Increased inspired oxygen concentration as a factor in improved brain tissue oxygenation and tissue lactate levels after severe human head injury

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Object. Early impairment of cerebral blood flow in patients with severe head injury correlates with poor brain tissue O₂ delivery and may be an important cause of ischemic brain damage. The purpose of this study was to measure cerebral tissue PO₂, lactate, and glucose in patients after severe head injury to determine the effect of increased tissue O₂ achieved by increasing the fraction of inspired oxygen (FiO₂).

Methods. In addition to standard monitoring of intracranial pressure and cerebral perfusion pressure, the authors continuously measured brain tissue PO₂, PCO₂, pH, and temperature in 22 patients with severe head injury. Microdialysis was performed to analyze lactate and glucose levels. In one cohort of 12 patients, the PaO₂ was increased to 441 ± 88 mm Hg over a period of 6 hours by raising the FiO₂ from 35 ± 5% to 100% in two stages. The results were analyzed and compared with the findings in a control cohort of 12 patients who received standard respiratory therapy (mean PaO₂ 136.4 ± 22.1 mm Hg).

The mean brain PO₂ levels increased in the O₂-treated patients up to 359 ± 39% of the baseline level during the 6-hour FiO₂ enhancement period, whereas the mean dialysate lactate levels decreased by 40% (p < 0.05). During this O₂ enhancement period, glucose levels in brain tissue demonstrated a heterogeneous course. None of the monitored parameters in the control cohort showed significant variations during the entire observation period.

Conclusions. Markedly elevated lactate levels in brain tissue are common after severe head injury. Increasing PaO₂ to higher levels than necessary to saturate hemoglobin, as performed in the O₂-treated cohort, appears to improve the O₂ supply in brain tissue. During the early period after severe head injury, increased lactate levels in brain tissue were reduced by increasing FiO₂. This may imply a shift to aerobic metabolism.

Key Words * brain metabolism * brain tissue oxygenation * glucose * head injury * hyperoxia * lactate

Secondary cerebral ischemia resulting in secondary brain damage is one of the major factors influencing prognosis and outcome in patients with severe head injury.[4,50,55] Histopathological examination of the brain tissue in 80 to 90% of the patients who die shows ischemic damage.[21,22] In animal models and human studies it has been shown that this ischemia is partly caused by a severe reduction in cerebral blood flow (CBF). Such a reduction during the very early period after the primary injury affects approximately 35% of patients with severe head injury and is worse in patients with brain swelling and subdural hematoma.[4,5,14,37,42] At the same time, the metabolic needs of injured brain tissue seem to be increased in this early phase. Glucose use may be a major source of energy-rich phosphate (adenosine triphosphate) production in neuronal tissue and is markedly stimulated in the early phase after primary brain injury. It may be followed by a severe reduction in glycolysis 7 to 10 days later.[3,31,62] This metabolic activation is at least in part caused by the need to restore ionic homeostasis immediately after the cerebral impact.[7,15,28,31,48] Bergsneider, et al.,[3] have demonstrated in an elegant positron emission tomography study in humans that increased glycolysis after severe head injury affects 30 to 40% of patients and is both locally adjacent to cerebral lesions as well as global in some cases. This has also been shown in animal models.[26,62]

When both phenomena (CBF reduction and metabolic stimulation) appear together, the result is a flow/metabolism mismatch. A concomitant increase in lactate in brain tissue, which is very common after severe head injury, probably indicates a shift from aerobic to anaerobic metabolic pathways in the neurons and astrocytes and may signify this flow/metabolism mismatch.[1,20,55,57] These processes may precede the delayed events of neuronal death, either by necrosis or possibly by apoptosis in certain circumstances.[26,47,55,57,65]

Recently, this knowledge about the pathogenesis of delayed secondary brain injury has led to attempts to establish better monitoring methods in patients to provide information about substrate delivery and the metabolic status of injured brain tissue. Over the last 2 years we and others have accumulated considerable experience in measuring brain O_2 delivery, using new microsensor technology combining a Clark PO_2 electrode, with CO_2 , pH, and temperature sensors in a single 0.5 X 25-mm fiber. We have shown that low brain tissue PO_2 occurs in approximately 25 to 30% of patients with severe head trauma in the first 12 hours postinjury. Low brain tissue PO_2 also closely correlates with low regional CBF.[18] Recently, we have combined microdialysis, using a 10 X 1-mm flexible probe with the multiparameter sensor to provide detailed, semicontinuous comprehensive local metabolic and substrate monitoring in focal zones of cerebral tissue.[17,18,64,65] This system has allowed us to measure brain PO_2 , PCO_2 , pH, and lactate and glucose in extracellular fluid in approximately 60 patients.

