Cerebral venous oxygen content as a measure of brain energy metabolism with increased intracranial pressure and hyperventilation

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In order to test the hypothesis that the cerebral arteriovenous oxygen difference (AVDO₂) and venous oxygen content (VO₂) could be used to monitor brain energy metabolism in the setting of increased intracranial pressure (ICP), 12 cats were studied with ³¹P-magnetic resonance spectroscopy. Six cats were subjected to intracranial hypertension by cisternal infusion of saline. Energy failure occurred at an average AVDO₂ of 8.4 ± 3.2 vol% (± standard deviation) (range 4.7 to 14.7 vol%). The VO₂ at the point of metabolic failure averaged 1.45 ± 0.6 vol% and extended over a narrower range (1.0 to 2.9 vol%). In an additional six cats, ICP was raised to the threshold of metabolic failure and hyperventilation was then instituted (pCO₂ 10 to 18 torr). Five of the six cats experienced a drop in VO₂ with hyperventilation. In two of these animals, hyperventilation resulted in a VO₂ of 1.1 vol% or less and in metabolic failure as evidenced by a fall in phosphocreatine. It is concluded that a VO₂ of less than 2 vol% is correlated with brain ischemia and that the safety of hyperventilation in the setting of increased ICP can be monitored by the use of VO₂.

Key Words: head injury • arteriovenous oxygen difference • hyperventilation • cerebral metabolism • magnetic resonance spectroscopy • intracranial pressure
nounced lowering of PaCO$_2$ may lower CBF to levels that are critical to oxygen delivery.$^{2,23,24}$ Other studies, however, have failed to show a reduction in CMRO$_2$ when PaCO$_2$ was reduced to 15 torr.$^{$3,15}$ It remains unclear whether hyperventilation in the setting of an already compromised CBF can further reduce flow and result in brain energy failure. Continuous monitoring of AVDO$_2$ has been proposed as a means of following the effects of hyperventilation, in that a high AVDO$_2$ would suggest the need for raising CBF by increasing pCO$_2$ or administering mannitol.$^{3,5}$

The study reported here was undertaken to: 1) ascertain in a model of intracranial hypertense the critical values for AVDO$_2$ and venous oxygen content (VO$_2$) at which brain energy failure occurs, as determined by $^{31}$P-magnetic resonance (MR) spectroscopy, to guide the management of head-injured patients; and 2) to examine the effects of intense hyperventilation on AVDO$_2$ and brain energy metabolism when CBF is already compromised by elevated ICP.

Materials and Methods

Animal Preparation

Experiments were conducted on adult cats in accordance with guidelines for the use of vertebrate animals as established by the Department of Health and Human Services and the National Institutes of Health. Anesthesia was induced by an intramuscular injection of 75 mg ketamine and maintained with a continuous infusion (200 mg ketamine and 2 mg pancuronium bromide (Pavulon) diluted to a volume of 10 cc) delivered at 2 cc/hr via a femoral venous catheter. The femoral artery catheter was inserted percutaneously into the cisterna magna and connected via a Y-shaped connector to a reservoir bag of isotonic saline which could be raised or lowered by a pulley system to vary the ICP. A surface coil 2 cm in diameter was then mounted on the skull over the parietal convexities.

The cradle was then placed inside a 2.7-tesla, 31-cm-bore horizontal superconducting magnet, used in conjunction with an MR spectrometer.* The surface coil was doubly tuned for $^1$H (116 MHz) and phosphorus (46.9 MHz) according to the design of Schnall, et al.$^{19}$ The $^{31}$P-MR spectra were obtained from the sum of 100 free induction decays (approximately 8 minutes) using a 50-µ/sec (90°) radiofrequency pulse with a 4.0-second delay. One of two experimental protocols was followed.

