

Normobaric hyperoxia–induced improvement in cerebral metabolism and reduction in intracranial pressure in patients with severe head injury: a prospective historical cohort–matched study

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Object. The effect of normobaric hyperoxia (fraction of inspired O₂ [FIO₂] concentration 100%) in the treatment of patients with traumatic brain injury (TBI) remains controversial. The aim of this study was to investigate the effects of normobaric hyperoxia on five cerebral metabolic indices, which have putative prognostic significance following TBI in humans.

Methods. At two independent neurointensive care units, the authors performed a prospective study of 52 patients with severe TBI who were treated for 24 hours with 100% FIO₂, starting within 6 hours of admission. Data for these patients were compared with data for a cohort of 112 patients who were treated in the past; patients in the historical control group matched the patients in our study according to their Glasgow Coma Scale scores after resuscitation and their intracranial pressure within the first 8 hours after admission. Patients were monitored with the aid of intracerebral microdialysis and tissue O₂ probes.

Normobaric hyperoxia treatment resulted in a significant improvement in biochemical markers in the brain compared with the baseline measures for patients treated in our study (patients acting as their own controls) and also compared with findings from the historical control group. In the dialysate the glucose levels increased ($369.02 \pm 20.1 \mu\text{mol/L}$ in the control group and $466.9 \pm 20.39 \mu\text{mol/L}$ in the 100% O₂ group, $p = 0.001$), whereas the glutamate and lactate levels significantly decreased ($p < 0.005$). There were also reductions in the lactate/glucose and lactate/pyruvate ratios. Intracranial pressure in the treatment group was reduced significantly both during and after hyperoxia treatment compared with the control groups ($15.03 \pm 0.8 \text{ mm Hg}$ in the control group and $12.13 \pm 0.75 \text{ mm Hg}$ in the 100% O₂ group, $p < 0.005$) with no changes in cerebral perfusion pressure. Outcomes of the patients in the treatment group improved.

Conclusions. The results of the study support the hypothesis that normobaric hyperoxia in patients with severe TBI improves the indices of brain oxidative metabolism. Based on these data further mechanistic studies and a prospective randomized controlled trial are warranted.

KEY WORDS • brain metabolism • glucose • head injury • hyperoxia • lactate • microdialysis

Depression of cerebral oxidative and glycolytic energy metabolism has frequently been shown in humans and animal models after TBI and has been correlated with poor recovery.^{5,6,23,36,38,62,65} Recently, mitochondrial dysfunction has been viewed as the most likely cause for this metabolic suppression.^{4,14,56,61} It is widely believed that maintenance of cerebral metabolism following TBI is vital for the generation of ATP, which in turn is necessary to reestablish the ionic homeostasis of the disturbed neuronal membrane, protect neuronal integrity, and

reestablish function.⁴⁹ Therefore, strategies to ameliorate posttraumatic cerebral metabolic depression appear attractive as theoretical treatment options. If it is assumed that some, but not all, mitochondria are dysfunctional, appropriate therapies might include protecting the mitochondria,^{3,20} providing supplemental metabolic substrates such as lactate or phosphocreatinine,^{1,27,44} and augmenting O₂ delivery to the injured brain.^{33,45,47}

Since the original work on hyperbaric O₂ therapy, there has been an increasing understanding of the role of free radicals and oxidative damage and a continuing debate about both the beneficial properties of hyperbaric O₂ therapy^{10,29,45,63} and its potentially harmful role as a generator of free radicals.^{11,41} Because hemoglobin is fully saturated at ambient air PaO₂ levels, increasing the O₂ transport to tissues can only be achieved under normal clinical circumstances by increasing nonhemoglobin-bound O₂, which can be

Abbreviations used in this paper: ANOVA = analysis of variance; ATP = adenosine triphosphate; BBB = blood–brain barrier; CPP = cerebral perfusion pressure; FIO₂ = fraction of inspired O₂; GCS = Glasgow Coma Scale; ICP = intracranial pressure; ICU = intensive care unit; L/G = lactate/glucose; L/P = lactate/pyruvate; MCV = Medical College of Virginia; MABP = mean arterial blood pressure; SEM = standard error of the mean; TBI = traumatic brain injury.

TABLE 1

Comparisons of mean ICP during the first 12 hours after injury, mean GCS after resuscitation, and mean age on admission between the historical control and 100% O₂ patients*

Group Comparison	ICP (mm Hg)	GCS Score (postresuscitation)	Age (yrs)
historical control	13.98 ± 3.50	5.2	35.0 ± 17.3
100% O ₂	15.96 ± 3.02	5.8	34.2 ± 19.3
p value	0.06 (NS)	0.8 (NS)	0.08 (NS)

* Values expressed as means ± standard errors. Comparisons are made using ANOVA. Abbreviation: NS = no significance.

achieved by increasing local PO₂ (hyperbaric therapy) or by using nonhemoglobin O₂ carriers such as perfluorocarbons.^{30,45,47} Although the use of hyperbaric O₂ treatment has achieved a reduction in mortality rates following TBI, as an option its feasibility remains limited because human chambers are large, expensive, and available only at a few large medical centers.