We have shown that during the 1st day posttrauma, brain PO_2 is frequently lower when compared with measurements obtained on subsequent days and is strongly correlated with high levels of dialysate lactate in the brain. We have therefore speculated that therapies that increase brain PO_2 immediately after severe head injury may be beneficial and may also lower local dialysate fluid lactate.[64] Increasing the concentration of inspired O_2 (FiO_2) to 100% during artificial ventilation has been reported to induce a rise in brain PO_2 values, both in animal studies and in humans.[44,53,58] The aim of our study was therefore to measure tissue oxygenation and brain dialysate lactate and glucose levels during the early period after severe head injury in patients who were treated according to a standard protocol of normoxia and normocapnia and to compare these levels with readings in patients to whom a period of supernormal

normobaric arterial O₂ tensions was administered at 1 atm (FiO₂ 100%).

CLINICAL MATERIAL AND METHODS

Patient Population

These studies were approved by the Committee for Conduct of Human Research of the Medical College of Virginia (MCV) and Virginia Commonwealth University. Twenty-four patients older than 16 years of age who were admitted to the neuroscience intensive care unit (ICU) at MCV with severe head injury and a Glasgow Coma Scale (GCS) score of 8 or less were included in this study (Table 1). Informed consent for the studies was given by a relative prior to microdialysis. We excluded patients for whom consent could not be obtained, those who were brain dead or close to brain death at admission, and those with lung contusion or pneumonia.

TABLE 1						
CHARACTERISTICS OF 24 PATIENTS WITH SEVERE HEAD INJURY ACCORDING TO VARIOUS MEASURES AT THE BEGINNING OF THE 6-HOUR OBSERVATION PERIOD*						
Case No.	Age (yrs), Sex	Initial GCS Score	Injury	Repeated CT Findings	Mean Lactate (mmol/L)	Mean PO ₂ (mm Hg)
control cohort						
1	30, M	3	diffuse swelling	SAH	777 ± 120	5 ± 1
2	31, M	6	diffuse swelling		3168 ± 330	13 ± 2
3	34, F	7	diffuse swelling		1213 ± 288	33 ± 1.5
4	32, M	7	diffuse swelling		1366 ± 370	18 ± 1
5	29, M	7	contusion		221 ± 15	23 ± 2.5
6	36, M	7	contusion	EDH	750 ± 80	31 ± 2
7	50, M	4	contusion	SAH	323 ± 48	21 ± 1.8
8	50, M	3	diffuse swelling	SDH	759 ± 122	21 ± 3.2
9	20, M	3	contusion		1272 ± 30	18 ± 1
10	37, M	5	contusion		1810 ± 370	40 ± 3
11	25, M	5	diffuse swelling	SDH	674 ± 55	36 ± 3.5
12	24, M	6	diffuse swelling	EDH	949 ± 138	33 ± 4
mn	33.2 ± 9.2	5.2 ± 1.7			1106 ± 787	24.3 ± 10.3
oxygen cohort						
1	20, M	7	contusion	SDH	3640 ± 658	38 ± 1.7
2	23, M	6	diffuse swelling	SDH	1005 ± 158	37 ± 3.5
3	22, M	7	diffuse swelling	SDH	1414 ± 62	30 ± 3
4	47, M	6	contusion	EDH	680 ± 24	35 ± 9
5	57, M	7	contusion	SDH	2223 ± 120	21 ± 2.2
6	74, M	3	diffuse swelling	SDH & EDH	1181 ± 248	15 ± 2
7	38, M	4	contusion	SDH	800 ± 173	17 ± 1.1
8	38, M	4	contusion		870 ± 26	23 ± 5.7
9	24, M	8	diffuse swelling	SDH	1463 ± 186	22 ± 0.6
10	22, M	3	diffuse swelling	SDH	906 ± 68	36 ± 1
11	38, M	8	contusion	SDH	934 ± 31	13 ± 3.7
12	24, F	8	diffuse swelling		277 ± 68	26 ± 2.44
mn	35.5 ± 16.8	5.9 ± 1.9			1282 ± 885	26.2 ± 8.9
* Values in the last two columns are for brain tissue lactate and PO ₂ , respectively, and are expressed as the mean ± SD. Abbreviations: EDH = epidural hematoma; mn = mean; SAH = subarachnoid hemorrhage; SDH, subdural hematoma.						

All patients were mechanically ventilated during the entire study period and underwent a ventriculostomy for intracranial pressure (ICP) monitoring. They received intensive cerebral perfusion pressure (CPP)-directed management that emphasized prevention of secondary cerebral insults and prompt evacuation of mass lesions, according to a standard protocol developed at MCV.

