Effect of hyperventilation on cerebral blood flow in traumatic head injury: Clinical relevance and monitoring correlates

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FEATURE ARTICLES

Effect of hyperventilation on cerebral blood flow in traumatic head injury: Clinical relevance and monitoring correlates

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REFERENCES

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Hyperventilation increases the volume of severely hypoperfused tissue within the injured brain, despite improvements in cerebral perfusion pressure and intracranial pressure.

Objective:

To investigate the effect of hyperventilation on cerebral blood flow in traumatic brain injury.

Design:

A prospective interventional study.

Setting:

A specialist neurocritical care unit.

Patients:

Fourteen healthy volunteers and 33 patients within 7 days of closed head injury.

Interventions:

All subjects underwent positron emission tomography imaging of cerebral blood flow. In patients, Pa_{co_2} was reduced from 36 ± 1 to 29 ± 1 torr (4.8 ± 0.1 to 3.9 ± 0.1 kPa) and measurements repeated. Jugular venous saturation (Sjv_{o_2}) and arteriovenous oxygen content differences ($AVDO_2$) were monitored in 25 patients and values related to positron emission tomography variables.

Measurements and Main Results:

The volumes of critically hypoperfused and hyperperfused brain (HypoBV and HyperBV, in milliliters) were calculated based on thresholds of 10 and 55 mL·100g^{-1}·min^{-1}, respectively. Whereas baseline HypoBV was significantly higher in patients ($p < .05$), baseline HyperBV was similar to values in healthy volunteers. Hyperventilation resulted in increases in cerebral perfusion pressure ($p < .0001$) and reductions in intracranial pressure ($p < .001$), whereas Sjv_{o_2} (>50%) and $AVDO_2$ (<9 mL/mL) did not exceed global ischemic thresholds. However, despite these beneficial effects, hyperventilation shifted the cerebral blood flow distribution curve toward the hypoperfused range, with a decrease in global cerebral blood flow (31 ± 1 to 23 ± 1 mL·100g^{-1}·min^{-1}; $p < .0001$) and an increase in HypoBV (22 [1–141] to 51 [2–428] mL; $p < .0001$). Hyperventilation-induced increases in HypoBV were apparently nonlinear, with a threshold value between 34 and 38 torr (4.5–5 kPa).

Conclusions:

Hyperventilation increases the volume of severely hypoperfused tissue within the injured brain, despite improvements in cerebral perfusion pressure and intracranial pressure. Significant hyperperfusion is uncommon, even at a time when conventional clinical management includes a role for modest hyperventilation. These reductions in regional cerebral perfusion are not associated with ischemia, as defined by global monitors of oxygenation, but may represent regions of potentially ischemic brain tissue.

Key Words: head injury; positron emission tomography; cerebral blood flow; ischemia; cerebral oxygenation; hyperventilation

Introduction

Reductions in Pa_{co_2} result in cerebral vasoconstriction and a reduction in cerebral blood volume ([1]). Consequently, hyperventilation has been extensively used in the past for the control of intracranial hypertension in patients with traumatic brain injury (TBI) ([2] [3] [4]). However, these reductions in cerebral blood volume are associated with reductions in cerebral blood flow (CBF) ([1] [5]). Increasing evidence suggests the presence of early cerebral hypoperfusion (and possibly ischemia) in patients with TBI ([6] [7] [8]), and there are concerns that hyperventilation-induced reductions in CBF may precipitate or worsen ischemia ([2] [9] [10] [11] [12]) and affect outcome ([13]). It has been suggested that the risk of such ischemia may be reduced by bedside measurement of CBF and indices of adequacy of CBF ([2] [6] [9] [14] [15]). These include oxygen saturation in jugular venous blood (Sjv_{o_2}) and arteriovenous differences in oxygen content ($AVDO_2$). CBF values of <20 mL·100g^{-1}·min^{-1} ([6] [7] [16] [17]), Sjv_{o_2} values of <50% ([18] [19]), and $AVDO_2$ of >9 mL/mL ([9] [18] [20] [21]) suggest significant ischemia. Whereas in comparison, CBF in excess of the normal range (>55 mL·100g^{-1}·min^{-1}) ([9] [14] [21] [22]), $AVDO_2$ values of <4 mL/mL ([9] [14] [18] [21] [22]), and Sjv_{o_2} of >75% ([18]) suggest hyperemia. In these circumstances, hyperventilation may reduce the extent or severity of hyperemia and help to normalize pathophysiology. Although these endpoints are commonly used as part of clinical protocols and in research studies, their relevance is questioned by studies that have used stable xenon-enhanced radiographic computed tomography (xenon CT) to demonstrate marked heterogeneity in regional CBF ([7] [10]) and cerebrovascular CO_2 reactivity following trauma

([10]).

These data raise the possibility that global measures of CBF adequacy (Sjv_{O_2} , $AVDO_2$) may miss critical regional hypoperfusion and potential ischemia. We have directly addressed this issue by mapping regional CBF in patients with severe head injury using oxygen-15 positron emission tomography (PET) at normocapnia and following hyperventilation. These three dimensional data sets not only provide information regarding mean CBF and its relation to global bedside monitors of cerebrovascular adequacy, but they also allow volumetric estimates of cerebral hypoperfusion. This has not been possible using xenon CT because imaging involves acquisition of data from a limited number of slices, which therefore limits coverage of the brain. We have sought to refine our understanding of how hyperventilation affects the injured brain and to emphasize the difficulty in detecting regional hypoperfusion and potentially ischemic brain tissue by using global monitors of cerebrovascular adequacy.

MATERIALS AND METHODS

Subjects.

PET studies were undertaken on 14 healthy volunteers and 33 patients within 7 days of head injury. Patients had a median (range) postresuscitation Glasgow Coma Scale score (GCS) of 8 (3–13) at presentation, but all subsequently developed elevation in intracranial pressure (ICP) severe enough to require mechanical ventilation for its control (Table 1). In 25 of these subjects, simultaneous measurement of Sjv_{O_2} and $AVDO_2$ were available.