The first protocol was designed to correlate AVDO$_2$ with brain energy failure. Six animals were prepared as above, and three baseline $^{31}$P-MR spectra were obtained as simultaneous 0.3-cc venous samples were withdrawn from the sagittal sinus catheter for measurement of oxygen content by means of an oxygen analyzer.$^{$†}$ A baseline arterial sample was obtained for arterial blood gas analysis and arterial oxygen determination, and throughout the remainder of the experiment, arterial or venous samples were obtained alternately with each 8-minute spectrum. The saline reservoir was then raised to obtain an ICP of 50 torr, and repeat spectra and AVDO$_2$ measurements were obtained. The ICP was raised in 5- or 10-torr increments until a clearcut drop in phosphocreatine (PCr) was seen; arterial and venous samples to determine AVDO$_2$ were then correlated with ICP and PCr (Fig. 1). Since the width of the PCr peak did not change throughout each experiment, the PCr concentration was assumed to be proportional to the peak height. Based on previous data,$^{12,22}$ it was assumed that a fall in PCr would not occur at a CPP over 50 torr, and studies were repeated. The ICP was then abruptly raised to 50 torr, and studies were repeated. The ICP was then raised in 5- to 10-torr increments until VO$_2$ was less than 4 vol% or AVDO$_2$ exceeded 9 vol%. Based on preliminary data from the animals used in the first protocol, it was considered that these parameters represented a significant compromise of CBF, and that any additional decrease in flow would be likely to result in metabolic decompensation. The ICP was held constant as two sets of AVDO$_2$ data and spectra were obtained. Then, as the ICP was maintained at a constant elevated level, hyperventilation to a pCO$_2$ of 10 to 18 torr was instituted for 20 minutes by increasing the tidal volume and rate of ventilation. Arterial and sagittal sinus blood samples were withdrawn for AVDO$_2$ determinations, and further spectra were obtained. In some animals, the hyperventilation was then discontin-


† Oxygen analyzer manufactured by Lexicon Instruments, Chestnut Hill, Massachusetts.
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Fig. 1. Results of a typical experiment for the first protocol group (Cat 5, Table 1). Intracranial pressure (ICP) is raised incrementally, as arteriovenous oxygen difference (AVDO₂, in vol%), venous oxygen content (VO₂, in vol%), and phosphocreatine (PCr) are observed. Energy failure (fall in PCr) occurred when AVDO₂ was 14 vol% and VO₂ was 2.9 vol%.

ued, and when pCO₂ was normalized, additional data were acquired (Fig. 2). The animals were sacrificed with intravenous potassium chloride.

Relative PCr values were determined for each animal immediately before and during hyperventilation. A 95% confidence interval was calculated for each cat using the seven PCr values obtained prior to instituting hyperventilation, and a significant drop in PCr with hyperventilation was defined as a value falling outside this limit. Summary data are expressed as the mean ± standard deviation.

Results

The results for the first protocol are presented in Table 1. The mean baseline AVDO₂ and VO₂ for the six animals in this group were 4.4 ± 1.5 and 8.4 ± 1.6

<table>
<thead>
<tr>
<th>Cat No.</th>
<th>Baseline</th>
<th>At Reduced PCr (Metabolic Failure)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AO₂ (vol%)</td>
<td>VO₂ (vol%)</td>
</tr>
<tr>
<td>1</td>
<td>13.7</td>
<td>10.4</td>
</tr>
<tr>
<td>2</td>
<td>11.9</td>
<td>6.7</td>
</tr>
<tr>
<td>3</td>
<td>9.2</td>
<td>5.9</td>
</tr>
<tr>
<td>4</td>
<td>13.9</td>
<td>9.1</td>
</tr>
<tr>
<td>5</td>
<td>16.1</td>
<td>8.9</td>
</tr>
<tr>
<td>6</td>
<td>12.1</td>
<td>9.5</td>
</tr>
</tbody>
</table>

mean ± SD 12.8 ± 2.3 8.4 ± 1.6 4.4 ± 1.5 35 ± 2.0 9.8 ± 3.8 1.4 ± 0.6 8.4 ± 3.2 84 ± 11.3 32 ± 13.1 32 ± 4.4

* PCr = phosphocreatine; ICP = intracranial pressure; AO₂ = arterial oxygen content; VO₂ = venous oxygen content; AVDO₂ = arteriovenous oxygen difference; SD = standard deviation.

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TABLE 2
Summary of results of raised ICP and hyperventilation in six cats (second protocol group)*

<table>
<thead>
<tr>
<th>Cat No.</th>
<th>VO2 (vol%)</th>
<th>AVDO2 (vol%)</th>
<th>pCO2 (torr)</th>
<th>ICP (mm)</th>
<th>Mean PCr (ram)</th>
<th>Pre-Hyperventilation</th>
<th>Post-Hyperventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.1</td>
<td>9.7</td>
<td>35</td>
<td>65</td>
<td>62 ± 2.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2.8</td>
<td>8.2</td>
<td>40</td>
<td>80</td>
<td>37 ± 2.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1.1</td>
<td>5.4</td>
<td>41</td>
<td>40</td>
<td>49 ± 3.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2.7</td>
<td>7.3</td>
<td>36</td>
<td>60</td>
<td>62 ± 2.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3.9</td>
<td>7.4</td>
<td>42</td>
<td>70</td>
<td>54 ± 3.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>3.2</td>
<td>6.5</td>
<td>34</td>
<td>60</td>
<td>75 ± 1.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>means</td>
<td>3.3 ± 1.5</td>
<td>7.4 ± 1.3</td>
<td>38 ± 31</td>
<td>62 ± 12</td>
<td>56</td>
<td></td>
<td>1.7 ± 0.97</td>
</tr>
</tbody>
</table>

* ICP = intracranial pressure; VO2 = venous oxygen content; AVDO2 = arteriovenous oxygen difference; PCr = phosphocreatine. Mean values are expressed ± standard deviation.
† Phosphocreatine levels significantly below pre-hyperventilation baseline values (95% confidence).