Twelve patients were selected as a control cohort; they were treated according to our standard management protocol and underwent cerebral microdialysis. The other 12 patients received a 6-hour administration of supernormal increased arterial O₂ concentration within the first 24 hours after admission to the hospital. Both patient cohorts were closely matched. The factors used to determine the matching of the groups included age, gender, initial GCS scores, average ICP and CPP levels, initial levels of dialysate lactate and glucose, brain PO₂ values, and the time of initiation of the FiO₂ protocol postinjury.

Physiological Parameters

The patients received a local anesthetic and a triple-lumen transcranial bolt was threaded and tapped into the frontal skull by using a 7-mm twist drill hole, either when the patient arrived in the ICU or in the operating room after evacuation of a hematoma, as described by Zauner, et al.[65] The bolt was used to grip and immobilize the ventricular catheter, the microdialysis probe, and the multiparameter sensor.

Monitoring of ICP. A frontal ventriculostomy was performed to measure the ICP by using a commercial ventriculostomy system and external strain gauge sensor.

Continuous Brain PO₂, PCO₂, pH, and Temperature Monitoring. A multiparameter, minimally invasive 0.5 X 35-mm sensor was used for continuous measurements of brain tissue PO₂, PCO₂, pH, and temperature. The device consists of two modified optical fibers for pH and PCO₂ measurements, a miniaturized Clark electrode for PO₂ measurements, and a thermocouple. The sensor is packaged within a tonometer containing buffer solution, which maintains its hydration and serves as a calibration medium. Before insertion into the patient, the sensor was calibrated with sterile, precision gases bubbled in sequence through the tonometer chamber under microprocessor control. The accuracy and precision of the sensor have been validated in previous in vitro and in vivo studies prior to intracranial use in humans.[41,59,63]

Microdialysis Technique

A custom-built 10-mm flexible microdialysis probe with an external diameter of 0.5 mm and a molecular weight cut-off of 20,000 D was sterilized in ethylene oxide. The probe was then inserted into the cortex along with the multisensor. The microdialysis probe was perfused at 2 µl/minute by using sterile 0.9% saline. Sixty-microliter dialysates were collected every 30 minutes into sealed glass tubes by using a refrigerated (4°C) automated collector system. The microdialysis probe was saved after removal for in vitro calibration. Analyte recovery rates were found to be approximately 35% for glucose and 42% for lactate. Glucose and lactate from the collected dialysate were measured offline by using an enzymatic technique.

Patient Groups and FiO₂ Protocol

Control Cohort. Immediately after admission to the ICU a standard protocol of respiratory therapy was administered to the patients and kept constant during the entire observation period. This protocol is

aimed at keeping the FiO_2 sufficient to establish a PaO_2 of approximately 100 to 150 mm Hg. These PaO_2 levels are generally considered to establish normoxic arterial conditions. Thus, 98 to 100% arterial hemoglobin saturation with O_2 can be achieved routinely. The PaCO_2 was kept between 28 and 34 mm Hg.

Arterial oxygenation and CO_2 status were monitored continuously by peripheral pulse oximetry (for peripheral hemoglobin saturation of O_2) and end-tidal CO_2 measurement. Additionally, arterial blood was drawn via a radial arterial catheter and blood gas levels were assessed hourly during the 6-hour observation period.

Oxygen Cohort. Within the first 18 hours after admission to the ICU, standardized PaO_2 enhancement was performed in two stages. The protocol was started as soon as the multimodal monitoring was established and at least 3 hours after stable values were obtained in continuous brain tissue PO_2 monitoring.

First, we determined the necessary FiO_2 to achieve a PaO_2 of approximately 130 mm Hg in each individual. The respiratory settings were then kept constant over a baseline period of 4 hours. The PaCO_2 was kept between 28 and 34 mm Hg for all patients during these studies. In a second step, we increased the FiO_2 to 60% for 3 hours. In a third step, FiO_2 was further increased to 100%, again for 3 hours. At the end of this observation period the FiO_2 was reduced to the individual baseline level.

Statistical Analysis

The ICP, mean arterial blood pressure, end-tidal CO_2 , and peripheral hemoglobin saturation of O_2 were continuously measured and automatically collected every 3 seconds from the bedside ICU monitors into a VAX mainframe computer. The automatically recorded data included brain PO_2 , PCO_2 , pH, and temperature and were downloaded every 5 minutes into a Macintosh personal computer. The intermittent hourly results (dialysate lactate, dialysate glucose, FiO_2 , and clinical events) were then time-locked and added to the software template. The continuously measured data were smoothed by rejecting obviously outlying points and the mean values over each 30-minute interval were calculated.

Commercially available statistical software was used. For comparisons between the characteristic data in both patient cohorts, analyses of variance (ANOVAs) and descriptive statistics were used.[54] Linear Pearson's correlation (r values), logistic linear regression (R values), paired comparisons, and nonparametric tests (Spearman's rank correlation) were also used. For calculating the mean values of the linear correlation coefficients, a Fisher Z-transformation of the individual r values was used. All values are expressed as the mean $\pm$ standard deviation (SD) if not otherwise indicated.