	Healthy Volunteers	Patients
Sex	2 women, 12 men	7 women, 26 men
Age, mean (range), yrs	44 (29–59)	32 (16–78)
Postresuscitation GCS, median (range)		8 (3–13)
Intracranial lesions		
Extradural hematoma		7
Subdural hematoma		8
Hemorrhagic contusion and/or traumatic subarachnoid hemorrhage		28
Diffuse axonal injury		1
Surgical evacuation of mass lesion [a]		12
Second-tier therapies [a]		
External CSF drainage		4
Decompressive craniectomy		10
Hypothermia, <34°C		5
Barbiturate coma		2
Extracranial injuries (%)		20 (61)
Interval between injury and PET imaging		
Within 24 hrs		4
Days 2–4		21
Days 5–7		8
Favorable outcome at 6 mos (%)		18 (55)

GCS, Glasgow Coma Scale; CSF, cerebrospinal fluid; PET, positron emission tomography.
[a] Patient management is detailed before PET imaging.

All volunteers provided informed consent for studies, and assent was obtained from the next of kin for all patient studies. All studies were approved by the Local Research Ethics Committee at Addenbrooke's Hospital, Cambridge, UK, and by the Administration of Radioactive Substances Advisory Committee of the United Kingdom. All studies were performed in accordance with the Declaration of Helsinki as revised in Edinburgh in October 2000.

Clinical Protocols.

All head-injured patients were managed with protocol-driven therapy aimed at maintaining ICP at <20 mm Hg and cerebral perfusion pressure (CPP) of >70 mm Hg

as described by Menon ([23]). Graded interventions used for CPP and ICP control included sedation (propofol up to 8 mg·kg^{-1}·hr^{-1} and fentanyl, 1–2 μg·kg^{-1}·hr^{-1}) and neuromuscular blockade, surgery for space-occupying lesions, drainage of cerebrospinal fluid, vasoactive agents for CPP augmentation, osmotic diuretics, mild hyperventilation (to ~34 torr [4.5 kPa]), mild to moderate hypothermia (33–36°C), decompressive craniectomy, and barbiturate coma. In addition, a fiberoptic right jugular bulb catheter (Baxter, Medford, MA) was inserted and its position confirmed radiologically. Samples of arterial and jugular venous blood were drawn for simultaneous measurement of arterial blood gases and Sjv_{O_2} and calculation of $AVDO_2$. Using protocol-driven therapy ([23]), Sjv_{O_2} was continuously measured and maintained above 50%, with regular calibration and measurement of $AVDO_2$.

In healthy volunteers, we monitored heart rate, mean arterial pressure, pulse oximetry, and arterial blood gases to ensure physiologic stability during PET imaging. In calculating CPP in healthy volunteers, we assumed an ICP of 10 mm Hg.

PET.

PET studies were undertaken on a General Electric Advance scanner (GE Medical Systems, Milwaukee, WI). Following a 10-min transmission scan using two rotating germanium-68/gallium-68 rods, performed to correct subsequent emission scans for photon attenuation, emission data were acquired in three-dimensional mode during the last 10 mins of a 20-min steady-state infusion of 800 MBq of $H_2{}^{15}O$. Images were reconstructed using the PROMIS three-dimensional filtered back projection algorithm ([24]), with corrections applied for attenuation, scatter, randoms, and dead time. The emission data were coregistered to anatomy using magnetic resonance or spiral CT images. Parametric maps of CBF were calculated from steady-state radioactivity concentrations in tissue (PET) and arterial blood (discrete samples) using previously published methods ([25]) and with a volume of distribution value set to 1.0.

The clinical protocols used in our patients are detailed elsewhere ([23]). Briefly, patients were managed with sedation and neuromuscular blockade, received boluses of 20% mannitol for acute intracranial hypertension, and were treated with volume supplementation and vasoactive agents (dopamine, norepinephrine, or both) for hemodynamic augmentation. Hyperthermia was treated vigorously, and mild hypothermia (35–36°C) was commonly employed to assist ICP control. Patients who received surgical intervention (cerebrospinal fluid drainage or decompressive craniectomy) or second-tier medical therapies (barbiturate coma or moderate hypothermia [33–34°C]) before PET imaging are specified in Table 1. Whereas hemodynamic stability was ensured during PET studies by titrating fluids and vasoactive agents, sedative infusions were left unchanged. It is important to emphasize that no other material changes in management occurred on the day of the PET study in any of the patients, thus ensuring stable physiology during the hypocapnic challenge.

Following measurement of baseline Sjv_{O_2} and $AVDO_2$ and acquisition of PET images at a Pa_{CO_2} of approximately 35–40 torr (5 kPa), minute ventilatory volume was increased to achieve a Pa_{CO_2} reduction to about 30 torr (4 kPa). If Pa_{CO_2} levels fell to <25 torr (3.3 kPa) or Sjv_{O_2} fell to <50%, the extent of hyperventilation was modulated. Following a 10-min period of stable arterial blood gas measurement, PET imaging was repeated as described above, and Sjv_{O_2} and $AVDO_2$ were measured.

Image Analysis.

Images were analyzed using custom-designed automated software (PETAN 2000) incorporating elements of several software packages, including Statistical Parametric Mapping (SPM99, Wellcome Department of Cognitive Neurology, London, UK), Matlab 5.2 (MathWorks, Natick, MD), Analyze 2.5 (AnalyzeDirect, Lenexa, KS), and registration by multiresolution optimization of mutual information (mpr, Department of Radiologic Sciences, Guys Hospital, London, UK ([26] [27])). Individual anatomic images were edited manually to extract a template that identified brain tissue voxels and excluded extracranial tissue, cerebrospinal fluid, and extra-axial hematomas. This individual brain template was applied to the corresponding median filtered (3 × 3 in transaxial planes), spatially coregistered PET images. These final images of perfusion within the injured brain were quantified using a voxel-based method. Voxels in whole-brain CBF images were binned from 0 to 100 mL·100g^{-1}·min^{-1} in divisions of 5 mL·100g^{-1}·min^{-1} , and a frequency histogram of CBF distribution was constructed (Fig. 1). An individual brain image typically consisted of 50–60,000 voxels, each of which had a nominal volume of approximately 25 mm^3 .