Approximately 5 years ago, pilot studies conducted at MCV³⁴ and confirmed by others^{33,42} demonstrated that increased FIO₂ in the early stages of human severe brain injury resulted in significant augmentation of brain tissue PO₂ and, counterintuitively, a concomitant significant reduction in the lactate level in the extracellular fluid of the brain. Similar work in animal models of stroke has confirmed that normobaric hyperoxia attenuates abnormalities identified on diffusion magnetic resonance imaging and reduces infarct volume⁵² without increasing oxidative stress.⁵³ The exact effects of normobaric hyperoxia on cerebral metabolism within the pathophysiology of human TBI, however, remain poorly understood. As a result, controversy over the effectiveness of such an intervention remains.^{7,32}

In this study, which was performed in two large neurosurgical ICUs, we tested the neurochemical and ICP effects of increasing the FIO₂ level to 100% for 24 hours in 52 prospectively admitted patients with severe brain injury and then compared these results with findings in a closely matched cohort of patients with TBI who had been treated without therapy to increase FIO₂. We used intracerebral microdialysis to assess the neurochemical alterations that our interventions had caused in patients in the treatment group. Intracerebral microdialysis is well established as a neuro-monitoring tool and has been used extensively in neurotrauma research,^{2,8,21,40,62,66} although there is a continuing debate on the exact interpretation of microdialysis values, especially as a guide to clinical management.^{25,48} Analyses of extracellular levels of glutamate, glucose, lactate, and pyruvate, however, have provided us with the only available continuous and dynamic "window" with which to assess human cerebral metabolism. It has been well recognized that after stability of the dialysate has been achieved any increase in glutamate in the dialysate, especially if associated with low glucose and high lactate levels, can be viewed as a hallmark of local ischemia or another high metabolic demand activity such as a seizure.^{8,15,17,48} Increased levels of lactate or glutamate and/or the disappearance of glucose in the dialysate have all been correlated with poor outcome.^{21,62} Moreover, especially under experimental conditions, an increase in the extracellular glucose has been correlated with cellular recovery.¹³ The value of pyruvate in the dialysate is not

well understood, but the L/P ratio is a well-known marker of the cellular redox state^{21,40} and increasing values (especially if > 20) have been considered indicative of ischemia. The L/G ratio, with normal values lower than 2, has been proposed as more indicative of mitochondrial function¹⁴ and, given that in the dialysate levels of lactate and glucose tend to move in opposite directions during true pathophysiological events, the L/G ratio can be a useful means of compensating for changes in tissue characteristics.^{5,21} The aim of our study was to investigate the effects of normobaric hyperoxia on these cerebral metabolic indices of TBI.

Clinical Material and Methods

Patient Population

During a period of 2 years, 52 consecutive patients with severe TBI (31 patients at MCV Hospital in Richmond, Virginia, and 21 at the Inselspital, University of Bern, Switzerland) were treated with normobaric hyperoxia (FIO₂ = 100%) for a period of 24 hours, starting within 6 hours after their admission to the neurosurgical ICU. The internal review boards at both institutions approved the treatment protocols and informed consent was obtained in all cases from patients' relatives before commencement of treatment. Inclusion criteria specified that any patient older than 16 years of age with severe TBI who was admitted to the ICU following intubation and ventilation and had at least one reactive pupil and no concomitant chest injury or respiratory ailment would be offered the increased inspired O₂ treatment protocol, provided that microdialysis monitoring, ICP monitoring, and brain tissue O₂ monitoring were also performed.

Control Cohort

The historical cohort population was selected from the Richmond Neuromonitoring Database, which includes neuromonitoring data obtained in more than 260 patients with severe TBI who have been admitted to the hospital of MCV since 1993. A cohort of 112 patients with severe TBI was selected. Neuromonitoring had been performed in these patients by using microdialysis and brain tissue O₂ sensors while the patients were receiving standard care for the TBI. The cohort was matched with the treatment population (100% O₂; Table 1) for age, sex, postresuscitation GCS scores, and mean ICP in the first 12 hours postinjury. Patients in whom the microdialysis probe was inserted next to a cerebral contusion (either inadvertently or by design) were excluded from the control group (18 patients).

Neuromonitoring of Patients

All patients at MCV received an intraventricular catheter for ICP monitoring and cerebrospinal fluid drainage and a microdialysis probe (CMA/Microdialysis AB; Solnar, Sweden). All patients in Bern received similar ICP monitoring, but only 11 received a microdialysis probe. All Bern patients were monitored with the aid of a Licox tissue PO₂ sensor (Integra Life Sciences, Plainsboro, NJ) and the MCV patients were monitored using a Neurotrend tissue PO₂ sensor (Diametrics Medical, Inc., St. Paul, MN). Continuous computerized recording of ICP, MABP, and CPP was standard for all patients at both centers. Management was further guided by clinical need. Standard microdialysis probes

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(CMA model 70) were inserted intracranially alongside the intraventricular catheter by using a commercial multiport cranial bolt (Integra Biosciences AG, Churr, Switzerland, or Codman, Raynham, MA) or a polycarbonate skull bolt built to accommodate three lumens.⁶⁶ The infusion rate for sterile 0.9% NaCl solution was set at 2 $\mu\text{l}/\text{minute}$ for the MCV patients and at 0.5 $\mu\text{l}/\text{minute}$ for the Bern patients by using an adjustable flow rate battery-operated pump (CMA model 170). Dialysate samples were collected hourly and frozen immediately (-20°C) until analyzed. Levels of glutamate, lactate, glucose, and pyruvate were determined later by using the CMA model 600 Microdialysis Analyzer.

Microdialysis Recovery Rates

To adjust different flow rates measured at the two centers, we performed an *in vitro* recovery study by using both standard CMA probes, which were perfused with normal saline and the same CMA pumps used in patient neuromonitoring. We measured the recovery rates for all standard dialysate analytes at flows ranging from 0.3 $\mu\text{l}/\text{minute}$ up to 2 $\mu\text{l}/\text{minute}$, using standard solutions of glucose/lactate/pyruvate/glutamate (CMA/Microdialysis AB). The recovery rate at 2 $\mu\text{l}/\text{minute}$ was approximately half of that at 0.5 $\mu\text{l}/\text{minute}$ for all analytes and approximately 35% of the true extracellular concentration (Fig. 1); therefore, we divided all microdialysis values from Bern by a factor of two before entering them in the database.

