# Effect of hyperventilation on extracellular concentrations of glutamate, lactate, pyruvate, and local cerebral blood flow in patients with severe traumatic brain injury*

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***Objective:*** **To determine the potential adverse effects of brief periods of hyperventilation commonly used for acute neurologic deterioration.**

***Design:*** **Prospective clinical trial.**

***Setting:*** **University medical school.**

***Patients:*** **Twenty patients with severe traumatic brain injury.**

***Interventions:*** **The effect of 30 mins of hyperventilation (mean $Paco_2$, 24.6 mm Hg) on the extracellular metabolites associated with ischemia, and on local cerebral blood flow was studied by using microdialysis and local cerebral blood flow techniques. Normal appearing brain adjacent to evacuated hemorrhagic contusions or underlying evacuated subdural hematomas was studied. Hyperventilation trials were done 24–36 hrs after injury and again at 3–4 days after injury. Dialysate concentrations of glutamate, lactate, and pyruvate were measured before and for 4 hrs after the hyperventilation trials.**

***Measurements and Main Results:*** **At 24–36 hrs, hyperventilation led to a ≥10% increase in the extracellular concentrations of glutamate in 14 of 20 patients, with concentrations in those 14 patients 13.7–395% above baseline; a ≥10% increase in lactate in 7 of 20 patients (11.6–211% above baseline); and a ≥10% increase in the lactate/pyruvate ratio in eight of 20 patients (10.8–227% above baseline). At 3–4 days after injury, ten of 13 patients had an increase in glutamate of ≥10%, while only three of 13 patients had an increase in extracellular lactate and two of 13 patients had an increase in the lactate/pyruvate ratio of this magnitude. The hyperventilation associated increases in extracellular glutamate and lactate concentrations were significant ($p < .05$; one-sample Student's *t*-test) at both time points after injury, as was the lactate/pyruvate ratio at 24–36 hrs. A ≥10% decline in local cerebral blood flow was observed with hyperventilation in five of 20 patients at 24–36 hrs (range, 10.2–18.7% below baseline), and in ten of 13 patients studied at 3–4 days (11.3–54% below baseline). There was no correlation with the presence or absence of local $CO_2$ vasoresponsivity and increases in the extracellular metabolites at either the early or late time points.**

***Conclusions:*** **In brain tissue adjacent to cerebral contusions or underlying subdural hematomas, even brief periods of hyperventilation can significantly increase extracellular concentrations of mediators of secondary brain injury. These hyperventilation-induced changes are much more common during the first 24–36 hrs after injury than at 3–4 days. (Crit Care Med 2002; 30:2619–2625)**

**KEY WORDS: severe traumatic brain injury; hyperventilation; microdialysis; local cerebral blood flow; glutamate; lactate**

Hypocapneic therapy (hyperventilation) was first described as a means of reducing elevated intracranial pressure (ICP) by Lundberg in the 1950s (1), and this treatment became widely accepted for treating the intracranial hypertension frequently associated with severe traumatic brain injury (TBI). Several reports described the reversal of clinical signs of herniation, such as fixed and dilated pupils, following aggressive hyperventilation (2, 3). In addition, the finding of elevated brain tissue concentrations of lactate caused by severe TBI led many to believe that the respiratory alkalosis associated with hyperventilation would be desirable (4).

Early intubation and controlled ventilation of comatose TBI patients have been shown to improve outcomes (5), but no study has shown that hyperventilation does. Studies of posttraumatic cerebral blood flow (CBF) done very early after severe TBI indicate that blood flow is typically less than half of normal in the first 4–12 hrs after impact (6). Bouma et al. (7) found that within 3 hrs of the injury, global or regional CBF was <18 mL/100 g/min in 31% of these patients (7). Abnormally low CBF was most common in the brain tissue within and surrounding hemorrhagic contusions and in the cortex underlying acute subdural hematomas (7, 8). Based in large part on these studies, many have concluded that ischemia is common early after severe TBI. This conclusion is supported by autopsy studies of Graham et al. (9), who found ischemic cell change in nearly 90% of TBI patients who died.

The practical implications of these physiologic abnormalities for the use of hyperventilation in the acute care of TBI patients are not clear. Kerr et al. (10) showed that brief periods of hyperventilation used immediately before endotracheal suctioning can blunt the increase in ICP commonly associated with this procedure. Newell et al. (11) found that

*See also p. 2774.

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short periods of hyperventilation improved the efficiency of the cerebral autoregulatory response to systemic blood pressure changes. Investigators also have examined the effects of hyperventilation on changes in the jugular venous glucose, lactate, and oxygen saturation and content and found either no change or an improvement in these concentrations associated with hyperventilation for up to 4 hrs (12, 13).