Oxygen Cohort. For analysis we divided the entire observation period into two sections. The first 4 hours of constant ventilation were regarded as the baseline period. The mean values of brain lactate, glucose, and PO_2 , PCO_2 , and pH were calculated and used as baseline levels (100%). The following 6 hours (2 X 3 hours) of increased FiO_2 up to 60% and 100% were regarded as the enhancement period.

Control Cohort. After establishment of the stable multimodality monitoring, and after 3 hours, a time period was chosen that showed stable results for continuous brain PO_2 , PCO_2 , and pH monitoring. The

changes in the monitored parameters in all individuals of both cohorts were used for statistical analyses to determine significant differences during the 6-hour observation period.

Sources of Supplies and Equipment

The external strain gauge sensor was acquired from Codman, Randolph, MA, and the Paratrend 7/Neurotrend microsensors were purchased from Diametrics Medical, Inc., Roseville, MN. The flexible microdialysis and the CMA 170 automated collector system were obtained from CMA Microdialysis, Acton, MA. The measurements of the glucose and lactate dialysates were performed using a model YSI 2700 Select device purchased from Yellow Springs Instruments Co., Inc., Yellow Springs, OH. The Macintosh personal computer was acquired from Apple Computers, Inc., Cupertino, CA. The StatView version 4.1 statistical software was obtained from Abacus Concepts, Berkeley, CA.

RESULTS

Cohort Characteristic Data

The characteristic data for both patient cohorts in this report are shown in Tables 1 and 2. The initial GCS scores for 22 of the patients ranged from 3 to 8. Two patients of the O₂ cohort had a GCS score of 10 at the time of admission, deteriorated into a coma during the first 6 hours after admission, and were subsequently monitored using the multimodal system. In total, 17 of the 24 enrolled patients underwent a craniotomy for hematoma removal. The ANOVAs revealed no significant differences between the characteristic data of the two cohorts except for the brain glucose results (Table 2).

TABLE 2 COMPARISON OF VARIOUS FACTORS MEASURED IN BRAIN TISSUE AT THE BEGINNING OF THE OBSERVATION PERIOD IN 24 PATIENTS WITH SEVERE HEAD INJURY*		
Factor	Control (12 patients)	Oxygen (12 patients)
start (hrs)	12.1 ± 7.0	11.9 ± 6.9
ICP (mm Hg)	19 ± 9	15 ± 5
CPP (mm Hg)	80 ± 21	73 ± 16
PaO ₂ (mm Hg)	136 ± 22	121 ± 30
pH	6.97 ± 0.36	7.02 ± 0.33
PCO ₂ (mm Hg)	57.2 ± 5.9	88.0 ± 114.8
glucose (μmol/l)	941 ± 477	559 ± 392†
* Start = interval between admission and start of the observation period.		
† Statistically significant according to unpaired t-test (p < 0.05).		

Control Cohort

During the 6-hour analysis period, no significant variations of PaO₂ were observed to result from the FiO₂ management. At the beginning, the mean PaO₂ was 136.4 ± 22.1 mm Hg compared with 154.2 ± 31.8 mm Hg at the end of the study period. The mean brain PO₂ increased slightly during this time, from 24.3 ± 10.3 to 29.8 ± 16 mm Hg (p > 0.05; Fig. 1 upper left). A statistically significant correlation existed between brain PO₂ and CPP (r = 0.34; p < 0.001). The parameters ICP, CPP, PCO₂, and pH showed no significant variations within the time period of observation.

Fig. 1. Graphs showing the time course of mean brain tissue PO_2 ([mean p_tO_2] upper left), mean brain tissue lactate ([mean lac_t] upper right), and mean brain tissue glucose ([mean $gluc_t$] lower), in 12 patients each in the control (C-Cohort) and the O_2 -treated cohort (O-Cohort). Error bars indicate the standard error of the mean.

The mean brain lactate measured by the microdialysis probe remained high during the entire study period: 1106.8 ± 787 at the beginning, rising to 1319.6 ± 948.7 μmol/L at the end (Fig. 1 upper right). Statistical analyses revealed no significant correlation between ICP, CPP, or PaO_2 and lactate. The time course of the mean brain glucose values is given in Fig. 1 lower. At the end of the observation period we found a mean glucose level of 844.3 ± 543.1 μmol/L compared with 941 ± 477.7 μmol/L at the start. When we tested the correlation between brain lactate and pH there was no significant relationship. In contrast, brain pH and PCO_2 showed a significant inverse correlation ($r = -0.4$; $p < 0.001$).