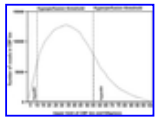

Figure 1. Cerebral blood flow (*CBF*) histogram from a single patient, showing the distribution of the number of voxels in each CBF bin. The hypoperfused brain volume (*HypoBV*) and hyperperfused brain volume (*HyperBV*) were calculated as the volume of voxels with CBF values outside critical CBF thresholds (<10 mL·100g^{-1}·min^{-1} and >55 mL·100g^{-1}·min^{-1} , respectively).

Estimation of Critically Hypoperfused and Hyperperfused Brain Volumes.

We defined a threshold for critical hypoperfusion, and the volume of voxels with blood flow below this threshold was calculated at relative normocapnia and at hypocapnia following hyperventilation. Our chosen threshold was comparable with that defined for short-term ischemia predictive of metabolic failure and infarction ([17] [28]) but lower than that quoted in the field of head injury and subarachnoid hemorrhage using xenon-133 clearance ([6] [7]) and xenon CT imaging ([8] [16]). We selected a lower value to examine those regions with severe reductions in CBF that were most likely to be representative of critical ischemia. We chose a cutoff value of 10 mL·100g^{-1}·min^{-1} for two reasons. This value approximates to both experimental data ([17] [28]) and the PET literature in cerebrovascular disease ([29] [30] [31]) that defines CBF thresholds in terms of subsequent tissue viability. This value was also concordant with a calculated threshold based on the lower 95% confidence interval of our data in healthy volunteers.

Whereas eventual infarction provides a hard outcome event that enables the detection of critical CBF thresholds for ischemia, no parallel exists for robust identification of hyperemia. Evidence within the literature is sparse, but several publications suggest a value in excess of the normal range (≥55 mL·100g^{-1}·min^{-1}) ([9] [14] [21] [22]), and choice of this figure was underpinned by the finding that the upper 95% confidence interval of our data in healthy volunteers was 55 mL·100g^{-1}·min^{-1} . However, a true definition of regional hyperemia would require measurement of regional tissue metabolism and CBF. Regional oxygen metabolism

($CMRO_2$) can be measured using triple-oxygen PET (with mapping of CBF, cerebral blood volume, $CMRO_2$, and oxygen extraction fraction), but it is not widely available within units treating head-injured patients. A technique employing CBF thresholds (such as xenon CT) is not only generally available, but it can demonstrate significant increases in CBF from control values that represent clinically important evidence of hyperemia. Application of these thresholds to CBF histograms allowed calculation of the extent of critical hypoperfusion (HypoBV) and hyperperfusion (HyperBV) in our patients (Fig. 1).

CO_2 Reactivity.

Global CO_2 reactivity was expressed both as an absolute CBF change ($mL \cdot 100g^{-1} \cdot min^{-1} \cdot torr^{-1}$) and as a percentage change from baseline (%/torr).

Statistical Analysis.

Statistical analysis was undertaken using Statview (Version 5, 1998, SAS Institute, Cary, NC). Data are expressed and displayed as mean ± se or as median (range), unless otherwise stated. Global- and voxel-based PET data from patient groups and healthy volunteers were compared using two-tailed unpaired and paired *t*-tests or Mann-Whitney U test and Wilcoxon's rank-sum test as appropriate. The effect of hyperventilation on clinical monitoring and the global monitors of oxygenation was compared using two-tailed paired *t*-tests. Relationships between PET measures of CBF and Pa_{co_2}, Sjv_{o_2}, and $AVDO_2$ were explored using linear regression, polynomial fitting, and nonparametric methods (Spearman's rank correlation test) to take account of nonlinear relationships between variables. A p value of <.05 was considered significant.

RESULTS

Baseline Physiology, Blood Flows, and the Burden of Hypoperfusion.

Baseline Pa_{co_2} for patients was lower than for healthy volunteers (36 ± 1 vs. 42 ± 1 torr [4.8 ± 0.1 vs. 5.6 ± 0.1 kPa]; $p < .0001$, unpaired *t*-test). In addition, CPP was significantly lower in patients than healthy volunteers (77 ± 2 vs. 89 ± 2 mm Hg; $p < .001$, unpaired *t*-test).

Global CBF (calculated as the average of all brain voxels) was similar for patients imaged at normocapnic baseline and healthy volunteers (30.3 ± 1.2 vs. 31.4 ± 1.1 $mL \cdot 100g^{-1} \cdot min^{-1}$). The mean CBF distribution histogram for all patients was similar to healthy volunteers (Fig. 2). However, data from individual patients showed marked heterogeneity (Fig. 3*a*). Many patients had CBF distributions suggestive of critical hypoperfusion.

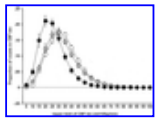

Figure 2. Mean ± se cerebral blood flow (*CBF*) histograms from 14 volunteers (*white*) and 33 patients at normocapnia (*gray*) and hypocapnia (*black*).

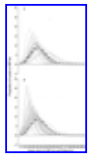

Figure 3. Individual patient CBF histograms. (*a*) Cerebral blood flow (*CBF*) histograms from patients at normocapnia (*gray*) compared with the mean ± 95% confidence interval for healthy volunteers (*black*). (*b*) CBF histograms from patients at hypocapnia (*gray*) compared with the mean ± 95% confidence interval for healthy volunteers (*black*).

Although several patients showed abnormally high Sjv_{o_2} and low $AVDO_2$, hyperperfusion was far less commonly observed on PET images. Only five patients showed CBF distribution curves with a high number of voxels in the hyperperfused range (i.e., exceeding 95% confidence intervals for normal volunteer curves). These five subjects were all imaged between the second and third day following injury. Patients had a significantly greater HypoBV when compared with healthy volunteers (22 [1–141] vs. 8 [2–32] mL; $p < .05$, Mann Whitney U Test). There was substantial variability between subjects. Large HypoBV figures were not restricted to patients within the first 24 hrs of head injury, with HypoBV as high as 141 mL (9% of total brain tissue) observed in a patient imaged on day 7 following injury (Fig. 4). Baseline HyperBV in patients was not significantly different from values in healthy volunteers (23 [0–384] vs. 23 [1–174] mL).