But others have found that hyperventilation is one of the most common identifiable causes of jugular venous oxygen desaturations (14, 15). In 1991, Muizelaar et al. (16) reported a prospective randomized trial which found that patients who were prophylactically hyperventilated for 5 days to achieve a mean $Paco_2$ of 25 mm Hg had worse clinical outcomes at 6 months after injury than those who were kept at a $Paco_2$ of 35 mm Hg. Although this effect was seen only in the subgroup of patients with an initial Glasgow Coma Scale (GCS) score of 5–8, the data were deemed of sufficient quality to be used as the basis for recommendations about hyperventilation in the *Guidelines for the Management of Severe Head Injury* (17). These guidelines recommended as a "standard" that prophylactic hyperventilation therapy for severe TBI should not be used in the absence of elevated ICP. At the level of a guideline, it was recommended that hyperventilation should be avoided whenever possible during the first 24 hrs after injury because of the risk of hyperventilation induced-ischemia.

While the evidence against the use of prophylactic hyperventilation is compelling, there is little or no evidence that brief periods of hyperventilation therapy will worsen ischemia or neurologic outcomes. We designed this study to characterize the local molecular and physiologic effects of brief periods of hyperventilation in highly vulnerable regions of the brain. Our hypothesis was that hyperventilation for 30 mins would lead to a significant reduction in local CBF and a significant increase in several extracellular molecules associated with posttraumatic ischemia, such as lactate and glutamate. The regions of the brain we studied were selected based on previous CBF studies which suggested that posttraumatic abnormalities of local CBF were most severe within and around cerebral contusions and in the cortex underlying subdural hematomas (7, 8).

## METHODS

This study was designed to identify changes in extracellular glutamate, lactate, and pyruvate concentrations and local cerebral blood flow in areas of the brain considered most at risk for ischemia following 30 mins trials of hyperventilation. Extracellular concentrations of glutamate, lactate, and pyruvate were measured using *in vivo* microdialysis, and local cerebral blood flow was measured using thermodiffusion blood flow probes. All TBI patients with a GCS score of $\leq 8$ and surgical intracranial mass lesions who were admitted to our hospital from 1997 to 2000 were considered for inclusion. Only these patients were selected for study because we wanted to insert microdialysis catheters into relatively normal appearing cortex adjacent to contusions or underlying subdural hematomas, and this could only be done under direct visualization at the time of surgery. Comatose patients (GCS $<8$) were the focus on our study because those with a higher GCS score are usually awake, extubated, and discharged from the intensive care unit within 24–48 hrs after admission. Therefore, the controlled hyperventilation trials we proposed would not be possible in the majority of those patients. The study was reviewed and approved by the University of Pittsburgh Biomedical Investigational Review Board. Before we enrolled patients in the study, written informed consent was obtained from the patient's legal next of kin.

*Microdialysis Procedure.* After evacuation of the mass lesion, a relatively normal appearing gyrus adjacent to the lesion was selected for placement of a microdialysis probe. A small hole was made in the pia matter and a microdialysis catheter inserted obliquely into the cortex approximately 12–15 mm. The distal end of the catheter was tunneled through the dura and scalp and secured to the scalp. Every effort was made to avoid any movement of the catheter after it had been placed. We used a CMA-20 microdialysis catheter (CMA Corporation, Boston, MA) with a 10-mm active end and a 20-kD molecular weight cutoff. Before insertion, the catheter was primed with sterile normal saline solution without preservatives.

When the patient was transferred to the intensive care unit, the in-flow end of the catheter was connected to a CMA Microdialysis 102 infusion pump, and sterile saline was infused at a rate of 2 $\mu$L/min. The outflow tubing was connected to a CMA Microdialysis 170 refrigerated, automated fraction collector, which was cooled to 4°C. Dialysate samples were collected at 30-min intervals. The samples were collected for a maximum of 5 days, or less if the patient died or regained consciousness during that time. Every 12 hrs, dialysate samples were removed from the fraction collector and stored in a $-80$°C freezer. Dialysate concentrations of glutamate were measured following precolumn derivatization with o-phthaldialdehyde using high-pressure liquid chromatography with fluorescence detection (474; Waters Corporation, Milford, MA), and lactate and pyruvate concentrations were measured using high-pressure liquid chromatography with ultraviolet detection (486; Waters Corporation). Pyruvate is not considered an intermediate of secondary brain injury, but concentrations of this molecule were measured so that we could calculate the lactate/pyruvate ratio. Severe TBI often causes cerebral edema, which is most intense within and surrounding contusions. A change in the tissue water content over time will obviously influence the absolute tissue concentration of soluble molecules such as lactate and glutamate. This can confound interpretation of dialysate concentrations of these molecules. Persson et al. (18) suggested that the determination of the lactate/pyruvate ratio can provide a more stable estimation of the level of anaerobic metabolism that is relatively immune to edema.

*Local CBF Monitoring.* After placement of the microdialysis probe in the operating room, a thermodiffusion blood flow probe (Flowtronics, Phoenix, AZ) was placed on the cortex overlying the microdialysis probe. The distal end of the blood flow probe was brought out through the craniotomy incision and secured to the scalp. In the intensive care unit, the blood flow probe was connected to a thermodiffusion flow monitor (MS7000; Flowtronics, Phoenix, AZ). Digitized CBF data were automatically sampled every minute, time/date stamped, and collected on a floppy disk for off-line analysis.