Statistical Analysis

All data points were collected in a computerized database (> 800,000 data points). The statistical analysis was performed using statistical software (SPSS version 11.0; SPSS, Inc., Chicago, IL). Each data point was assigned a time-after-injury value for analysis and comparisons. All values of the continuously monitored parameters (ICP, CPP, MABP, tissue PO_2 , and the microdialysate analytes [glutamate, lactate, glucose, and pyruvate]) were averaged for every hour postinjury. Thus the numerical value assigned to each hourly point postinjury for each individual parameter during this analysis represents the mean of values recorded for that parameter during that particular hour in the patient group of interest. Two sets of statistical comparisons were made for each parameter tested: first, among the three time periods in the 100% O_2 group alone (patients acting as their own controls) and subsequently between the 100% O_2 group and the historical cohort. Significance was tested using repeated-measures ANOVA and values were presented as means \pm SEMs. Significance was assumed at a probability value of 0.05.

All patients at both institutions were admitted to their respective ICU within 4 hours postinjury and began to receive normobaric hyperoxia treatment within 6 hours after admission and no later than 10 hours postinjury. Using brain tissue PO_2 values, three main analysis periods were defined (Fig. 2): treatment within less than 10 hours postinjury (Period A); treatment between 16 and 34 hours postinjury (Period B); and treatment later than 40 hours postinjury (Period C). These periods were used throughout the analysis for comparisons between the control and 100% O_2 groups. All our comparisons were performed during Period B, well within the normobaric hyperoxia period, so that any variability in enrollment times would not affect our conclusions.

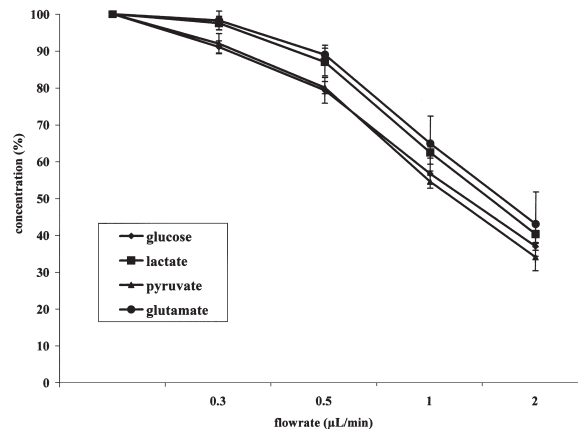


Fig. 1. Graph depicting relative recovery rates at different microdialysis flow rates *in vitro*.

Outcome Assessment

Neurological outcome was assessed at 3 and 6 months postinjury by using the five-point Glasgow Outcome Scale.²⁸

Results

A total of 40 male and 12 female patients (25 male and six female patients at MCV and 15 male and six female patients at Bern) were enrolled in the treatment arm of this study. The mean age in these patients was 34.2 years (range 16–74 years, median 29 years) and the mean GCS score after resuscitation was 5.8 (median 4). The control group consisted of 78 male and 34 female patients with a mean age of 35 years (range 16–90 years, median 32 years). The mean GCS score after resuscitation for the control patients was 5.2 (median 4) (Table 1).

Hyperoxia treatment resulted in significant increases in brain tissue PO_2 between 10 and 37 hours postinjury (Fig. 2). Although there was no significant difference in brain tissue PO_2 between the 100% O_2 group and the control cohort before hyperoxia treatment, brain tissue PO_2 progressively increased after induction of hyperoxia from a mean admission value of 21.8 ± 1.47 mm Hg and peaked in the treatment group between 10 and 16 hours postinjury (mean brain tissue PO_2 57.04 mm Hg ± 4.5 mm Hg in the treatment group and 34.3 mm Hg ± 1.3 in the control group, $p < 0.005$). Brain tissue PO_2 remained significantly elevated for the rest of the hyperoxia period and returned to lower levels at the end of the 24-hour treatment period.

Comparisons of Microdialysate Concentrations Between the Time Periods in the 100% O_2 Patient Group

For this portion of the study each patient served as his or her own control.

Glutamate. The level of glutamate in the dialysate was reduced significantly ($p < 0.001$) on institution of normobaric hyperoxia treatment (Period B: 4.9 ± 1.7 $\mu\text{mol}/\text{L}$), compared with the pretreatment period (Period A: 51.48 ± 26.05 $\mu\text{mol}/\text{L}$) and remained significantly reduced compared with Period A throughout most of the posttreatment period (Period C: 3.12 ± 2.5 $\mu\text{mol}/\text{L}$) (Fig. 3A and Table 2).

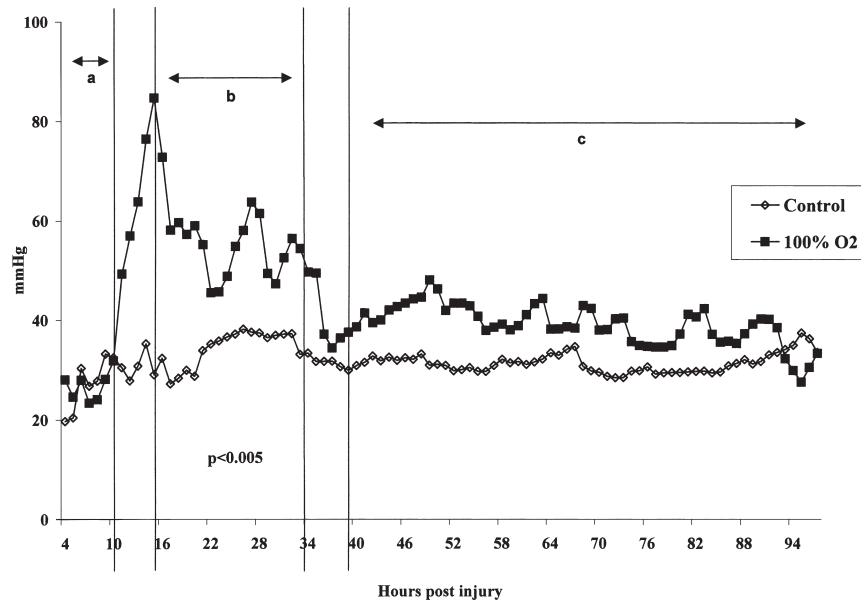


FIG. 2. Graph showing the hourly mean brain tissue PO₂ in the hyperoxia and control patient groups throughout the entire monitoring period. Periods A through C were used for a comparison between groups. The probability value signifies statistical significance when the mean values of patient groups in Period B were compared.