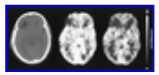

Figure 4. Effect of hyperventilation on the burden of hypoperfusion. Radiographic computed tomography (*left*) and gray scale positron emission tomographic imaging of cerebral blood flow obtained from a 31-yr-old man 7 days after injury at relative normocapnia (*middle*), Pa_{co_2} 35 torr (4.7 kPa), and hypocapnia (*right*), 26 torr (3.5 kPa). Voxels with a cerebral blood flow of <10 $mL \cdot 100g^{-1} \cdot min^{-1}$ are shaded in *black*. Note the right frontal contusion and small parietal subdural hematoma. Baseline ICP was 21 mm Hg and baseline CPP was 74 mm Hg. Baseline Sjv_{o_2} values of 70% and $AVDO_2$ of 3.7 mL/dL are consistent with hyperemia and support the use of hyperventilation for ICP control. Hyperventilation did result in a reduction in ICP to 17 mm Hg and an increase in CPP to 76 mm Hg, with maintenance of

Sjv_{O_2} and $AVDO_2$ within desirable ranges (58% and 5.5 mL/mL respectively). However, despite these Sjv_{O_2} and $AVDO_2$ figures, baseline HypoBV was 141 mL and increased to 428 mL with hyperventilation. These increases were observed in both perilesional and normal regions of brain tissue.

Effect of Hyperventilation on Global Physiology in Patients.

A reduction of Pa_{CO_2} from 36 ± 1 to 29 ± 1 torr (4.8 ± 0.1 kPa to 3.9 ± 0.1 kPa) led to a significant and consistent reduction in global CBF (31 ± 1 to 23 ± 1 mL·100g^{-1}·min^{-1}; $p < .0001$, paired *t*-test). This reduction in blood flow occurred despite a fall in ICP from 19.5 ± 1.4 to 16.5 ± 1.2 mm Hg and an increase in CPP from 77 ± 2 to 83 ± 2 mm Hg ($p < .001$ and $p < .0001$, respectively, paired *t*-test). Sjv_{O_2} was reduced from 72 ± 2% to 60 ± 2% and $AVDO_2$ was increased from 3.7 ± 0.2 to 5.6 ± 0.3 mL/mL ($p < .0001$, paired *t*-test). In no subject did Sjv_{O_2} or $AVDO_2$ reach ischemic thresholds (<50% and >9 mL/mL). The mean (range) relative global CO_2 reactivity for CBF was 1 (0.3–1.8) mL·100g^{-1}·min^{-1}·torr^{-1} (3.3 [1–5.4] %/torr).

Effect of Hyperventilation on HypoBV and HyperBV.

When compared with normocapnic baseline values, the HypoBV was significantly elevated following hyperventilation (from 22 [1–141] to 51 [2–428] mL; $p < .0001$, Wilcoxon's signed-rank test), with individual values as high as 428 mL (or 28% of total brain volume). The HyperBV was significantly reduced following hyperventilation (23 [0–384] to 1 [0–197] mL; $p < .0001$, Wilcoxon's signed-rank test). Hypoperfused voxels were commonly observed adjacent to contusions or intracranial hematomas, but also within regions of the brain with no apparent lesions on CT imaging (Fig. 4). In contrast, the few "ischemic" voxels that were observed in volunteers were usually the consequence of partial volume effects at ventricular or cortical margins and were no more than 3% of the total brain volume. CBF histograms constructed from data obtained at hypocapnia were shifted toward the left when compared with normocapnic data and healthy volunteers, with a greater proportion of brain voxels within the critically hypoperfused range (Fig. 3).

Pa_{CO_2} Thresholds for Critical Cerebral Hypoperfusion.

Global CBF was clearly related to Pa_{CO_2} (Fig. 5), although there was marked heterogeneity in individual responses. Importantly, only in one subject did hyperventilation result in a small reduction in HypoBV, and in no subject was there an increase in global CBF (Fig. 6). HypoBV was dependent on Pa_{CO_2} (Fig. 7*a*), but this relationship was highly variable between subjects (Fig. 7*b*) and was clearly nonlinear, with the data suggesting a possible threshold value between 34 and 38 torr (4.5–5 kPa). However, within the range of Pa_{CO_2} values studied, the magnitude of Pa_{CO_2} reduction (ΔPa_{CO_2}) did not predict the extent of change in CBF or HypoBV (ΔCBF and ΔHypoBV) (Fig. 6).

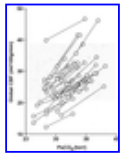

Figure 5. Relationship of positron emission tomographic–derived global cerebral blood flow (*CBF*) to Pa_{CO_2} in patients imaged at baseline and following hyperventilation. The 95% confidence interval for global CBF in healthy volunteers is shown in *hatched gray*.

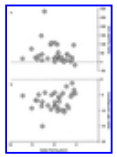

Figure 6. Relationship of measures of hypoperfusion to Pa_{CO_2}. Bivariate plot of changes in Pa_{CO_2} (*delta* Pa_{CO_2}) vs. changes in hypoperfused brain volume (*delta HypoBV*) (*a*) and changes in cerebral blood flow (*delta CBF*) (*b*) after hyperventilation in patients.

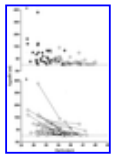

Figure 7. Pa_{CO_2} thresholds for cerebral hypoperfusion. (*a*) Plot of hypoperfused brain volume (*HypoBV*) vs. Pa_{CO_2} in healthy volunteers (*white*), normocapnic baseline (*light gray*), and posthyperventilation (*dark gray*). (*b*) Relationship of HypoBV to Pa_{CO_2} in patients imaged at baseline and after hyperventilation. The 95% confidence interval for HypoBV in healthy volunteers is shown in *hatched gray*.

Global Monitors of Oxygen Delivery.