*Hyperventilation Trials.* Hyperventilation trials were conducted 24–36 hrs after injury and again at 3–4 days after injury. Baseline dialysate samples and local CBF measurements were obtained and the arterial $Pco_2$ documented. The ventilatory rate was then increased to cause an 8 to 12 mm Hg reduction in the arterial $Pco_2$. The increased ventilatory rate was maintained for 30 mins. A second arterial blood gas analysis was obtained, and then the ventilatory rate was reduced to baseline. This level of hyperventilation ($Paco_2$ reduction) was selected for study because it is commonly used for brief periods to reduce acutely elevated ICP, particularly when transporting the patient to the operating room or computed tomography (CT) scanner. Although concerns may be raised that even these brief periods of hyperventilation will cause ischemia, it is precisely this issue that our study was designed to address. Regional loss of $CO_2$ vasoresponsivity has been shown to occur in the brain tissue surrounding contusions (19). Local CBF was recorded every minute during and for 4 hrs after the hyperventilation trials, and dialysate samples were obtained every 30 mins for the same period. The first trials were performed 24–36 hrs after injury to allow for stabilization of the extracellular neurochemical and physiologic environment and to avoid artifacts from catheter insertion, as well as transient changes that may have occurred immediately after the injury and surgery. Because maximum brain swelling often does not occur until the third

or fourth day after injury, we included a second hyperventilation trial at that time. In our experience, this is the time when we are most likely to need hyperventilation to augment other medical measures for the treatment of intracranial hypertension.

In all cases, the ICP, cerebral perfusion pressure, mean arterial pressure, $Paco_2$, and $Pao_2$ were measured at various time intervals before and after hyperventilation (Table 1). The administration of mannitol was avoided during these trials. For the first trials (24–36 hrs after injury), seven of 20 patients were treated with therapeutic moderate hypothermia. None of the patients studied on day 3–4 were cooled.

*Data Analysis.* To determine the effect of 30 mins of hyperventilation on extracellular concentrations of lactate, pyruvate, the lactate/pyruvate ratio, and glutamate, as well as the local CBF, the maximum percent change from baseline for each metabolite, and for the local CBF, was calculated for 4 hrs after the hyperventilation trial. A one-sample Student's *t*-test was used to test the null hypothesis of no change vs. the alternative hypothesis of an increase in the dialysate concentration of metabolites or decrease in local CBF. A decrease in dialysate concentrations of metabolites or an increase in local CBF associated with hyperventilation was not considered in this model, since changes in those directions would not be caused by hyperventilation. We arbitrarily selected a ≥10% increase in the extracellular neurochemicals, or a ≥10% decrease in the local CBF, as significant because these levels frequently varied up to 10% of "baseline" in the absence of any medical intervention during our 5-day period of monitoring. Thus, we did not consider changes of <10% as clinically meaningful. The frequency of significant (>10%) changes in these variables caused by hyperventilation was determined. The effect of time after injury, hypothermia, initial GCS score, CT-defined injury, 6-month Glasgow Outcome Scale score, cerebral perfusion pressure, ICP, and mean arterial pressure was determined by using Fisher's exact tests or chi-square analyses as appropriate. Local $CO_2$ vasoreactivity (percentage change in local CBF/torr change in $Pco_2$) was calculated and was considered present if there was a ≥1% change in local CBF per torr change in $Pco_2$. The presence or absence of local $CO_2$ vasoreactivity was then correlated with changes in the extracellular metabolites using Fisher's exact test.

The primary goal of this study was to determine whether there was a significant increase in the maximum percentage change in dialysate lactate and glutamate concentrations and in the lactate/pyruvate ratio, or a significant decrease in the maximum percentage change in local CBF, associated with hyperventilation. Using a one-sample Student's *t*-test, with a one-sided alternative hypothesis and a type I error rate of 0.05, there would be 80% power to detect a change of 0.58 standard deviations on day 1 (sample size of 20) and 0.73 standard deviations on day 3 (sample size of 13).

## RESULTS

Twenty patients were studied at 24–36 hrs after injury, and 13 of these patients at 3–4 days, for a total of 33 trials. The mean baseline $Paco_2$ was 35 ± 3.6 mm Hg and, after 30 mins of hyperventilation, 24.8 ± 3.9 mm Hg for the 20 patients tested at 24–36 hrs after injury. Mean baseline and posthyperventilation $Paco_2$ values were 35.1 ± 3.5 mm Hg and 24.4 ± 4.5 mm Hg, respectively, for those studied at 3–4 days after injury. Reasons for the lower number of patients eligible for study on days 3–4 were patient intolerance to $Pco_2$ changes for ICP and pulmonary reasons (n = 2), death (n = 1), patient regained consciousness (n = 2), and technical difficulties with the dialysate catheter and/or CBF probe (n = 2). The demographic profile, admission GCS scores, and type of surgical mass lesions are described in Table 2. The majority of the patients had hemorrhagic contusions, most commonly in the temporal lobe.