Oxygen Cohort

Baseline Period. The mean PaO_2 was 121.4 ± 30 mm Hg over the entire baseline period, the mean PaCO_2 was 32 ± 4 mm Hg, and the pH of the arterial blood was 7.44 ± 0.05 . The peripheral hemoglobin saturation measured by pulse oximetry ranged between 98% and 100%. The mean values of brain lactate and PO_2 , measured during the initial baseline observation period, are given for each patient in Table 1. Dialysate lactate ranged from 277 to 3640 $\mu\text{mol/L}$ (mean lactate 1282 ± 885 $\mu\text{mol/L}$). Dialysate glucose ranged from 118 to 1370 $\mu\text{mol/L}$ (mean glucose 412 ± 358 $\mu\text{mol/L}$). The lowest brain PO_2 level was 13.2 mm Hg and the highest was 38 mm Hg (mean PO_2 26.2 ± 8.9 mm Hg) on an FiO_2 of $35 \pm 5\%$. Brain lactate and PO_2 showed no close relationship during this period.

The mean values of ICP, CPP, pH, and PCO_2 are summarized in Table 2. Analysis of the correlation between brain pH and lactate within the 12 individuals showed no significant inverse relationship ($r = -0.33$; $p > 0.05$). These findings were consistent with those seen in the control cohort.

Oxygen Enhancement Period. Analyses of the time course of CPP and ICP revealed no significant variations during the 6 hours. The mean ICP at the end of the study period was 13.2 ± 2.7 mm Hg compared with 15 ± 5 mm Hg at the beginning of the experiment. The mean CPP was found to be 77.9 ± 13.5 mm Hg compared with 73 ± 16 mm Hg.

Brain Tissue Oxygen Levels. Increasing FiO_2 to 60% resulted in an increase in the PaO_2 in all patients (mean PaO_2 240.1 ± 57.2 mm Hg). At 100% FiO_2 , PaO_2 increased further to 441.2 ± 88.2 mm Hg). This represents a 264% increase in the mean PaO_2 during 100% FiO_2 ventilation.

The brain PO_2 increased in each patient, as did the PaO_2 ($R = 0.36$; $p < 0.05$). At 60% FiO_2 the percentage change was increased by $109 \pm 90\%$ of the baseline value, and at 100% FiO_2 the mean PO_2 increased by $259 \pm 39\%$ compared with the baseline (Fig. 1 upper left). Thus, in this cohort the mean brain PO_2 was found to be 82.7 ± 44.1 mm Hg.

However, analyses of the individual patients revealed a broad heterogeneity in the PO_2 response to the induced changes of the PaO_2 . Two illustrative cases of patients with different clinical situations are given in Figs. 2 and 3. These indicate a different time course for individual PO_2 values.

Fig. 2. Case 3. Graph showing the time course of mean brain tissue PO_2 ($p_{ti}O_2$), brain tissue PCO_2 ($p_{ti}CO_2$), CPP, dialysate lactate ($lact_{ti}$), and glucose ($gluc_{ti}$) at different FiO_2 levels during the enhancement period.

Fig. 3. Case 1. Graph showing the time course of the brain tissue PCO_2 ($p_{ti}CO_2$), CPP, dialysate lactate ($lact_{ti}$), and glucose ($gluc_{ti}$) at different FiO_2 levels during the enhancement period.

Lactate Levels. The levels of lactate in the brain decreased during the period of increased FiO_2 in proportion to its average value during the baseline period (Fig. 1 upper right). The mean lactate level at the end of the O_2 enhancement period was $754 \pm 527 \mu\text{mol/L}$. This represents a decrease of 40% ($p < 0.001$, ANOVA). We found a linear relationship between the percentage change in the brain lactate and

PO₂ values in all individual measurements obtained during the O₂ enhancement period ($R = 0.215$; $p < 0.05$). Figure 4 shows the distribution of the individual coefficients of linear regression between lactate and PO₂.

Fig. 4. Histogram showing the individual linear regression R values between the absolute values of brain tissue lactate and brain tissue PO₂ during the O₂ enhancement period in the 12 patients in the O₂-treated cohort. The mean of the r value distribution was significantly different from zero (one sample t-test, $p < 0.05$).

By using this method of analysis, it is seen that the majority of the individual R values are located in the range between 0.5 and 0.7. Tests of the distribution of the individual R values showed a significant difference of the mean from zero (one sample t-test, $p < 0.05$). The linear regression model (Fig. 5) revealed a close relationship between the brain lactate levels and the pH values during the period of increased FiO₂ ($R^2 = 0.61$; $p < 0.001$).

Fig. 5. Scatterplot showing linear regression between the individual brain tissue lactate (lac_{ti}) values and the brain tissue pH (pH_{ti}) levels of the O_2 -treated cohort (12 patients) during the O_2 enhancement period ($r^2 = 0.613$; $p < 0.001$). The dotted lines indicate the 95% confidence area.