Lactate. The level of lactate in the dialysate declined rapidly and significantly ($p = 0.02$) compared with pretreatment levels after induction of hyperoxia (Period A: $935.87 \pm 53.2 \mu\text{mol/L}$, Period B: $790.7 \pm 28.5 \mu\text{mol/L}$)

and remained reduced even after completion of the hyperoxia treatment (Fig. 3B and Table 2).

Glucose. The mean dialysate concentrations of glucose declined significantly between the pretreatment period and the hyperoxia period and between the hyperoxia and post-treatment periods (Fig. 4A and Table 2). During hyperoxia treatment, however, the rate of decline in the extracellular levels of glucose slowed significantly and resumed a more rapid decline during the posttreatment period.

Pyruvate. The mean pyruvate concentrations were not significantly different during the period of hyperoxia treatment when compared with the pretreatment period (Period A: $21.6 \pm 2.5 \mu\text{mol/L}$; Period B: $23.92 \pm 1.93 \mu\text{mol/L}$; but these concentrations were reduced significantly during the posttreatment period [Period C], $p < 0.005$) (Fig. 4B and Table 2).

Lactate/Pyruvate Ratio. Although the L/P ratio decreased during the treatment period from the high values observed during the pretreatment period (Period A: 41.6 ± 6 ; Period B: 35.5 ± 7.7), this difference was not statistically significant (Table 2).

Lactate/Glucose Ratio. The L/G ratio was already low in the 100% O₂ group during the pretreatment period (1.65 ± 0.06), and the mean values did not change significantly during (1.66 ± 0.22) or after (2.2 ± 0.26) hyperoxia treatment (Table 2).

Comparisons Between the 100% O₂ Group and the Historical Cohort

Glutamate. During pretreatment (Period A) the 100% O₂ group had a significantly higher mean glutamate concentration ($51.48 \pm 26.05 \mu\text{mol/L}$) than the control group ($14.35 \pm 2.1 \mu\text{mol/L}$) ($p = 0.011$). Following the introduction of hyperoxia treatment, a rapid reduction in glutamate concentrations occurred much earlier (by 12 hours com-

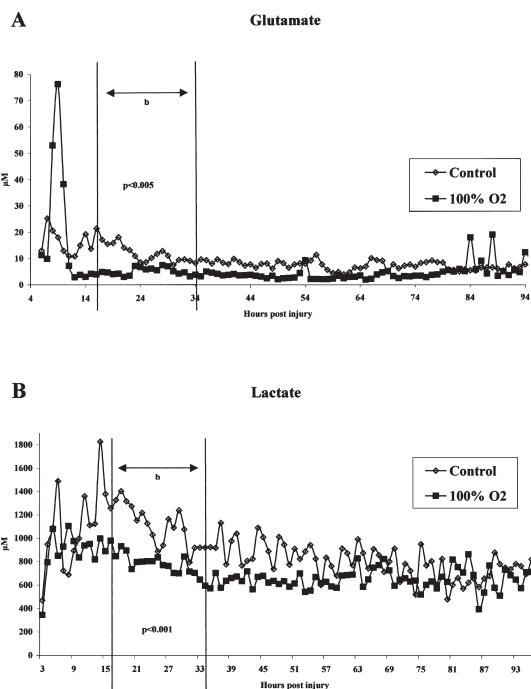


FIG. 3. Graphs demonstrating the hourly mean dialysate concentrations of glutamate (A) and lactate (B) in the hyperoxia and control patient groups throughout the entire monitoring period. Hyperoxia treatment was given during Period B. The probability value signifies statistical significance when the mean concentrations of analytes in the patient groups in Period B are compared.

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TABLE 2
Mean concentrations of analytes in the dialysate and analyte ratios measured in the hyperoxia treatment group: comparison between periods*

Period	Glutamate (μmol/L)	Lactate (μmol/L)	Glucose (μmol/L)	Pyruvate (μmol/L)	L/P Ratio	L/G Ratio
A, pretreatment	51.48 ± 26.05	935.87 ± 53.2	609.23 ± 47.5	21.6 ± 2.5	41.6 ± 6	1.65 ± 0.06
B, treatment	4.90 ± 1.7	790.70 ± 28.5	466.90 ± 20.4	23.92 ± 1.93	35.5 ± 7.7	1.66 ± 0.22
C, posttreatment	3.12 ± 2.5	651.57 ± 15.52	276.24 ± 8.9	18.69 ± 0.9	44.5 ± 2.9	2.20 ± 0.26
p value (A compared w/ B)	<0.001	0.02	0.003	0.59 (NS)	0.16 (NS)	0.16 (NS)
p value (B compared w/ C)	0.1 (NS)	<0.001	<0.001	0.003	0.3 (NS)	(NS)

* Values expressed as means ± SEMs. Comparisons were made using ANOVA.

pared with 24 hours postinjury) and to a significantly lower level compared with the control group ($4.9 \pm 1.7 \mu\text{mol/L}$ in the 100% O₂ group and $11.11 \pm 3.2 \mu\text{mol/L}$ in the control group, $p = 0.05$) (Fig. 3A and Table 3).