*Effect of Hyperventilation on Extracellular Concentrations of Glutamate, Lactate, and the Lactate/Pyruvate Ratio.* At 24–36 hrs after injury, hyperventilation led to a significant increase in dialysate glutamate (mean 49.65 ± 93.4%, $p$ = .014) and lactate (mean 25.9 ± 48.8%, $p$ = .014) and in the lactate/pyruvate ratio (mean 21.4 ± 49.8%, $p$ = .035). Fourteen of the 20 patients had a >10% increase in glutamate; seven of 20 patients had a >10% increase in lactate; and eight of 20 patients had an increase in the lactate/pyruvate ratio of this magnitude (Figs. 1 and 2). At 3–4 days after injury, hyperventilation also led to a significant increase in dialysate glutamate (mean 106.9 ± 124.64%, $p$ = .005) and lactate (mean 13.63 ± 16.22%, $p$ = .007), although not in the lactate/pyruvate ratio (mean 7.02 ± 14.01%, $p$ = .055). At this later time point, ten of 13 patients had a >10% increase in extracellular glutamate concentrations, but only three of 13 patients had a >10% increase in lactate and two of 13 had such an increase in the lactate/pyruvate ratio (Figs. 1 and 2).

*Effect of Hyperventilation on Local CBF.* At 24–36 hrs after injury, a >10% decrease in the local CBF was observed in five of 20 patients ($p$ > .05), and at 3–4 days after injury ten of 13 patients had a decrease in local CBF of this magnitude following 30 mins of hyperventilation ($p$ = .001; Fig. 3). If we assume that there should normally be a 3% reduction in CBF per torr decrease in the arterial $Pco_2$, the expected CBF decrease for the early and late hyperventilation trials would have been 30% and 31.5%, respectively; we observed an average decrease in local CBF of only 4.6 ± 8.6% at 24–36 hrs after injury and 19.89 ± 12.9% at 3–4 days after injury.

*Correlation of Local $CO_2$ Vasoreactivity With Hyperventilation-Induced Changes in Extracellular Glutamate Concentrations and the Lactate/Pyruvate Ratio.* At 24–36 hrs after injury, the local $CO_2$ vasoresponsivity (decrease in CBF/torr decrease in $Paco_2$) was 0.46 ± 0.86%

**Table 1.** Mean and SE of relevant physiologic variables, mm Hg, measured 1 hr before hyperventilation (HV; baseline), at the end of HV (just before restoring baseline ventilatory rate), and at 1 hr after restoring the baseline ventilatory rate

| | ICP | MAP | CPP | $PaCO_2$ | $PaO_2$ |
|---|---|---|---|---|---|
| 24- to 36-hr trial | | | | | |
| Baseline | 16.0 ± 5.8 | 95.2 ± 18.1 | 80.5 ± 18.5 | 34.6 ± 4.3 | 162.6 ± 61.1 |
| End of HV | 15.5 ± 7.3 | 99.0 ± 15.8 | 85.7 ± 15.0 | 26.1 ± 4.0 | 149.2 ± 66.3 |
| 1 hr after HV | 16.6 ± 5.9 | 102.8 ± 16.3 | 83.3 ± 9.4 | 31.4 ± 3.0 | 164.8 ± 67.9 |
| 3- to 4-day trial | | | | | |
| Baseline | 19.6 ± 4.4 | 102.6 ± 23.5 | 83.2 ± 25.1 | 35.9 ± 3.0 | 116.2 ± 50.1 |
| End of HV | 16.3 ± 4.9 | 96.9 ± 13.2 | 80.4 ± 12.5 | 24.9 ± 4.7 | 107.0 ± 56.1 |
| 1 hr after HV | 19.4 ± 5.7 | 102.8 ± 19.8 | 83.4 ± 22.7 | 32.7 ± 3.1 | 115.5 ± 49.0 |

ICP, intracranial pressure; MAP, mean arterial pressure; CPP, cerebral perfusion pressure.

**Table 2.** Patient profile

| | |
|---|---|
| Age, mean | 38.8 yrs |
| Gender | 66.7% males |
| Admission GCS, patients | 5.7 (mean) |
| 3–4 | 5 |
| 5–8 | 16 |
| Pupils: one or more unreactive | 52% |
| 6-month GOS, patients | 3.2 (mean) |
| 1–3 | 14 |
| 4–5 | 7 |
| Initial CT scan, patients | |
| Contusion only | 7 |
| Subdural hematoma + contusion | 12 |
| Subdural hematoma only | 1 |

GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; CT, computed tomography.