Glucose Levels. The levels of glucose in the brain showed no clear trend during the O_2 enhancement period and seemed not to be influenced by the O_2 enhancement maneuver. The heterogeneity of the glucose behavior is demonstrated by the SD at the endpoint of the observation period at 100% FiO_2 (mean glucose $480 \pm 418.6 \mu\text{mol/L}$). Figure 1 lower shows the time course of the mean glucose values in comparison with the glucose of the control cohort. None of the other monitored parameters was significantly related to the time course of the glucose values.

ILLUSTRATIVE CASES

Case 3

This 22-year-old man had an initial GCS score of 7 after a motor vehicle accident. His admission computerized tomography (CT) scan revealed diffuse brain swelling and a thin subdural hematoma over the left hemisphere. Eleven hours postinjury, the O_2 enhancement period was begun and maintained for 6 hours. The dialysate lactate level was high, and CPP, PO_2 , and PCO_2 were normal (Fig. 2). An increase in brain PO_2 was seen, corresponding to the FiO_2 increase. The high PO_2 values on 100% FiO_2 showed a broad heterogeneity and were influenced by the course of the CPP. Brain tissue lactate levels decreased during this period and glucose was unaffected. The patient had made a good recovery at the 3-month follow-up visit.

Case 1

This 20-year-old man was admitted after a motor vehicle accident, with a GCS score of 7. His initial CT

scan revealed multiple left frontotemporal contusions and a large left-sided subdural hematoma. Before his admission to the ICU, craniotomy was performed and the hematoma was removed. Over the next 48 hours the patient developed uncontrollably high ICP of approximately 40 mm Hg, and he died despite full therapy with mechanical ventilation, pressors, cerebrospinal fluid drainage, and mannitol administration. The initial brain PCO₂ and lactate values were dangerously high. His ICP was initially 20 mm Hg, and his CPP was less than 70 mm Hg before pressor therapy was begun. His brain PO₂ was greater than 30 mm Hg. By increasing FiO₂ to 100%, a corresponding increase in the PO₂ values was seen. However, while the patient was still at 100% FiO₂, his brain PO₂ values started to decrease and fell to zero, when FiO₂ was reduced to 60% (Fig. 3). The initial drop in lactate at the start of the FiO₂ enhancement reversed simultaneously with a decrease in the PO₂ and lactate values, and then climbed again to extremely high levels of more than 3000 μmol/L. The brain PCO₂ showed the same behavior as lactate. The CPP was inconsistent during this period and most of the time it was close to the threshold level of 60 to 70 mm Hg, despite maximal pressor therapy.

DISCUSSION

Cerebral oxygenation is currently monitored in two different ways. The global cerebrovenous O₂ measurement in the bulb of the jugular vein is an established method that reflects the relationship between O₂ delivery to the brain and the extraction of O₂ by the brain.[6,8,50,51] Local brain tissue oximetry by single Clark-type electrodes or multiparameter probes measuring PO₂, PCO₂, pH, and temperature simultaneously in brain tissue is a more recent monitoring method that gives information about substrate delivery and neuronal homeostasis in the locally studied cerebral region, depending on the position in which the measurement probe is placed.[16,19,24,32,44,58,63] The interdependence of the jugular saturation of O₂ and PO₂ on CBF has been well demonstrated in several clinical studies.[12,51,58,65]

Only a few reports describe the response of PO₂ measurement to the induction of different arterial O₂ concentrations.[36,40,44,53,58] In these animal studies brain tissue oxygenation was monitored using different technical approaches in healthy noninjured brains. Van Santbrink, et al.,[58] first described the effect of increasing brain tissue PO₂ in patients with severe head injury in response to normobaric hyperoxia induced by mechanical ventilation with 100% inspiratory O₂ over a period of approximately 30 minutes.

This pilot study has shown that increasing the PaO₂ to levels higher than needed to fully saturate hemoglobin apparently can increase PO₂, especially when it is low, and that this effect continues over a period of several hours. However, this simple interpretation of our data depends on what exactly the "tissue O₂" probe is measuring. The concomitant reproducible decrease in lactate (40%) in the O₂-treated cohort indicates that the increase in tissue O₂ is real, and that it affects oxidative metabolism favorably. This interpretation is supported by the findings in the control cohort of our study. Increased brain tissue lactate levels frequently occur in the early period after severe head injury, during the 1st day of the trauma. The implications of these findings may be very important, although validation is clearly needed in other centers and in more patients.