Lactate. Levels of lactate in the dialysate were not significantly different between the two groups during the pretreatment period (Period A, $963.5 \pm 76.9 \mu\text{mol/L}$ in the control group and $935.7 \pm 53.2 \mu\text{mol/L}$ in the 100% O₂ group; $p = 0.785$). During Period B, however, during hyperoxia, the 100% O₂ group had significantly lower lactate levels than the control group (Period B, $1102.27 \pm 38.8 \mu\text{mol/L}$ in the control group and $790.7 \pm 28.5 \mu\text{mol/L}$ in the 100% O₂ group; $p < 0.001$). Concentrations of lactate continued to be significantly lower in the 100% O₂ group for more than 12 hours following termination of hyperoxia treatment (Fig. 3B and Table 3).

Glucose. There was no significant difference between the two groups before treatment (Period A, $486.43 \pm 53.9 \mu\text{mol/L}$ in the control group and $590.23 \pm 70.32 \mu\text{mol/L}$ in the 100% O₂ group; $p = 0.295$; Fig. 4A) and the dialysate values declined at similar rates (Fig. 5A). During hyperoxia treatment, however, the mean glucose concentration in the dialysate in the 100% O₂ group was significantly higher than that in the control group (Period B, $369.02 \pm 20.1 \mu\text{mol/L}$ in the control group and $466.9 \pm 20.39 \mu\text{mol/L}$ in the 100% O₂ group; $p = 0.001$; Fig. 4 and Table 3), and the rate of decline in glucose concentration was significantly slower. In the hyperoxia treatment group, glucose concentration decreased four times more slowly (slope -2.9) than in the control group (slope -12.03) (Fig. 5A). Before hyperoxia treatment the level of glucose was increasing in both groups, whereas after treatment the relative rates of change in glucose concentration were almost identical in both groups (Fig. 5A).

Pyruvate. Our treatment population had significantly lower concentrations of pyruvate in the dialysate during the pretreatment period in contrast with the controls (Period A, $p < 0.005$) (Fig. 4B). Hyperoxia treatment resulted in an increase in the dialysate concentration of pyruvate (Fig. 4B and Table 2), whereas during the same period concentrations of this analyte continued to decrease in controls. The rate and direction of change in pyruvate concentration between Periods A and B were, therefore, significantly different between the two groups. In the control population, the mean pyruvate concentration declined between Periods A and B (mean change $-23.23 \pm 5.7 \mu\text{mol/L}$), whereas in the 100% O₂ group there was a significant ($p = 0.05$) increase (mean change $1.84 \pm 3.99 \mu\text{mol/L}$). During Period C, the

microdialysate pyruvate concentration rate of change was similar in both groups.

Lactate/Pyruvate Ratio. On admission (Period A) the 100% O₂ group had L/P ratios that were significantly higher than those found in the control group (Period A, 41.6 ± 6 in the 100% O₂ group compared with 20.35 ± 4.7 in controls; $p = 0.001$). Institution of hyperoxia in the 100% O₂ group resulted in a reduction in the ratio between Periods A and B, whereas in the control population, the L/P ratio increased significantly between the same periods (mean changes: 13.97 ± 0.094 in the control group and -6.04 ± 1.68 in the 100% O₂ group; $p < 0.005$).

Lactate/Glucose Ratio. The mean L/G ratio was not significantly different on admission or during hyperoxia treatment between the two groups, in contrast to the L/P ratio. The L/G ratio declined during hyperoxia in the 100% O₂

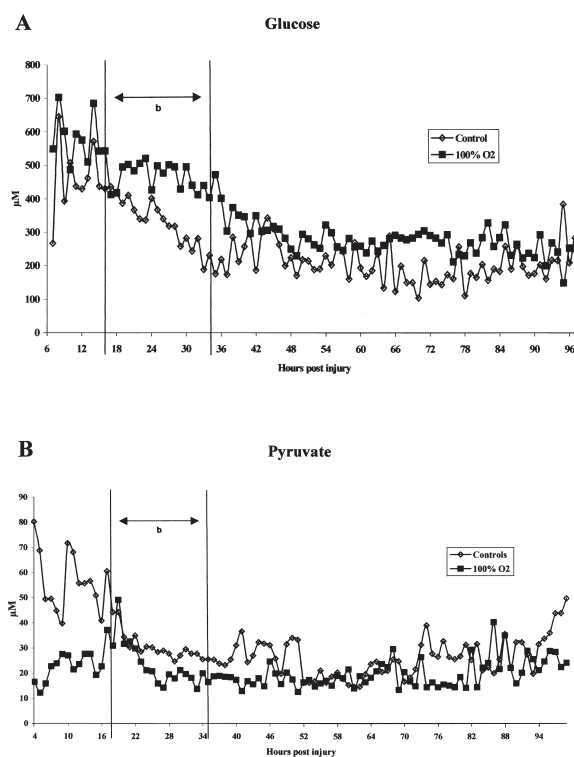


FIG. 4. Graphs demonstrating the hourly mean dialysate concentrations of glucose (A) and pyruvate (B) in the hyperoxia and control patient groups throughout the entire monitoring period.

TABLE 3

Mean concentrations of analytes in the dialysate and analyte ratios measured during normobaric hyperoxia treatment (Period B): comparisons with historical controls*

Group Comparison	Glutamate ($\mu\text{mol/L}$)	Lactate ($\mu\text{mol/L}$)	Glucose ($\mu\text{mol/L}$)	Pyruvate ($\mu\text{mol/L}$)	L/P Ratio	L/G Ratio
historical control	11.11 ± 3.2	1102.27 ± 38.8	369.02 ± 20.10	35.84 ± 8.60	34.33 ± 4.84	3.43 ± 0.68
100% O ₂	4.90 ± 1.7	790.70 ± 28.5	466.90 ± 20.39	24.81 ± 6.95	35.58 ± 7.74	1.66 ± 0.22
p value	0.05	<0.001	0.001	0.4 (NS)	0.24 (NS)	1.19 (NS)

* Values expressed as means \pm SEMs. Comparisons were made using ANOVA. Period B covered 16 to 34 hours postinjury.

group (slope -0.02), whereas it continued to rise in the control group (slope 0.06) (Fig. 5B). Following hyperoxia treatment the rate of change in the L/G ratio was almost equal in both groups (slope 0.05 in the control group, slope 0.03 in the 100% O₂ group).