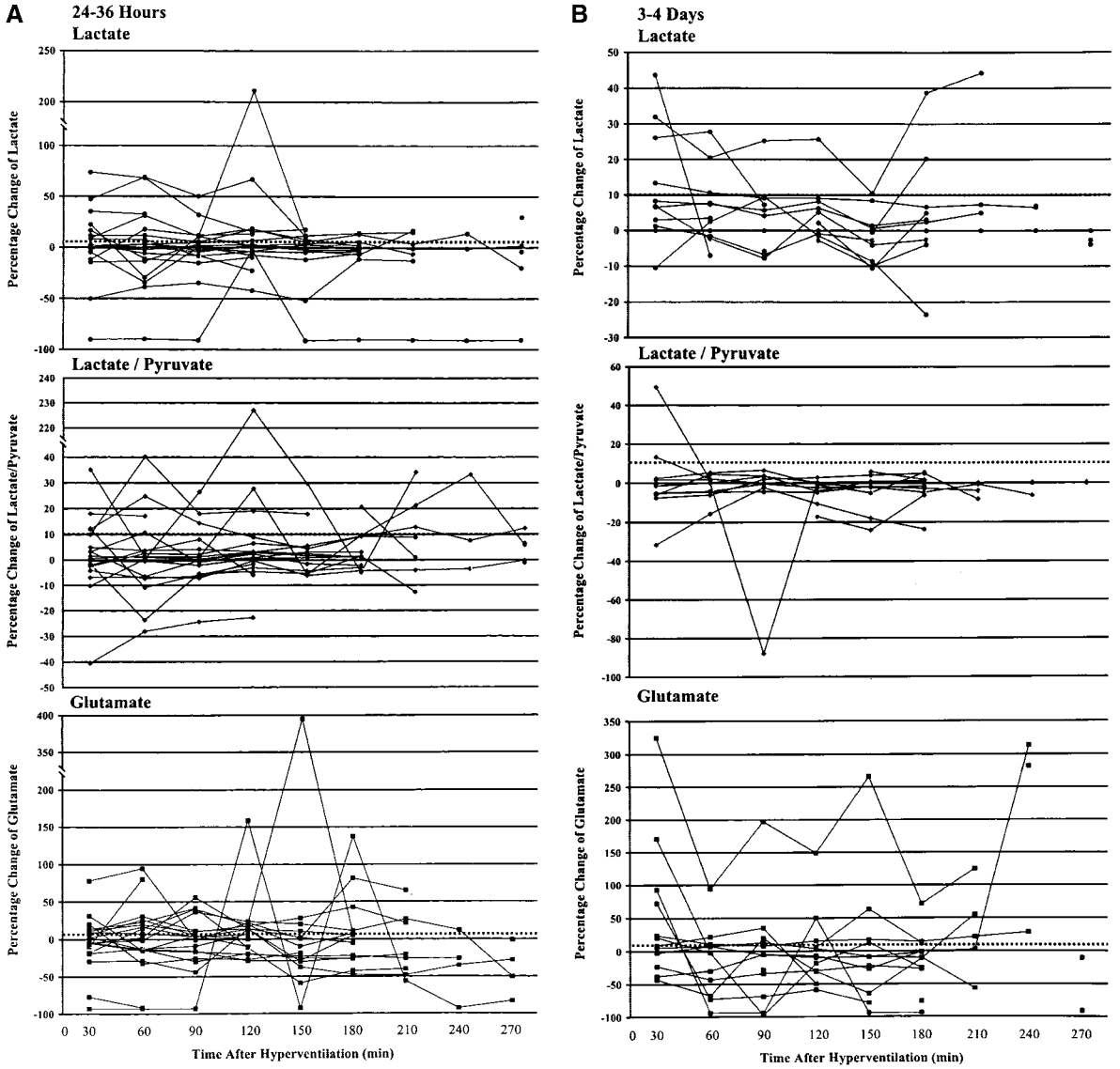


Figure 1. The percentage change of the dialysate concentrations of lactate, glutamate, and the lactate/pyruvate ratio following 30 mins of hyperventilation are presented for each patient at 30-min intervals for up to 4 hrs after hyperventilation. *A*, the 20 patients studied at 24–36 hrs after injury; *B*, the 13 patients studied at 3–4 days after injury. At 0 on the x-axis, all data points were 0 on the y-axis. The dotted line indicates the 10% threshold below which we consider fluctuations in the dialysate concentrations to be physiologic.

for the entire group, and only six of 20 patients had a >1% decrease in CBF/torr decrease in $P_{CO_2}$. At 3–4 days after injury, the local $CO_2$ vasoresponsivity was 1.89 ± 1.23% for the entire group, and ten of 13 patients had at least a 1% decrease in CBF/torr decrease in $P_{CO_2}$. At both time points there was considerable variability, but none of the 20 patients had vasoresponsivity as high as 3% at 24–36 hrs, and only two of 13 patients had vasoresponsivity of 3% at 3–4 days after injury. Five of the patients who previously were unresponsive regained $CO_2$ vasoresponsivity, and two patients lost it by days 3–4. No correlation was observed between the presence or absence of $CO_2$ vasoreactivity and increases in extracellular glutamate or lactate concentrations or the lactate/pyruvate ratio.