Parameter Changes at Normoxic PaO₂

Our findings for brain PO₂, PCO₂, and pH in the control cohort and in the O₂ cohort during the baseline period are in accordance with results reported in the literature, in both human studies and animal experiments.[24,32,44,53,58,63,65] The PO₂ measurement in both cohorts showed no relationship to the lactate concentrations in brain tissue during constant arterial normoxic conditions. This is consistent with the results of a previous study conducted by our group.[65]

The CPP and ICP levels showed no major influences on the brain tissue measurement results in our study. However, these parameters were rather constant during the observation period, because the patients were all undergoing intensive care treatment, and in the matching of the cohorts we aimed to achieve comparable stable patient populations.

Oxygen Enhancement Period

Effects on Dialysate Lactate. In our study, brain dialysate lactate decreased during the 6-hour period of increased PaO₂ in the O₂-treated cohort. This neurochemical finding was significantly correlated with an increase in brain tissue PO₂ and pH, as measured by the multiparameter probe. Microdialysis findings in 24 patients after severe head injury, as described previously in a study in which the same microdialysis technique was used,[65] revealed that a dialysate lactate level of greater than 300 µmol/L generally was seen in patients with a poor prognosis after severe head injury.

Under normal conditions, brain lactate output is suppressed in the presence of sufficient O₂. [1,10,27,33,35] The conventional view regarding lactate accumulation claims that oxidative energy metabolism is rendered inoperative, either through substrate (O₂) unavailability (ischemia) or damage to mitochondria. Lactate is thus the product of a metabolic switch away from the aerobic tricarboxylic acid cycle pathway within the mitochondria to the anaerobic utilization of glucose. Pyruvate is the product of the glycolytic breakdown of glucose. If O₂ is lacking, or the transport mechanisms or mitochondria are damaged, pyruvate undergoes anaerobic conversion to lactate by the enzyme lactate dehydrogenase.[33] During this metabolic conversion of lactate the reduced form of nicotinamide adenine dinucleotide is reoxidized to NAD⁺, which is necessary for the continuation of glucose breakdown into pyruvate. Thus, in the presence of a preserved glucose supply, an O₂ delivery/demand mismatch, such as occurs under the condition of incomplete ischemia, causes glycolytic accumulation of lactate in brain tissue to develop.[11] Thus, elevated lactate concentrations in neuronal tissue are considered to indicate an anaerobic metabolic status.[11,27,30,33,43,55]

On the other hand, lactate increase is not only induced by ischemia. Andersen and Marmarou[1] demonstrated increased glycolysis and cerebral acidosis in cats by using a fluid-percussion injury model in nonischemic, normoxic animals. These authors proposed a metabolic compartmentalization of neuronal energy production because of a disparity between the maximal rates of glycolysis and oxidative phosphorylation. Thus, some of the lactate that is present after brain injury may be the result of a normal physiological rather than a pathological response to trauma. Furthermore, elevations in the excitatory neurotransmitter glutamate have been shown to increase lactate production by astrocytes.[47] Thus, increased brain lactate levels may be due to several mechanisms.

It has also been shown recently that neuronal mitochondria show a specific functional deficit that appears to be calcium-mediated after severe head injury.[60] Thus, independent of the actual status of CBF and O₂ delivery to the tissue, neuronal mitochondrial perturbation may induce a specific, posttraumatic

transient impairment of tricarboxylic acid cycle metabolism, leading to a compensatory increase in anaerobic glycolysis.[7,26] Such a posttraumatic mitochondrial perturbation, independent of CBF, could also explain our finding that the brain PO_2 levels during normoxic periods in our investigation showed no correlation to the levels of baseline dialysate lactate. However, when O_2 availability to these damaged mitochondria is increased, we speculate that their function may be ameliorated by a "mass action" effect of increased O_2 .

Elevations of cerebral lactate have also been described in head-injured patients experiencing delayed clinical and physiological deterioration.[7,13,20,37,38,45,48,49,57,65] The presence of high levels of lactate in the brain has been shown to be a prognostically relevant factor after severe head injury.[13] Valadka, et al.,[57] reported on six patients suffering from incurable ICP elevation after severe head injury. Their clinical deterioration was accompanied by a significant increase in brain tissue lactate levels. Goodman, et al.,[20] demonstrated that administration of barbiturates to patients after severe head injury influences pathologically high lactate levels.

We speculate that postinjury mitochondrial membrane alterations lead to a partial functional failure of aerobic metabolism. Microvascular failure and intermittent CBF reduction also cause a relatively hypoxic situation. Oxygen flux out of the capillaries into the tissue and subsequently into the neurons and then the mitochondria is impaired by alterations of the compartment interface conditions. Diffusion distances are lengthened because of cytotoxic cell swelling, and arteriovenous shunts may direct CBF away from the capillaries. Thus, an O_2 delivery/metabolism mismatch develops after severe head injury. Increasing the driving force of capillary/tissue O_2 flux should therefore be an effective measure to push more O_2 into the mitochondria. The reduction in tissue lactate, as compared with the baseline levels of the O_2 -treated patients or to the time course of lactate within the control cohort, indicates that cerebral oxidative energy production resulting from Krebs cycle activity in mitochondria may be increasing following O_2 increase, according to our findings.