Intracranial Pressure

In the 100% O₂ group ICP fell significantly after institution of hyperoxia treatment and continued to decrease post-treatment (Fig. 6). There was no significant difference in ICP between the 100% O₂ and control populations during baseline (Period A). During hyperoxia treatment, mean ICP was significantly lower in the 100% O₂ group than in the control group (Period B: 15.03 ± 0.8 mm Hg in the control

group and 12.13 ± 0.75 mm Hg in the 100% O₂ group; $p < 0.005$), and ICP remained lower after the end of hyperoxia treatment and throughout the monitoring period (Period C: 15.6 ± 0.75 mm Hg in the control group and 11.9 ± 0.6 mm Hg in the 100% O₂ group; $p < 0.005$).

Cerebral perfusion pressure did not change significantly between the three periods in the 100% O₂ group (mean CPP for the whole neuromonitoring period 75.2 ± 5.6 mm Hg). There was also no significant difference between CPP values in controls (85.1 ± 3.5 mm Hg) and in the 100% O₂ group.

Outcome Measures

Both at 3 and 6 months postinjury the mean GOS score in the 100% O₂ group was higher than in the control group (3-month GOS Score 3 compared with 2.8, 6-month GOS Score 3.2 compared with 2.8); however, the differences were not statistically significant.

Discussion

Our study clearly demonstrates that normobaric hyperoxia applied early and for a period of 24 hours after severe head injury in patients from two different institutions resulted in the following: 1) significant alterations in the concentrations of several brain microdialysis analytes (lactate, glutamate, pyruvate) and the L/P ratio compared with pre-treatment levels and with microdialysis measurements in a matched historical TBI cohort; 2) a significant reduction in the mean ICP compared with the same historical cohort; and 3) a trend toward improvement in outcome in a patient group that had worse biochemical indications of brain tissue damage on admission, compared with the controls.

To understand these results we need to take into account three interrelated variables: 1) the methodological limitations of microdialysis; 2) our current understanding of cerebral metabolism; and 3) the effects of O₂ on cerebral metabolism and variability within the head injury population.

Human brain microdialysis provides an indirect, but dynamic, time-dependent picture of the cerebral extracellular microenvironment over several days. Our practice of inserting the microdialysis probe into the less affected hemisphere, approximately 10 mm from the ventriculostomy and away from cerebral contusions, provides us with a global measurement that reflects changes affecting the whole brain.^{9,54} The composite picture provided by microdialysis in this way can be viewed as a dynamic glimpse of the effects of brain metabolism fluctuations on the composition of the extracellular environment.

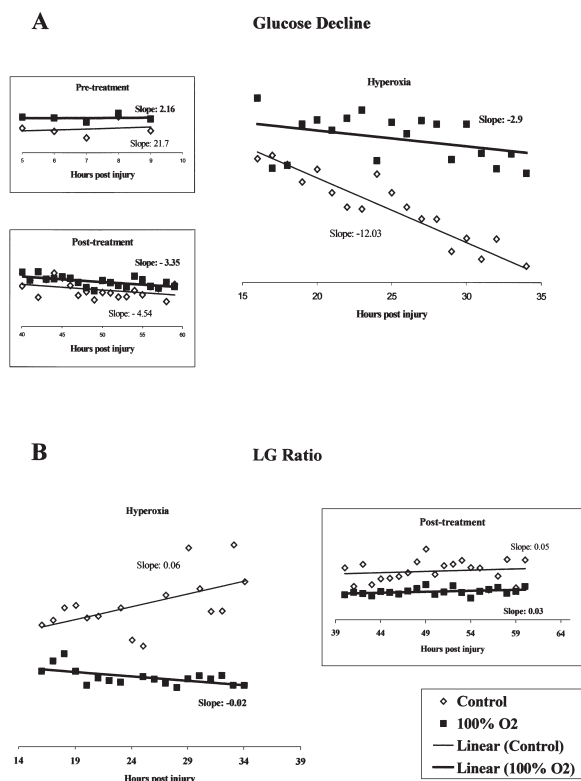


FIG. 5. A: Graphs showing the rate of decline in the glucose concentration of the dialysate in the hyperoxia and control groups before, during, and after treatment. B: Graphs demonstrating the rate of decline in the L/G ratio in the hyperoxia and control groups before and after treatment.

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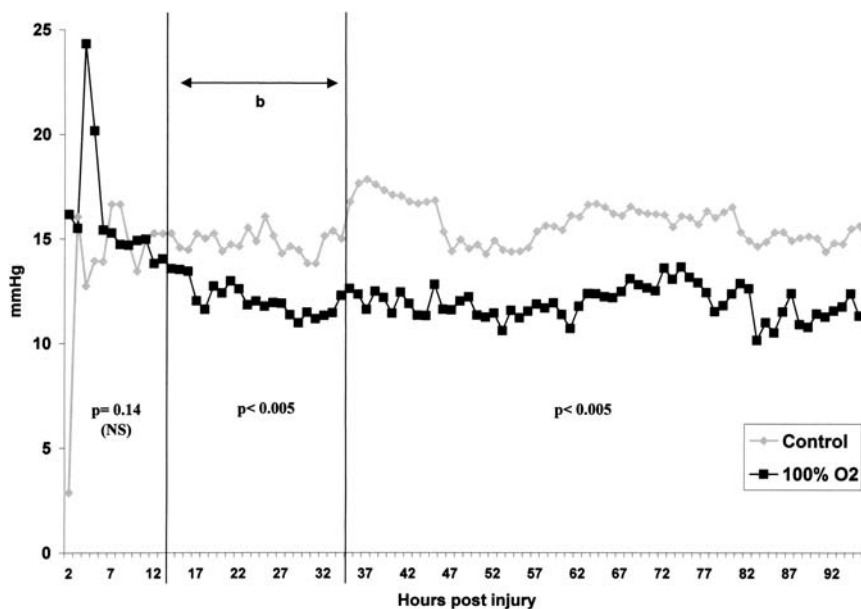