We considered the possibility that those patients with a low baseline CBF would be most likely to have an increase in extracellular neurochemical concentrations following hyperventilation, so the effect of hyperventilation on dialysate neurochemical concentrations was examined in patients with low (<20 mL/100 g/min), medium (21–40 mL/100 g/min), and high (>40 mL/100 g/min) local CBF. Those with a low baseline CBF were no more likely to have a hyperventilation-induced increase in glutamate, lactate, or the lactate pyruvate ratio than those with a high baseline CBF.

*Effect of Treatment and Physiologic Variables.* Using Fisher's exact test we attempted to identify independent effects of type of brain injury (contusion vs. subdural hematoma), initial GCS, therapeutic hypothermia, ICP, cerebral perfusion pressure, mean arterial pressure, and 6-month Glasgow Outcome Scale score on the likelihood that hyperventilation would increase the extracellular concentrations of glutamate, lactate, and the lactate/pyruvate ratio or decrease local CBF.

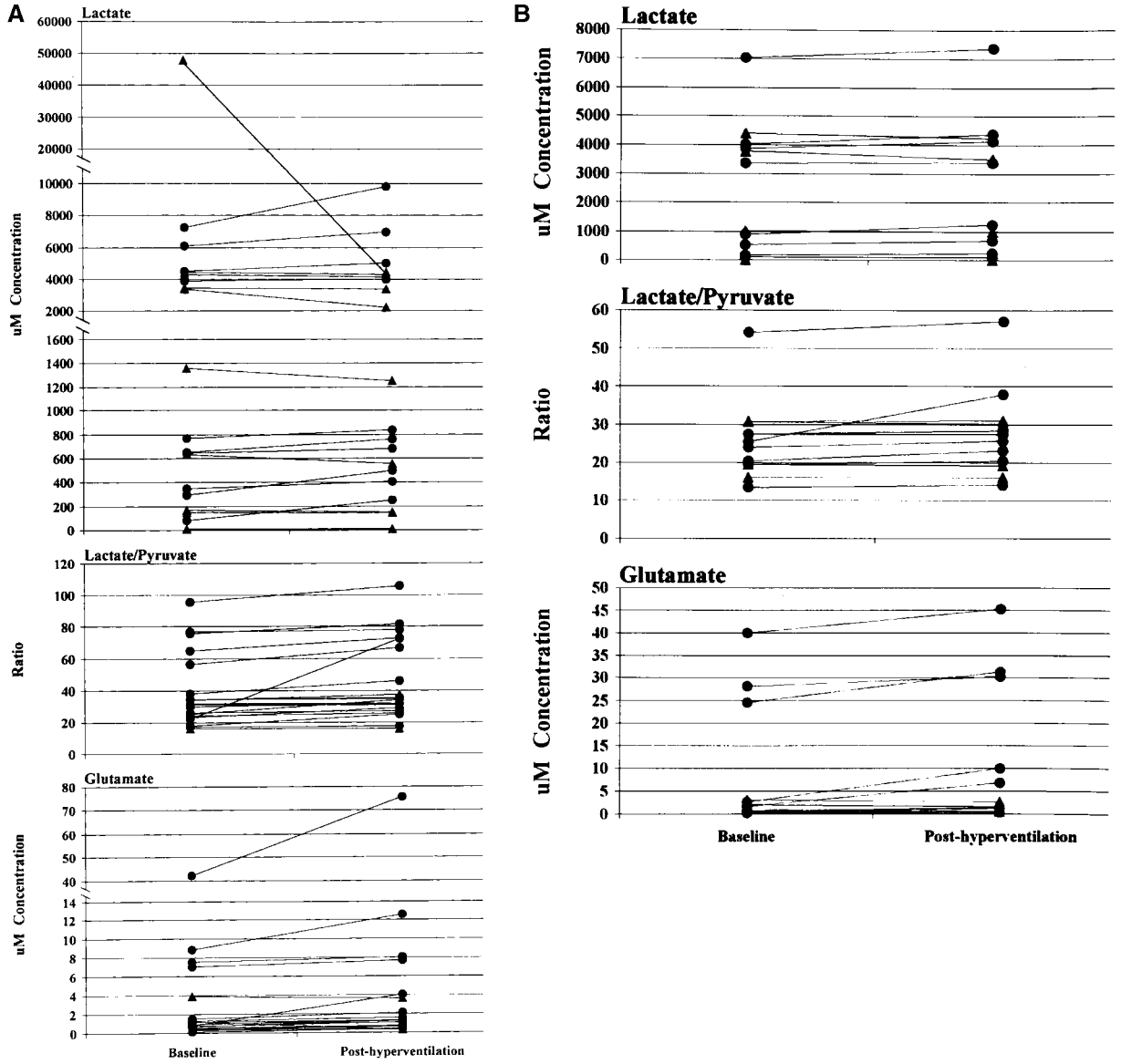


Figure 2. Maximum increase or decrease in actual dialysate concentrations of lactate and glutamate, and in the lactate/pyruvate ratio, during the 4 hr period of observation following 30 mins of hyperventilation. *A*, data from the trial at 24–36 hrs and *B*, from the trial at 3–4 days. *Circles*, patients with an increase following hyperventilation; *triangles*, patients with a decrease in metabolite concentrations.