Vol%, respectively. At the point at which PCr had dropped significantly below baseline, the AVDO2 had increased to a mean of 8.4 ± 3.2 vol% (range 4.7 to 14.7 vol%). The VO2 at the point of metabolic failure averaged 1.45 ± 0.6 vol% and varied within a much narrower range (1.0 to 2.9 vol%). Metabolic failure occurred at a mean ICP of 84 ± 11 torr, which corresponded to a mean CPP of 32 ± 13 torr.

The results for the hyperventilation protocol are presented in Table 2. At normocapnia and mean ICP of 62 ± 12 torr, the AVDO2 averaged 7.4 ± 1.3 vol% and the VO2 averaged 3.3 ± 1.5 vol%. After hyperventilation, pCO2 averaged 13.5 ± 3.1 torr, the AVDO2 increased to a mean of 8.9 ± 2.1 vol%, and the VO2 had fallen to an average of 1.7 ± 0.97 vol%. Five of the six cats experienced a drop in VO2 with hyperventilation (Fig. 3). In two animals, hyperventilation resulted in a significant drop in PCr. In both instances, the drop in PCr occurred simultaneously with a sagittal sinus VO2 of 1.1 vol% or less, with the PCr value returning to normal when hyperventilation was discontinued (Fig. 2). In the four animals in which PCr did not fall with hyperventilation, the simultaneous VO2 was 2 vol% or greater (Figs. 3 and 4, and Table 2).

**Discussion**

**Definition of Terms**

Cerebral AVDO2 represents the quantity of oxygen which the brain is extracting from the circulating blood at a given point in time, and is estimated by subtracting the oxygen content of the jugular venous or sagittal sinus blood (VO2) from the oxygen content of the peripheral arterial blood (AO2): (AO2 - VO2). Oxygen content (expressed in volumes percent) refers to the total amount of oxygen being carried in a volume of blood, and must be distinguished from the more familiar "oxygen tension," which is usually expressed as a partial pressure (torr), or oxygen saturation, which is expressed as a percent. Blood oxygen content may be measured directly using an oxygen-dependent electrochemical reaction, as was done in these experiments, or calculated by the use of the formula AO2 = Hb x 1.34 (SaO2), where SaO2 represents the percent of arterial hemoglobin (Hb) saturation. Thus, AVDO2 in the clinical setting may be calculated by obtaining an arterial blood sample from a radial artery catheter and a simultaneous sample for a venous saturation measurement from a percutaneously inserted jugular vein catheter with its tip advanced to the level of the jugular bulb (SJBO2), and applying the formula AVDO2 = Hb x 1.34 (SaO2 - SJBO2). In humans, the normal range is 5 to 7.5 vol%.

**Correlation of AVDO2 and CBF**

The data presented in this study generally confirm the model that, in the absence of necrosis, AVDO2 and CBF are inversely related. As ICP was gradually increased above 50 torr, AVDO2 increased and VO2 decreased, reflecting increased oxygen extraction as blood flow was reduced. Energy failure, as evidenced by a drop in PCr, occurred at a wide range of perfusion pressures, as previously noted, and also at a wide range of AVDO2 values. In particular, if the AO2 was low, metabolic failure occurred at a "normal" AVDO2. The VO2, however, reliably predicted brain energy failure in that a significant fall in PCr was associated with a VO2 in the 1- to 2-vol% range. This is similar to the findings of Eklof and Siesjö, who observed energy failure in globally ischemic rats when the pVO2 was in the 25- to 30-torr range. It must be emphasized, however, that in the cisternal infusion model employed in our experiments, blood flow is globally reduced; if regions of perfused but infarcted brain or areas of "preferential perfusion" were present, one might expect regional metabolic failure with a higher VO2. In the absence of such areas, however, VO2 does appear to reliably reflect the adequacy of CBF to support brain energy metabolism.