Cerebral Oxygenation

The valuable information provided by brain O_2 monitoring either in the cerebrovenous blood or in the brain tissue in patients after severe head injury has been extensively demonstrated.[6,8,12,16,24,32,51,65] As a result, a better understanding of cerebral O_2 consumption and metabolic needs in different pathological settings after severe head injury has been achieved. The importance of periods of desaturation of the cerebrovenous blood, as measured by jugular fiberoptic catheters after severe head injury, is an example.[6,8,12,50,51]

More recently, attempts have been made to identify a critical threshold for brain tissue PO_2 as measured by Clark electrodes in the brains of patients with severe head injury.[16,18,32,64] Increasing FiO_2 in patients at high risk for cerebral O_2 deficiency caused by an incomplete saturation of hemoglobin with O_2 is a well-established therapy in clinical ICU management of severely head injured patients. The current thinking is that achieving an arterial hemoglobin saturation of 100% is the upper limit of usefulness. Furthermore, increasing the FiO_2 to greater than 40% in patients with intact respiration, when arterial hemoglobin is completely saturated, results in an increase of only the physiologically dissolved O_2 in plasma, which represents only approximately 2 to 3% of overall O_2 transport. The quantitative

effect of this physically dissolved O_2 in blood is small. Thus, an increase of in PaO_2 beyond the level necessary for 100% saturation of hemoglobin has not yet been established as a therapeutic measure to improve cerebral O_2 supply.

However, if it is assumed that the results of brain PO_2 measurement reflect the actual O_2 delivery to the neurons, then our data are mechanistically attractive.[16-18,40,58,65] Recently, several other groups have reported the direct dependence of the brain PO_2 levels on the PaO_2 . [44,53,58] This relationship was found across a wide range of PaO_2 values.

Cerebral O_2 Flux After Severe Head Injury

The physiology of O_2 distribution between the peripheral cerebral microvasculature and the brain tissue remains poorly understood. The interface conditions between the different compartments of O_2 distribution in the brain and the microvasculature are not yet well described.[29,39] However, meeting actual neuronal tissue energy requirements by maintaining adequate O_2 flux is the fundamental requirement of the cerebral O_2 exchange apparatus. Thus, the magnitude of O_2 flux is the decisive quantity that needs to be maximized when the system is stressed, and capillary PO_2 represents the "driving force" that is available for O_2 exchange and is the limiting factor on its magnitude.[9,23,29,59,61] Confocal microscopy of rat brain cortex indicates that 10 to 20% of cerebral capillaries may not contain erythrocytes at any given time.[34,56] Thus, nonhemoglobin O_2 transport may be more significant than was previously thought. This assumption is the rationale for various attempts to establish hyperbaric oxygenation as a treatment modality.[2,25,38,52] Holbach, et al.,[25] investigated the effect of hyperbaric O_2 treatment on global cerebral lactate metabolism in patients after severe head injury. They demonstrated a reduction of the cerebrovenous lactate concentration in these patients by using 1.5 atm of hyperbaric O_2 treatment. Furthermore, increased FiO_2 of up to 100% under normobaric conditions also reduced the cerebrovenous lactate in these patients after severe head injury, as seen in our study.

Clinical Implications

A simplistic interpretation of these data suggests that ventilation with 100% O_2 should be considered at least for the first 6 to 18 hours after any severe head injury, when metabolic demand on the neuronal energy systems is greatest. Emergency personnel may improve the chances of restoring brain energy homeostasis by using 100% O_2 , at least until the patient's condition is stable in the ICU. However, further validation of this study is needed, and it must first be shown that oxidative metabolism, with increased adenosine triphosphate generation, increases as a result of this O_2 enhancement in severe head injury.

Our data cannot establish the optimal level of the inspiratory O_2 concentration or the duration of increased FiO_2 that is most beneficial in individuals with severe head injury. Comparing CBF findings with the achievable response of brain PO_2 to changes in FiO_2 could provide a better understanding of the relationship between blood flow autoregulation and brain tissue PO_2 and PCO_2 . This could be especially important if one considers the fact that application of FiO_2 levels higher than 60% may be harmful when used for longer than 24 hours in adults.[46] An inflammation of the tracheal surface can occur, and the

induction of pulmonary atelectases is critically dependent on the application time of the increased FiO_2 when it is close to 100%. This results in an increased incidence of pulmonary infections and structural damage to the lungs. Nevertheless, if it can be more widely shown that administration of 100% O_2 to patients with severe head injury can indeed improve cerebral O_2 delivery and metabolism during the critical early period, then this simple maneuver may improve outcome.

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