FIG. 6. Graph demonstrating the hourly mean ICPs in the hyperoxia and control patient groups throughout the entire monitoring period. The probability values signify statistical significance when mean concentrations of ICP in the patient groups were compared in each period.

In severe head injury, as we and others reported earlier, the largest fluctuations in concentrations of microdialysate analytes occur mainly during the first 24 to 48 hours postinjury, and these variations are more pronounced in the most severely injured patients.^{8,21,62} By 48 hours postinjury the dialysate analytes have settled to relatively low levels in the majority of patients and, as a rule, acute changes signify a neurological crisis, for example, ischemia, seizure, or hematoma progression.^{21,62} Outside of these periods of metabolic crisis, we and many other authors have documented a relatively consistent gradual normalization of changes in dialysis analyte.^{8,21,43} This underlying analyte behavior, inherent in TBI and/or reflected by changes in microdialysis recovery, can be seen in our control population and has to be taken into consideration when interpreting the effects of any therapeutic intervention in these patients.

It has long been recognized that ischemia is an important component in the pathophysiology of TBI.^{18,35,67} Ischemia results in the anaerobic metabolism of glucose (hyperglycolysis) and the release of lactate. A high level of extracellular lactate has been viewed as a marker of anaerobic metabolism and significant increases in this substance have been demonstrated in the brains of patients following severe TBI and stroke.^{26,50} Such episodes of lactate increase are usually seen in cases of terminal herniation and/or severe ischemia associated with both trauma and subarachnoid hemorrhage.^{25,57,62} In such cases massive increases in the extracellular level of lactate are followed by the virtual disappearance of glucose from the dialysate and are accompanied by significant increases of the L/P ratio. Apart from these crisis periods, however, the dialysate level of glucose is usually detectable, although it is approximately 40% lower than that found in the normal mammalian brain,^{3,43,51} and gradually declines with time until a steady state is achieved.

In our control population, by 48 hours postinjury, the mean glucose concentrations in the dialysate had reached approximately half that of values measured during the first

24 hours postinjury. Probe dysfunction (for example, progressive surface gliosis) was probably not a factor during this short period, as has been demonstrated by other researchers.^{46,62} Moreover, throughout our 4-day monitoring period, any metabolic crises resulted in fast and significant changes in analyte values in individual patients, even days after injury. Focal microenvironmental changes cannot be excluded, but, in agreement with other investigators,⁶² no computerized tomography–demonstrated low-density lesions had occurred in the area of probe insertion on follow-up imaging.

An attractive hypothesis to explain these changes would be the progressive dysfunction of cerebral glucose metabolism, which has been demonstrated in both animal models of head injury and human patients with TBI.^{9,21,62} This metabolic dysfunction is incompletely understood, but the massive metabolic load imposed by the ionic flux of TBI is known to increase glucose use against a background of reduced O₂ consumption.^{6,65} This process is in agreement with the so-called compartmentalization theory of energy utilization in the brain, with functional coupling of astrocytes and neurons.³⁹ Astrocytes are known to use glucose either from their own glycogen stores or directly across the BBB, through their perivascular foot processes.⁵⁵ Glucose can be metabolized anaerobically into lactate, which is released directly into neurons and is subsequently metabolized aerobically. No change in the extracellular levels of glucose would be evident under such conditions.⁵⁵ Following injury, due to the concomitant augmented release of excitatory amino acids such as glutamate, the rate of glycolysis in astrocytes rapidly increases.³⁹ Initially no reduction in the extracellular level of glucose would be evident because astrocytic processes (the main component of the BBB) have not yet been affected by edema, particularly in areas away from the ischemic penumbra of contusions, and thus astrocytes can continue to use glucose directly from the circulation. We speculate that such conditions exist early after human

TBI and might explain, at least in part, the relatively high extracellular levels of glucose observed at this point. This astrocytic hyperglycolysis would result in increased lactate production, which can be only partially used aerobically by the neurons because of their concomitant mitochondrial dysfunction.^{14,64} This hypothesis is also supported by the finding of high levels of pyruvate in the dialysate and by the low L/P ratios.⁶² This neurochemical picture was present in the early postinjury period in our own control population.

Glucose in the Dialysate

As the postinjury period progresses the gradual decrease in the extracellular level of glucose, as measured by microdialysis, that we see in the control population is more difficult to explain. We speculate that this may be evidence of accelerated regional glucose utilization especially by astrocytes, but also possibly by neurons (using their own glycolytic processes). This hypothesis is consistent with the fact that L/P and L/G ratios remained low during the same period and would agree with the microdialysis findings of Vespa and associates⁶² and with the increase in the rate of cerebral glucose utilization following TBI reported by Bergsneider, et al.⁶ The resulting net decrease in extracellular glucose can thus best be understood by considering both availability and demand. Glucose is transported into the brain cells by saturable carrier mechanisms¹⁸ and, although neuronal transporters are upregulated after TBI, the same may not be true for astrocytic ones.²² Transport may be also complicated by the effects of postinjury edema, which may reduce glucose uptake from blood vessels. The presence of edema may be associated with an increased uptake of glucose from the reduced extracellular space and thus may explain the reduction in glucose in the dialysate.