A clear relationship between global monitors and PET-derived summary measures (CBF, HypoBV, and HyperBV) was demonstrable within individual subjects (Fig. 8, Fig. 9). However, the magnitude of changes in Sjv_{O_2} and $AVDO_2$ (ΔSjv_{O_2} and $\Delta AVDO_2$) did not predict the extent of change in CBF, HypoBV, or HyperBV (ΔCBF, ΔHypoBV, or ΔHyperBV) across the study population. Importantly, although Sjv_{O_2} and $AVDO_2$ reflected changes in global CBF, conventional thresholds based on

these bedside monitors performed poorly at identifying patients in whom critical regional hypoperfusion was large or was significantly increased by hyperventilation. We could demonstrate no level of Sjv_{O_2} or $AVDO_2$ that excluded a significant HypoBV while discriminating patients with large HyperBV values (Fig. 9). Indeed, many subjects showed clinically significant increases in HypoBV with hyperventilation, whereas Sjv_{O_2} and $AVDO_2$ remained at >50% and <9 mL/mL, respectively (figure 4, figure 9, *a* and *b*).

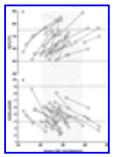

Figure 8. Relationship of positron emission tomographic–derived global cerebral blood flow (*CBF*) to Sjv_{O_2} (*a*) and $AVDO_2$ (*b*) in 25 subjects imaged at baseline and after hyperventilation. The 95% confidence interval for global CBF in healthy volunteers is shown in *hatched gray*. The ischemic and hyperemic thresholds based on Sjv_{O_2} and $AVDO_2$ monitoring are displayed with *black dashed lines*.

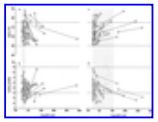

Figure 9. Relationship of critically hypoperfused (*HypoBV*) and hyperperfused (*HyperBV*) brain volume to Sjv_{O_2} and $AVDO_2$ (*a–d*, respectively) in 25 subjects imaged at baseline and after hyperventilation. The 95% confidence intervals for HypoBV and HyperBV in healthy volunteers are shown in *hatched gray*. The ischemic and hyperemic thresholds based on Sjv_{O_2} and $AVDO_2$ monitoring are displayed with *black dashed lines*.

DISCUSSION

We have shown that moderate hypocapnia (<34 torr [4.5 kPa]) can significantly reduce global CBF and result in significant increases in the volume of critically hypoperfused tissue in the injured brain. These increases are observed in the face of apparently beneficial changes in ICP and CPP. The extent of reduction in Pa_{CO_2} seems less important than the actual value achieved, with an apparent threshold value of about 34 torr (4.5 kPa) for significant increases in HypoBV. These reductions in regional cerebral perfusion are not associated with ischemia, as defined by global monitors of oxygenation, but may represent regions of tissue at risk of ischemic injury. Although global monitors of brain oxygenation generally correlate significantly to global (i.e., averaged) CBF, they perform poorly at detecting regional hypoperfusion, even when the integrated volume of such hypoperfused tissue is relatively large.

Methodologic Issues.

Conventional imaging approaches in severe TBI have used CBF thresholds for ischemia based on xenon CT and ^{133}Xe clearance imaging ([6] [7] [8] [16]). Although xenon CT studies are more widely available, brain coverage is limited. For example, a typical implementation of the technique provides three slices of data at the cost of an estimated radiation burden of 1.6 mSv ([32]). Our CBF PET protocol provides whole-brain coverage in 20 mins, with a volumetric data set, and a radiation burden of 1.06 mSv. Data from head injury in the PET literature are sparse. However, data from clinical and experimental stroke provide useful predictive values for tissue survival and death ([29] [30] [31]). Application of these thresholds to head injury requires some methodologic adaptation. Ischemia in stroke usually conforms to topographic patterns, with identification of an ischemic core and penumbra ([33]). Although ischemia may be prominent in perilesional areas in head injury ([7] [10]), significant ischemia may also be observed in structurally normal brain. Consequently, we needed to identify methods that estimated the burden of critical hypoperfusion across the entire brain, making no assumptions regarding its location. Our estimate of HypoBV fulfills these requirements. In addition, the visual comparison of CBF histograms provides us with a clear way of defining the shift in tissue physiology following hyperventilation.

Although analysis of CBF histograms provides a novel way of identifying hypoperfusion, in practice, true ischemia can only be defined in the context of a blood flow that is inappropriately low for tissue metabolism. Mitochondrial dysfunction occurs following human TBI ([34]), and trauma patients receive sedative drugs that lead to reductions in $CMRO_2$. This may lead to coupled reductions in CBF, and present difficulties in using ischemic thresholds based on cerebral perfusion. Estimates of regional oxygen metabolism are not widely available, except in centers with triple-oxygen PET (with mapping of CBF, cerebral blood volume, $CMRO_2$, and oxygen extraction fraction). In the one study using triple-oxygen PET in head injury, although there was no evidence of ischemia, no regional assessment was made ([35]). Classically, thresholds based on CBF have been useful in predicting tissue outcome and suggest that if CBF is reduced below 12 $mL \cdot 100g^{-1} \cdot min^{-1}$ and not restored within a 2- to 3-hr period, it is likely to infarct ([17] [28]). Using PET imaging, CBF was as useful in predicting eventual tissue outcome as $CMRO_2$ following acute stroke ([29]). However, it was less useful in a study comprising normal subjects and patients with subacute or chronic cerebrovascular disease ([30]).

Triple-oxygen PET studies obviously hold great potential for unraveling complex pathophysiologic abnormalities in head injury, and other studies from our center will address this issue. However, we chose to employ CBF thresholds in this study for several reasons. Methods for CBF measurement are more widely available in clinical centers, and evidence would suggest it to be a useful predictive marker of cerebral ischemia and tissue viability in acute disease states ([29]). Furthermore, triple-oxygen PET studies are more time consuming (typically 3–4 hrs for two triple-oxygen studies separated by stabilized hyperventilation). As a consequence, these studies are less applicable to patients who are not clinically stable. Furthermore, molecular ^{15}O scans are unsatisfactory in patients who have high Fi_{O_2} requirements as a consequence of coexisting lung injury or sepsis, since signal to noise is low as the tracer competes with high levels of natural oxygen. The use of CBF studies may not allow us to address the metabolic issues in as much depth as triple-oxygen studies, but it allows us to study a wider spectrum of patients to derive data that may be more generally applicable.

