction (open arrows), AVDO₂ and CBF have an unpredictable relationship.

creased. If CBF is decreased, AVDO₂ will proportionally increase as the brain compensates for the decreased flow by extracting a greater amount of oxygen. As long as increased extraction of oxygen completely compensates for the decreased blood flow, CMRO₂ remains unchanged. However, a point will be reached at which further decreases in CBF cannot be compensated for by increased oxygen extraction and ischemia follows, manifested by a fall in CMRO₂ and an increase in cerebral lactate production. Initially these metabolic changes of ischemia may be reversible. However, as time passes, irreversible ischemic injury or infarction may develop. The time required for the changes to become irreversible depends on the severity of the reduction in CBF. In experimental studies, a CBF of 0.18 ml/gm/min is tolerated for several hours before changes become irreversible, while a CBF of less than 0.10 ml/gm/min produces infarction in minutes. As the tissue dies, CMRO₂ falls, although cerebral lactate production may remain elevated. Increases in CBF after the tissue has become infarcted will not result in a significant increase in CMRO₂, but instead will be expressed as a decrease in AVDO₂.

In this series, it was uncommon to find a cerebral metabolic pattern that has been considered representative of early cerebral ischemia. This pattern, characterized by a low CBF, an elevated AVDO₂, and an increased cerebral lactate production, with an increase in CMRO₂ and a decrease in cerebral lactate production on treatment of the low CBF, occurred on only one occasion in the 100 patients studied. Much more common was a pattern of low CBF, an increased AVDO₂, and a normal CMRL, which we have called "compensated hypoperfusion" or a pattern of low CBF, normal or decreased AVDO₂, and an increased cerebral lactate production, which we have called "ischemia/infarction."

The compensated hypoperfusion pattern may be the most important to recognize clinically. The increased AVDO₂ suggests that the brain is compensating for the decreased blood flow by extracting oxygen more completely, but because anaerobic metabolism is not increased and because CMRO₂ does not change as CBF is increased, the low blood flow does not appear to have altered overall cerebral energy metabolism. Although the patients are not truly ischemic at the moment of the CBF measurement, they have exhausted the brain's compensatory mechanism for maintaining cerebral metabolism in the presence of decreased oxygen availability. In such cases, small decreases in either CBF or arterial oxygen content could produce significant cerebral ischemia.

The ischemia/infarction pattern is also important to identify, because sometimes this ischemia pattern is reversible. Because AVDO₂ is low, this pattern is often assumed to indicate that brain tissue is irreversibly injured and that the CBF is adequate for the markedly reduced metabolic requirements. Although this is often the case, the presence of reversible ischemic changes are best determined by a trial of increasing CBF. The reason for the low AVDO₂ in patients with reversible ischemia is not entirely clear. It may be that the blood flow is not homogeneous and that areas of very low flow and markedly increased oxygen extraction are mixed with areas of normal oxygen extraction. Alternatively, it may be that, with very low CBF, venous blood in the jugular bulb is contaminated with more extracerebral blood than when blood flow is normal. Studies conducted in normal adults have shown that extracerebral contamination is only 2% to 3%; however, no studies have documented that this remains the case when blood flow to the brain is markedly reduced.

Several factors could potentially affect the ability of the LOI to identify patients with ischemic injury. Other causes for cerebral lactic acidosis, such as ventriculitis, could cause an increase in the LOI in the absence of ischemia. Since the samples for AVDO₂ and AVDL are obtained from only one internal jugular vein, the possibility exists of overlooking an infarction in brain tissue draining by the opposite jugular vein. Studies of oxygen and glucose concentrations performed on samples drawn simultaneously from both internal jugular veins have demonstrated small differences in normal adults, while marked differences can occur in patients with unilateral lesions. Since the movement of lactate across the blood-brain barrier is dependent upon the relative concentrations of lactate in the brain tissue and in blood, an increase in cerebral lactate production could be obscured in the presence of a systemic lactic acidosis. As long as arterial lactate concentration is normal, increases in cerebral lactate production should be reflected by a net efflux of lactate. In a previous study,
an increased cerebral lactate production was present in
patients that developed a cerebral infarction, even when
arterial lactate concentration was increased.\textsuperscript{12}

Although the underlying physiology of the injury is
more easily understood if CBF measurements are avail-
able, reliable deductions about CBF can be made from
measurements of AVDO\textsubscript{2} and AVDL, which can be
easily obtained in the intensive care unit. If the LOI is
less than 0.08, cerebral ischemia is probably not present
and CBF can be predicted reliably from the AVDO\textsubscript{2}.
This permits identification of those patients with com-

compenated hypoperfusion who may benefit from increasing
CBF and of those patients with severe hyperemia.
When the LOI is 0.08 or greater, ischemia or infarction
is present, and the exact level of the CBF cannot be
reliably predicted from the AVDO\textsubscript{2}. Actual measure-
ment of CBF in this circumstance would be necessary.
However, if treatment of the ischemia is successful in
increasing CMRO\textsubscript{2}, the LOI will decrease, so that some
clinically useful information can still be obtained with-
out measuring CBF.

For future studies, continuous monitoring of jugular
venous oxygen saturation, with periodic measurements
of AVDO\textsubscript{2} and AVDL, may be a valuable adjunct to
intracranial pressure monitoring in comatose patients.
A drop in jugular venous oxygen saturation or an
increase in the LOI should trigger a search for causes
of decreased oxygen delivery, such as a decrease in
arterial pO\textsubscript{2}, hemoglobin, or CBF. Early identification
and treatment of ischemic episodes may prevent sec-

Another study in man of cerebral blood flow and cerebral glucose, lactate
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Address reprint requests to: Claudia S. Robertson, M.D., Department of Neurosurgery, Baylor College of Medicine,
One Baylor Plaza, Houston, Texas 77030.