Lactate in the Dialysate

The gradual decline in lactate in the dialysate, which we also observed in the control population, may be easier to explain. As the ionic shifts caused by TBI become normalized and mitochondrial function improves, more lactate is consumed by both neurons and astrocytes.^{21,36,62} Moreover, general patient improvement results in a concomitant lowering of blood lactate and thus a further reduction in the direct transport of lactate across the BBB into the extracellular fluid and also into astrocytes.¹² These explanations are, moreover, in agreement with the observation that, in the control population, a rapid decline in the level of lactate started much earlier (approximately 14 hours postinjury) than that in the level of glucose, which was obvious only after 24 hours postinjury (Figs. 4 and 5).

Effects of Normobaric Hyperoxia

Are the unequivocal changes in dialysate concentrations in the 100% O₂ patient group indicative of a salvage mechanism following TBI and can these changes be beneficial? If we consider what is already known about the effects of increased O₂ tension on brain injury (traumatic or otherwise), we can make the following suppositions.

First, it is well established that increasing the FIO₂ to 100% increases the dissolved portion of O₂ in arterial blood, because hemoglobin is fully saturated even at lower inspired O₂ contents. This normobaric hyperoxia results in

a significant increase in brain tissue (PO₂ tension) as measured using the Neurotrend and Licox sensors in this study (Fig. 2). Although an interpretation of changes in brain tissue PO₂ remains controversial,^{19,29,59} it is becoming increasingly clear that we should view brain tissue PO₂ values as a general depiction of the balance between local tissue O₂ tension, blood flow, anatomy (capillary density, astrocytic swelling), and cellular metabolism.

The critical O₂ tension required for mitochondrial function is extremely low.²⁴ Mitochondrial oxidoreductases are normally not subject to limitations on their reaction rates because the concentration of O₂ that allows a half maximal rate of reaction is far larger than that commonly present in brain tissue O₂ under physiological conditions.^{19,60} Only cytochrome c oxidase is normally saturated with its substrate. Because brain tissue PO₂ is commonly marginal or substantially reduced following TBI,⁵⁸ we speculate that the increased tissue O₂ tension achieved in this study (and also with hyperbaric O₂ therapy) may be sufficient to augment mitochondrial function significantly via substrate-dependent mitochondrial enzyme systems.^{34,42} Moreover, in our own animal studies brain tissue O₂ consumption and concomitant ATP generation also increased significantly following fluid-percussion injury in a rat after the combined administration of O₂ (50% FIO₂) and intravenous lactate.^{16,31}

Second, if we assume that the microdialysis probes monitored brain tissues with preserved astrocyte–neuron coupling, an increase in aerobic lactate consumption (presumably by neurons) would reduce the need for hyperglycolysis and account for the attenuation of the decrease in the level of glucose in the dialysate that was observed during hyperoxia treatment. This assertion is further supported by the accelerated decline in the L/G ratio that was concurrently observed.

Third, the decrease in the L/P ratio among patients who received hyperoxia treatment from the high values measured on admission (in contrast to the trends observed in the control population) can be explained as indicative of an improvement in the cerebral redox state.

Fourth, improved cerebral function may also be reflected by the significant and sustained reduction in the extracellular concentration of glutamate during and after hyperoxia treatment. This reduction could be explained by either a reduced excitotoxic load or an improved glutamate uptake; both would be consistent with an overall improvement in brain function.

Fifth, hyperoxia has been known for some time to cause local vasoconstriction in normal brain and paradoxical elevations of blood flow in ischemic areas.^{18,37} This shunting effect may account for some of the overall improvement in lactate values. This effect would not be immediately reflected in the microdialysis values as we monitor nonischemic brain areas, but it could have a bearing on overall brain recovery and ICP reduction.

Finally, the timing and duration of hyperoxia treatment in our study may be of vital importance for observing significant alterations in dialysate values and in achieving favorable results after TBI. Application of the high concentration of FIO₂ as early after injury as possible may influence the transition toward increasing glucose metabolism, as well as reduce early transient episodes of ischemia. The efficacy of early administration of FIO₂ has been reported in experimental stroke studies^{52,53} and may also offer an explanation

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for the lack of effectiveness of hyperoxia in the recent study conducted by Magnoni, et al.,³² in which hyperoxia treatment was initiated more than 45 hours postinjury.

Clearly, however, an improvement in cerebral neurochemistry may not translate into improved neuronal function or outcome. Our study was not designed to investigate outcome, but the trends in patient outcome were favorable; the significant reduction in the mean ICP in the treatment group, which was sustained throughout the monitoring period, even after hyperoxia treatment had ended, indicated that the improved cerebral neurochemistry may correlate with significant clinical effects as well.

This study was not randomized and we therefore caution that interpretation of the results must take into account inherent biases inevitable in such a design. We chose a control cohort while blinded to neurochemical values so that we could clinically match the patients undergoing hyperoxia therapy. We demonstrated a significant improvement in dialysate values and in ICP, even though the control cohort was less neurochemically injured before treatment. The sizes of the groups were the largest reported to date for such a neurochemical study and our findings support those of three previous publications on the subject.^{33,34,42} Nevertheless, more studies need to be performed in humans to show that increased ATP generation occurs during hyperoxia (positron emission tomography and magnetic resonance spectroscopy studies), and a large randomized trial should be conducted to investigate the effects of hyperoxia on ICP and outcome.

Conclusions

We have demonstrated that early application of normobaric hyperoxia following severe head injury resulted in a significant improvement in the microdialysate indices of cerebral metabolism, as well as in a significant reduction in ICP compared with a matched historical cohort. These findings support the importance of cerebral metabolism in the pathophysiology of severe TBI and strongly support the need for a randomized trial on the use of normobaric hyperoxia in treatment protocols used in these patients.

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