None of these variables were found to have a significant influence on hyperventilation-induced changes in the extracellular metabolites and local CBF with one exception: during the trials at 3–4 days after injury, a significant association between elevated ICP and elevated posthyperventilation glutamate concentrations was observed ($p = .005$). Mean CBF, lactate, glutamate, and lactate/pyruvate concentrations pre- and posthyperventilation were not significantly different for the seven patients treated with hypothermia compared with the 13 normothermic patients at 24–36 hrs after injury.

## DISCUSSION

We conducted this study using *in vivo* microdialysis to allow sampling of extracellular metabolites and correlation of changes in those compounds with local CBF changes caused by hyperventilation. We found that hyperventilation for 30 mins led to a significant increase in extracellular lactate and glutamate concentrations and in the lactate/pyruvate ratio at 24–36 hrs after injury and, with the exception of the lactate/pyruvate ratio, at 3–4 days. A significant decrease in the local CBF only was observed at the later time point, however. While the majority of patients had an increase in dialysate glutamate concentrations of >10% following hyperventilation, the absolute increase in dialysate concentrations of this metabolite often remained within published normal values (18). We found that hyperventilation was more likely to be associated with an increase in extracellular glutamate and was less likely to cause an increase in lactate concentrations and the lactate/pyruvate ratio on days 3–4 after injury than at 24–36 hrs after injury. We also found a larger hyperventilation-associated decrease in local CBF and a higher proportion of patients with partially preserved $CO_2$ vasoresponsivity

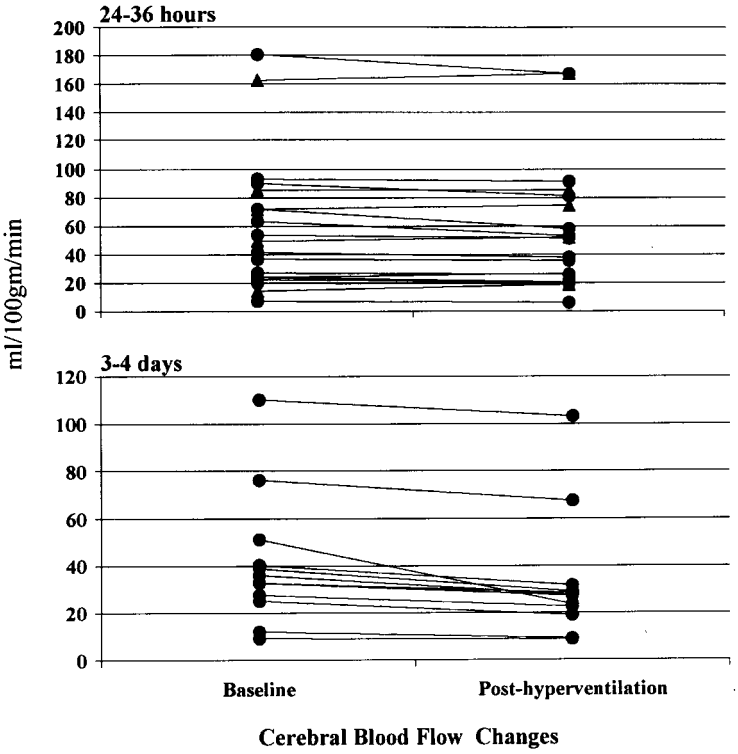


Figure 3. The maximum decrease, or increase, in local CBF during the 4 hrs after hyperventilation are depicted for the 20 patients studied at 24–36 hrs after injury and the 13 patients studied at 3–4 days after injury. *Circles*, patients with a decrease after hyperventilation; *triangles*, patients with an increase in local CBF.

at the later time point. However, we found no correlation between the presence or absence of $CO_2$ vasoresponsivity and significant increases in any of the extracellular metabolites at either time point after injury. These findings are consistent with those of our previous report of 12 patients with severe TBI (20), and both studies appear to support our hypothesis that CBF information alone is not sufficient to detect regional ischemia as had been suggested by others (7, 21).

Microdialysis has been used to monitor cerebral metabolism in TBI patients for more than a decade, but there remain important limitations of the technology that limit its use to a few highly specialized research programs. The degree to which dialysate concentrations of small hydrophilic molecules accurately reflect the extracellular concentrations of those molecules (the recovery rate) depends not only on the concentration gradient of those molecules over the semipermeable membrane but also on several predictable and unpredictable variables. The predictable variables include the membrane pore size (molecular weight cutoff), the length of the exposed membrane (active end), and the perfusion rate. Unpredictable or dynamic variables that also can effect the recovery rate include the temperature of the tissue being monitored, interstitial diffusion characteristics, size of the interstitial compartment, and inflammation or gliosis related to injury caused by catheter insertion.

To estimate our recovery rates for glutamate, lactate, and pyruvate, we measured *in vitro* recovery rates with the dialysis catheter placed in standard solutions of these molecules for all of our catheters after they were removed on completion of the study. Using the same perfusion rate we used for the *in vivo* studies (2 μL/min), our *in vitro* recovery rate for glutamate was 34%, for lactate 62%, and for pyruvate 63%.