We chose a threshold CBF value of 10 $mL \cdot 100g^{-1} \cdot min^{-1}$ based on the experimental literature ([17] [28]), the PET literature ([29] [30] [31]), and the lower limit of the

95% confidence interval of our data in healthy volunteers (10–55 mL·100g^{-1}·min^{-1}). Although this value is concordant with data predicting metabolic failure and infarction following short periods of ischemia ([17] [28]), it is somewhat lower than that quoted traditionally following TBI using xenon CT ([8] [16]) and ^{133}Xe clearance imaging ([6] [7]). We considered that our threshold would reflect those regions of the brain with the greatest potential for ischemic damage, even after short periods of hyperventilation. In addition, statistical noise and partial volume effects can lead to inaccuracies in PET data analysis. Voxels with very low PET values at the periphery of brain tissue, or voxels with a poor signal-to-noise ratio, may be falsely categorized as hypoperfused. Our policy of calculating a threshold based on control data applied to patients at baseline and following the physiologic stress provided by hyperventilation would account for this possibility and provide an accurate description of disordered perfusion. Finally, although we included all voxels in our prediction of critical hypoperfusion, it is clear that gray and white matter have differing CBF and $CMRO_2$ ([36]) and might therefore have different thresholds for viability ([37] [38]). Although separate analysis of gray and white matter is possible using PET data coregistered to T1-weighted magnetic resonance images, the latter were not available to us during acquisition of these data. Furthermore, acute traumatized brains do not segment well into gray and white matter due to regional structural abnormalities, such as contusions and hematomas. The inclusion of both gray and white matter in our analysis explains why our threshold is lower than some traditional thresholds, which were determined following placement of regions of interest within predominantly cortical regions. Our choice of threshold represents a value that is based on previous PET data and takes some account of statistical noise, partial volume effects, and variable physiology in gray and white matter.

There may also be concerns regarding inclusion of intra-axial hematoma or infarcted tissue in the volume of hypoperfused (and by inference, critically ischemic) tissue because these may lead to falsely elevated values. However, most lesions in the patients we studied were of mixed density, and we found it difficult to find consistent and objective methods for differentiating contused tissue from intra-axial hematoma. It is reassuring, however, that the volume of critically hypoperfused tissue at baseline (22 [1–141] mL) was chiefly made up of tissue in the CBF range of 5–10 mL·100g^{-1}·min^{-1} (16 [1–129] mL). This would suggest that most of this tissue was under perfused brain, rather than intra-axial hematoma. In fact, the mean volume of tissue with CBF of <5 mL·100g^{-1}·min^{-1}, which would include such "irrelevant" voxels, was only 6 mL. This suggests that our segmentation technique substantially excluded intra-axial hematoma or areas of pan-necrosis. There are potential errors associated with our measurement of hypoperfused tissue at baseline, but we do not believe that these are large.

Definition of a hyperperfusion threshold is more difficult because little objective guidance is available in the literature ([9] [14] [21] [22]). We defined a threshold based on a blood flow in excess of the 95% confidence interval of our control mean (>55 mL·100g^{-1}·min^{-1}). In only five patients, all imaged at baseline between the second and third day, were voxels with blood flow within the hyperperfusion range identified. Following hyperventilation, CBF was only reduced below this threshold in three of these patients. Some authors have suggested that hyperperfusion and hyperemia in sedated head-injured patients should be defined by a blood flow that is not only in excess, but that is within the normal range for healthy conscious adults ([9]). Our data would suggest that for those patients with blood flow comparable with unsedated controls, hyperventilation shifts the distribution markedly toward potentially detrimental hypoperfusion.

Clinical Correlates.

It is well known that reductions in Pa_{co_2} lead to cerebral vasoconstriction and a reduction in both cerebral blood volume and CBF ([1] [2] [9] [10] [11] [12]). For this reason, it has been recommended that prophylactic hyperventilation therapy (≤35 torr) should be avoided during the first 24 hrs after severe TBI ([2]). However, it may still be considered necessary for brief periods of management or for refractory intracranial hypertension unresponsive to other therapies ([2]). The literature suggests that such interventions may be particularly appropriate in patients beyond the first 24 hrs after head injury who are believed to exhibit hyperemic CBF levels ([9] [14] [21] [22]). In addition, several authors suggest a role for Sjv_{o_2} and $AVDO_2$ monitoring in detecting ischemia in patients who are hyperventilated below a Pa_{co_2} of 30 torr ([2] [39]).

It is interesting to consider these recommendations in the context of our findings. We show that hypocapnic increases in HypoBV continue to be observed beyond the first day after head injury, at times when the literature suggests the common presence of hyperemia ([9] [14] [21] [22]). In addition, our data suggest that potentially harmful reductions in CBF can occur even with brief periods of hyperventilation when Pa_{co_2} is reduced below 34 torr (4.5 kPa). This threshold is in broad agreement with international recommendations during the first 24 hrs of severe TBI but not for later time periods ([2]). Although the increases in hypoperfusion involve relatively small volumes, we employed a stringent threshold, and selection of higher CBF thresholds is likely to identify larger volumes with a reduced but still significant risk of infarction. Importantly, even with the thresholds that we used, the volume of tissue at risk is comparable with perfusion deficits observed in ischemic stroke ([40]). In addition, relatively small regions of ischemia in frontal and temporal regions may have important consequences in terms of functional recovery ([41]).

We attempted to correlate global monitoring tools to our indices of regional hypoperfusion and hyperperfusion using linear, polynomial, and nonparametric methods with little success. Sjv_{o_2} and $AVDO_2$ monitoring are insensitive to regional increases in the volume of critically hypoperfused and hyperperfused brain, and are unlikely to provide useful safeguards in this setting. In contradiction to international recommendations ([2]), our data would suggest that maintaining Sjv_{o_2} at >50% and $AVDO_2$ at <9 mL/mL ([9] [18] [19] [20] [21]) may prevent global ischemia but may not protect patients from the deleterious effects of short periods of hyperventilation. These findings provide one explanation for the discrepancy between the apparent efficacy of hyperventilation in reducing ICP and its lack of benefit (or possibly detrimental effect) on outcome ([42]).