**Value of Continuous AVDO2 Monitoring**

The value of continuous AVDO2 monitoring in the setting of acute head injury lies in its ability to guide therapy. Hyperventilation is frequently employed...
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FlG. 4. Sagittal sinus venous O$_2$ plotted pre- and post-hyperventilation. Solid lines represent animals in which phosphocreatine (PCr) remained constant with hyperventilation, and broken lines represent animals in which a significant drop in PCr was noted following hyperventilation.

FIG. 3. Results of another example of a second protocol experiment. Hyperventilation was begun after intracranial pressure (ICP) was raised to 65 torr. Although arteriovenous oxygen difference (AVDO$_2$, in vol%) increased and venous O$_2$ (in vol%) decreased, there was little change in phosphocreatine (PCr).

to reduce ICP, and it has been proposed that the AVDO$_2$ might serve as a guide to its safe use.$^{3-5}$ According to this scheme, an increased AVDO$_2$ (or decreased VO$_2$) would be interpreted as “relative ischemia” and would indicate the need to increase CBF. On the other hand, an elevated AVDO$_2$ may simply reflect “compensated hypoperfusion,”$^{19}$ in which decreased CBF is compensated for by increased oxygen extraction and may not reflect any significant alteration in brain metabolism at all. An important question, therefore, is whether intense hyperventilation, particularly in the setting of already compromised cerebral perfusion, can result in further vasoreactivity and decrease in flow and thus precipitate brain energy failure, and whether this is reflected by cerebral oxygen extraction.

Despite considerable work on this problem, the answer is unclear. Alexander, et al.,$^1$ showed that, despite no change in glucose or oxygen utilization across the brain, there was an increase in lactate production from the brain at a PaCO$_2$ of 20 torr in healthy volunteers. This was taken as an indication of increased anaerobic glycolysis secondary to ischemia. Subsequent animal studies by McMillian and Siesjö,$^14$ in which rats were hyperventilated to a PaCO$_2$ below 10 torr, demonstrated a small drop in PCr. This finding was confirmed by Gibbons, et al.,$^9$ who also noted an increase in brain lactate when cats were hyperventilated. The best interpretation of available data is that extreme hypocapnia induces small changes in brain energy metabolism, which might result from either of two mechanisms. First, hyperventilation might reduce CBF and give rise to increased oxygen extraction with a concomitant fall in VO$_2$. Second, due to an increase in blood pH there is a shift in the oxyhemoglobin dissociation curve to the left, and for a given AVDO$_2$ this will cause a decrease in VO$_2$ (the “Bohr effect”).$^{1,11,21}$ Cain$^2$ concluded that both mechanisms are important, but that the effect of decreased CBF is more important.

The Role of Hyperventilation in Increased ICP

Our data suggest that when CBF is already compromised by intracranial hypertension, intense hyperventilation can result in a decrease in PCr which is rapidly reversible by reestablishing normocapnia. That this occurred in only two of six animals could be explained by the fact that only in these animals did VO$_2$ fall below 2 vol% with hyperventilation. The other animals were presumably able to compensate for the decrease in CBF induced by hyperventilation by increased oxygen extraction and thus avoid energy failure. How long CO$_2$ reactivity would remain under these circumstances was not addressed by these experiments, in which hyperventilation was only continued for 20 minutes. There is evidence that CO$_2$ reactivity is relatively short-lived. Experiments with rabbits, for example, indicate that hyperventilation is effective in reducing cerebral blood volume for less than 24 hours, and that when it is discontinued a rebound vasodilatation may occur.$^{16}$ It has been suggested that the use of chronic hyperventilation to prevent a rise in ICP might be counterproductive and that hyperventilation should be used only
intermittently to treat active ICP elevation. Further studies would be required to determine whether the lowered PCr and VO₂ seen in some of our animals would have recovered spontaneously, even if the hyperventilation had been continued.

A problem in generalizing the cisternal infusion model to the clinical arena is that it clamps the ICP at a given level despite hyperventilation. In cases of diffuse swelling from head injury, hyperventilation would likely have complex effects, lowering ICP and decreasing CBF by vasoconstriction. Our data suggest, however, that CO₂ reactivity persists in uninjured brain even in the face of already compromised blood flow, and that this can be detected by changes in the AVDO₂. Furthermore, a VO₂ of less than 2 vol% is highly correlated with brain ischemia.

The results of these experiments suggest that a low (< 2 vol%) jugular bulb VO₂ may be a sensitive indicator of inadequate global CBF in the setting of intracranial hypertension. These experiments thus support the use of VO₂ to guide hyperventilation therapy in clinical head injury.

References


Manuscript received February 23, 1990. Accepted in final form May 25, 1990.
This work was supported by NIH Grant NS08803 and the neurosurgical research fund of the Children’s Hospital of Philadelphia.
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