The influence of the dynamic variables associated with *in vivo* microdialysis on our recovery rates is difficult if not impossible to predict since the recovery rate of microdialysis catheters cannot be directly determined once they are inserted. In an effort to address this issue, Ronne-Engstrom et al. (22) compared recovery rates of urea from microdialysis catheters placed in the brain and abdominal subcutaneous tissues in a series of patients with TBI and cerebral vascular disease. Comparisons of 2414 pairs of dialysate urea samples obtained from these catheters over the course of up to 6 days of continuous dialysis yielded a correlation coefficient of .88. The correlation coefficient for simultaneous brain dialysate and blood urea comparisons over the same time interval was .89. Since glutamate, lactate, and pyruvate are small hydrophilic molecules similar in diffusion characteristics to urea, the authors concluded that changes in brain dialysate concentrations of those molecules were closely related to changes of their concentrations in the extracellular environment.

In addition, we believe that the design of our study minimized the potential influence of interstitial factors on our recovery rates because we did intrapatient comparisons over a maximum of 4 hrs. Significant changes in local edema, temperature, or gliosis are unlikely during that period of time. Also, we report dialysate rather than extrapolated extracellular concentrations of glutamate, lactate, and pyruvate and simply suggest that the changes in dialysate concentrations reflect changes in the extracellular concentrations of these molecules. We agree with others that it is not possible to reliably calculate the actual extracellular concentrations of these molecules from *in vitro* recovery rate determinations.

Our finding that more than half (14 of 20) of the patients at 24–36 hrs had $CO_2$ vasoresponsivity of $<1\%$ in the brain tissue surrounding contusions appears to conflict with our previous report of the integrity of vasoresponsivity within and surrounding contusions (19). In that study of seven patients (ten contusions), we evaluated $CO_2$ vasoresponsivity in the rim of tissue surrounding contusions with xenon-enhanced CT CBF studies. We found that $CO_2$ vasoresponsivity was $<1\%$ in only one of the cases and ranged from 0.4% to 9.1%. However, there are several important differences between the two studies. With xenon/CT CBF techniques, we measured blood flow in a much larger volume of brain tissue: 20.7–85.5 mL vs. the estimated 2 cm of cortex monitored with the thermodiffusion flow probe. It is possible that a much larger proportion of relatively normal tissue was included in the volume measured with xenon/CT CBF studies. A second important distinction is that none of the patients in the first study (xenon/CT CBF) had contusions that were severe enough to require surgical evacuation at the time of study, whereas all of the patients in the present study underwent surgical re-

*We therefore continue to recommend that the acute care of patients with severe traumatic head injury focus on enhancing cerebral perfusion and avoiding therapies with the potential to cause ischemia, such as aggressive hyperventilation, whenever possible.*

moval of their contusions before study. Thus, one might expect that the tissue surrounding the contusions in the current study was more severely damaged.

It is possible that other factors confounded our interpretation of these data. For example, it could be argued that extraordinarily high concentrations of glutamate or lactate in the tissue surrounding a severe hemorrhagic contusion are not affected by therapeutic interventions such as hyperventilation. However, others have shown that barbiturate therapy can significantly reduce the extracellular glutamate concentrations (23). An increase in the inspired oxygen to 100% also has been shown to cause demonstrable decreases in extracellular lactate (24). An alternative interpretation of our results, and one that we favor, is that the extraordinarily high concentrations of extracellular lactate are associated with abnormalities of cerebral $CO_2$ vasoresponsivity. As a result, hyperventilation does not lead to the degree of vasoconstriction that might be predicted for the normal cerebral vasculature. None of our patients had as much as a 3% decrease in local CBF/torr decrease in $Paco_2$ at 24–36 hrs after injury, and only two of 13 patients had this level of vasoresponsivity by days 3–4.

## CONCLUSION

The use of even brief periods of hyperventilation during the first 4 days after a severe TBI can significantly increase extracellular lactate and glutamate concentrations and the lactate/pyruvate ratio in selectively vulnerable regions of the brain. Patients appear to be most at risk for these hyperventilation-induced changes during the first 24–36 hrs after injury and less so by 3–4 days after injury. In our study, these changes were not associated with a significant decrease in local CBF.

We emphasize that this study was not designed to evaluate the effect of brief or prolonged hyperventilation on clinical outcomes. Although we found no correlation with worse 6-month outcomes and elevated dialysate concentrations of glutamate, lactate, or the lactate/pyruvate ratio, the possibility that such a correlation exists cannot be reliably excluded in a study of only 20 patients. At least one prospective trial has demonstrated worse clinical outcomes with the prolonged use of hyperventilation (16), and our study did find a significant elevation of intermediates of secondary brain injury with 30 mins of hyperventilation. We therefore continue to recommend that the acute care of patients with severe TBI focus on enhancing cerebral perfusion and avoiding therapies with the potential to cause ischemia, such as aggressive hyperventilation, whenever possible.

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