These findings do not completely negate the possibility that hyperventilation may be useful in selected patients with refractory intracranial hypertension. However, they do underline the difficulty of using conventional thresholds, based on global monitors of brain oxygenation, to select patients for such therapy or monitor its safety. Bedside measures of global CBF (e.g., with ^{133}Xe clearance methods) provide no safeguard against regional ischemia. However, CBF imaging provides a robust method of detecting regional hypoperfusion, and it may be useful in optimizing ventilatory strategies in individual patients. We believe that our data provide support for studies that prospectively address this issue.

Could we have refined our use of global cerebrovascular monitoring to provide better discrimination of ischemia? Various groups have suggested more targeted lateralization of Sjv_{o_2} monitoring and expressed doubt regarding the reliability of unilateral monitoring ([43] [44]). Furthermore, some authors have employed more focused measures of ischemia, such as the lactate oxygen index ([21]), the modified lactate oxygen index ([45]), and the cerebral extraction of oxygen (which uses direct measurement of saturation differences between arterial and jugular blood) ([39] [46]). Although these approaches may offer some advantages, we do not believe that they can successfully overcome the fundamental failure of a global monitor to detect regional ischemia.

Global CO_2 reactivity in our patients was comparable with previous values quoted in the literature ([2] [8] [9]). Previous authors have shown that CO_2 reactivity may vary across the injured brain ([10]). We chose to focus on the effect of hyperventilation on the burden of hypoperfusion. Further analysis will be required to address the issue of regional CO_2 reactivity.

Although we have defined the effect of acute hypocapnia on the injured brain, it is important to emphasize that we have no data that describe the subsequent effects if hyperventilation is maintained over a period of hours or days. This would require further studies of chronic hyperventilation and detailed outcome studies incorporating neurocognitive assessment.

CONCLUSIONS

We believe that these findings are important for several reasons. First, the use of hyperventilation below 34 torr (4.5 kPa) leads to an increase in the volume of critically hypoperfused tissue within the injured brain, even in patients who achieve improvement in CPP and ICP levels. We could find limited evidence for significant hyperperfusion within the first week of injury, which is significant because conventional wisdom accepts a role for modest hyperventilation during this hyperemic phase of head injury ([9] [14]). Although there is little evidence for global ischemia in head injury, increases in the burden of hypoperfusion may reflect regions of cerebral tissue at risk of ischemic damage that are underestimated by monitoring of Sjv_{O_2} and $AVDO_2$. If global monitoring modalities are to be employed, individual thresholds may need to be set with reference to measurements of regional CBF. Future studies are required to examine the effect of prolonged moderate hyperventilation on blood flow and eventual outcome. In particular, definition of the effect of regional hypoperfusion within functionally important frontal and temporal regions of the brain will require detailed neurocognitive assessments that relate acute physiology to late outcome.

REFERENCES

1. Madden JA : The effect of carbon dioxide on cerebral arteries . Pharmacol Ther 1993 ; 59 : 229–250 Abstract

2. The Brain Trauma Foundation : The American Association of Neurological Surgeons. The joint section on neurotrauma and critical care. Hyperventilation . J Neurotrauma 2000 ; 17 : 513–520 Abstract

3. Yundt KD , Diringer MN : The use of hyperventilation and its impact on cerebral ischemia in the treatment of traumatic brain injury . Crit Care Clin 1997 ; 13 : 163–184 Full Text

4. Marion DW , Firlik A , McLaughlin MR : Hyperventilation therapy for severe traumatic brain injury . New Horiz 1995 ; 3 : 439–447 Abstract

5. Kety SS , Schmidt CF : The effects of active and passive hyperventilation on cerebral blood flow, cerebral oxygen consumption, cardiac output, and blood pressure of normal young men . J Clin Invest 1946 ; 25 : 107–119

6. Bouma GJ , Muizelaar JP , Choi SC , et al: Cerebral circulation and metabolism after severe traumatic brain injury : The elusive role of ischemia . J Neurosurg 1991 ; 75 : 685–693 Abstract

7. Bouma GJ , Muizelaar JP , Stringer WA , et al: Ultra-early evaluation of regional cerebral blood flow in severely head-injured patients using xenon-enhanced computerized tomography . J Neurosurg 1992 ; 77 : 360–368 Abstract

8. Marion DW , Darby J , Yonas H : Acute regional cerebral blood flow changes caused by severe head injuries . J Neurosurg 1991 ; 74 : 407–414 Abstract

9. Obrist WD , Langfitt TW , Jaggi JL , et al: Cerebral blood flow and metabolism in comatose patients with acute head injury : Relationship to intracranial hypertension . J Neurosurg 1984 ; 61 : 241–253 Abstract

10. McLaughlin MR , Marion DW : Cerebral blood flow within and around cerebral contusions . J Neurosurg 1996 ; 85 : 871–876 Abstract

11. Skippen P , Seear M , Poskitt K , et al: Effect of hyperventilation on regional cerebral blood flow in head-injured children . Crit Care Med 1997 ; 25 : 1402–1409 Full Text

12. Stringer WA , Hasso AN , Thompson JR , et al: Hyperventilation-induced cerebral ischaemia in patients with acute brain lesions : Demonstration by xenon-enhanced CT . AJNR Am J Neuroradiol 1993 ; 14 : 475–484 Abstract

13. Muizelaar JP , Marmarou A , Ward JD , et al: Adverse effects of prolonged hyperventilation in patients with severe head injury : A randomized clinical trail . J Neurosurg 1991 ; 75 : 731–739 Abstract

14. Martin NA , Patwardhan RV , Alexander MJ , et al: Characterization of cerebral hemodynamic phases following severe head trauma : Hypoperfusion, hyperemia, and vasospasm . J Neurosurg 1997 ; 87 : 9–19 Abstract

15. Cruz J : The first decade of continuous monitoring of jugular bulb oxyhemoglobin saturation : Management strategies and clinical outcome . Crit Care Med 1998 ; 26 : 344–351 Full Text

16. Yonas H , Sekhar L , Johnson DW , et al: Determination of irreversible ischaemia by xenon-enhanced computed tomographic monitoring of cerebral blood flow in patients with symptomatic vasospasm . Neurosurgery 1989 ; 24 : 368–372 Abstract

17. Jones TH , Morawetz RB , Crowell RM , et al: Thresholds of focal cerebral ischaemia in awake monkeys . J Neurosurg 1981 ; 54 : 773–782 Abstract

18. Gibbs EL , Lennox WG , Nims LF , et al: Arterial and cerebral venous blood : Arterial-venous differences in man . J Biol Chem 1942 ; 144 : 325–332

19. Robertson CS , Cormio M : Cerebral metabolic management . New Horiz 1995 ; 3 : 410–422 Abstract

20. Kety SS , Schmidt CF : The nitrous oxide method for the quantitative determination of cerebral blood flow in man : Theory, procedure, and normal values . J Clin Invest 1948 ; 27 : 476–483

21. Robertson CS , Narayan RK , Gokaslan ZL , et al: Cerebral arteriovenous oxygen difference as an estimate of cerebral blood flow in comatose patients . J Neurosurg 1989 ; 70 : 222–230 Abstract

22. Kelly DF , Kordestani RK , Martin NA , et al: Hyperemia following traumatic brain injury : Relationship to intracranial hypertension and outcome . J Neurosurg 1996 ; 85 : 762–771 Abstract

23. Menon DK : Cerebral protection in severe brain injury : Physiological determinants of outcome and their optimisation . Br Med Bull 1999 ; 55 : 226–258 Abstract

24. Kinahan PE , Rogers JG : Analytic 3D image reconstruction using all detected events : Institute of Electrical and Electronic Engineers . Trans Nucl Sci 1989 ; 36 : 964–968

25. Frackowiak RSJ , Lenzi GL , Jones T , et al: Quantitative measurement of regional cerebral blood flow and oxygen metabolism in man using ^{15}O and positron emission tomography : Theory, procedure, and normal values . J Comput Assist Tomogr 1980 ; 4 : 727–736 Abstract

26. Studholme C , Hill DLG , Hawkes DJ : Automated three-dimensional registration of magnetic resonance and positron emission tomography brain images by multiresolution optimisation of voxel similarity measures . Med Phys 1997 ; 24 : 25–35 Abstract

27. Studholme C , Hawkes DJ , Hill DLG : Automated 3D registration of MR and CT images of the head . Med Image Anal 1996 ; 1 : 163–175 Abstract

28. Astrup J , Siesjö BK , Symon L : Thresholds in cerebral ischemia : The ischemic penumbra . Stroke 1981 ; 12 : 723–725 Citation

29. Marchal G , Benali K , Iglesias S , et al: Voxel-based mapping of irreversible ischaemic damage with PET in acute stroke . Brain 1999 ; 123 : 2387–2400 Abstract

30. Powers WJ , Grubb RL , Darriet D , et al: Cerebral blood flow and cerebral metabolic rate of oxygen requirements for cerebral function and viability in humans . J Cereb Flow Metab 1985 ; 5 : 600–608

31. Powers WJ : Hemodynamics and metabolism in ischemic cerebrovascular disease . Neurol Clin 1992 ; 10 : 31–48 Abstract

32. Seifert H , Blass G , Leetz HK , et al: The radiation exposure of the patient from stable-xenon computed tomography . Br J Radiol 1995 ; 68 : 301–305 Abstract

33. Baron JC : Mapping the ischemic penumbra with PET : Implications for acute stroke treatment . Cerebrovasc Dis 1999 ; 9 : 193–201 Abstract

34. Verweij BH , Muizelaar JP , Vinas FC , et al: Impaired cerebral mitochondrial function after traumatic brain injury in humans . J Neurosurg 2000 ; 93 : 815–820 Abstract

35. Diringer MN , Yundt K , Videen TO , et al: No reduction in cerebral metabolism as a result of early moderate hyperventilation following severe traumatic brain injury . J Neurosurg 2000 ; 92 : 7–13 Abstract

36. Marchal G , Rioux P , Petit-Taboué MC , et al: Regional cerebral oxygen consumption, blood flow, and blood volume in healthy human aging . Arch Neurol 1992 ; 49 : 1013–1020 Abstract

37. Marcoux FW , Morawetz RB , Crowell RM , et al: Differential regional vulnerability in transient focal cerebral ischemia . Stroke 1982 ; 13 : 339–346 Citation

38. Pantoni L , Garcia JH , Gutierrez JA : Cerebral white matter is highly vulnerable to ischemia . Stroke 1996 ; 27 : 1641–1647 Abstract

39. Cruz J : Combined continuous monitoring of systemic and cerebral oxygenation in acute brain injury . Crit Care Med 1993 ; 21 : 1225–1232 Abstract

40. Staroselskaya IA , Chaves C , Silver B , et al: Relationship between magnetic resonance arterial patency and perfusion arterial patency and perfusion-diffusion mismatch in acute ischemic stroke and its potential clinical use . Arch Neurol 2001 ; 58 : 1069–1074 Abstract

41. Mattson AJ , Levin HS : Frontal lobe dysfunction following closed head injury : A review of the literature . J Nerv Ment Dis 1990 ; 178 : 282–291 Abstract

42. Schierhout G , Roberts I : Hyperventilation therapy for acute traumatic brain injury . Cochrane Database Syst Rev 2000 ; CD000566 Abstract

43. Metz C , Holzschuh M , Bein T , et al: Monitoring of cerebral oxygen metabolism in the jugular bulb : Reliability of unilateral measurements in severe head injury . J Cereb Blood Flow Metab 1998 ; 18 : 332–343 Abstract

44. Stocchetti N , Paparella A , Bridelli F , et al: Cerebral venous saturation studied with bilateral samples in the internal jugular veins . Neurosurgery 1994 ; 34 : 38–44 Abstract

45. Cruz J , Hoffstad OJ , Jaggi JL : Cerebral lactate-oxygen index in acute brain injury with acute anemia : Assessment of false versus true ischemia . Crit Care Med 1994 ; 22 : 1465–1470 Abstract

46. Cruz J , Jaggi JL , Hoffstad OJ : Cerebral blood flow and oxygen consumption in acute brain injury with acute anemia : An alternative for the cerebral metabolic rate of oxygen consumption?

Crit Care Med 1993 ; 21 : 1218–1224 Abstract

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