

Clinical Article

Effects of cerebral perfusion pressure and increased fraction of inspired oxygen on brain tissue oxygen, lactate and glucose in patients with severe head injury

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Summary

Objective. The purpose of the study was to measure the effects of increased inspired oxygen on patients suffering severe head injury and consequent influences on the correlations between CPP and brain tissue oxygen (PtiO₂) and the effects on brain microdialysate glucose and lactate.

Methods. In a prospective, observational study 20 patients suffering severe head injury (GCS ≤ 8) were studied between January 2000 and December 2001. Each patient received an intraparenchymal ICP device and an oxygen sensor and, in 17 patients brain microdialysis was performed at the cortical-subcortical junction. A 6 h 100% oxygen challenge (FiO₂ 1.0) (*Period A*) was performed as early as possible in the first 24 hours after injury and compared with a similar 6 hour period following the challenge (*Period B*). Statistics were performed using the linear correlation analysis, one sample t-test, as well as the Lorentzian peak correlation analysis.

Results. FiO₂ was positively correlated with PtiO₂ ($p < 0.0001$) over the whole study period. PtiO₂ was significantly higher ($p < 0.001$) during *Period A* compared to *Period B*. CPP was positively correlated with PtiO₂ ($p < 0.001$) during the whole study. PtiO₂ peaked at a CPP value of 78 mmHg performing a Lorentzian peak correlation analysis of all patients over the whole study. During *Period A* the brain microdialysate lactate was significantly lower ($p = 0.015$) compared with *Period B*. However the brain microdialysate glucose remained unchanged.

Conclusion. PtiO₂ is significantly positively correlated with FiO₂, meaning that PtiO₂ can be improved by the simple manipulation of increasing FiO₂ and ABGAO₂. PtiO₂ is positively correlated with CPP, peaking at a CPP value of 78 mmHg. Brain microdialysate lactate can be lowered by increasing PtiO₂ values, as observed during the oxygen challenge, whereas microdialysate glucose is unchanged during this procedure. Extension of the oxygen challenge time and measurement of the intermediate energy metabolite pyruvate may clarify the metabolic effects of the intervention. Prospective comparative studies, including analysis of outcome on a larger multicenter basis, are necessary to assess the long term clinical benefits of this procedure.

Keywords: Traumatic brain injury; brain tissue oxygen; energy metabolites; hyperoxygenation.

Introduction

Evidence that cerebral blood flow (CBF) is decreased but oxygen consumption is increased in the acute phase after severe brain injury [4, 26, 27, 41] suggests that treatment aimed at preventing cerebral ischaemia may improve outcome. Secondary mechanisms, such as neuroexcitotoxicity can worsen brain swelling and intracranial pressure (ICP), further impairing cerebral perfusion pressure (CPP) and brain oxygenation [9, 19, 23, 24, 47]. The challenge, therefore, is two-fold, to maintain sufficient blood supply to the brain and to improve oxygen delivery to brain cells [38, 63, 67]. A consensus has been reached that CPP of around 70 mmHg may provide optimal blood supply to the brain [43]. In contrast, there is no definition of the optimal values for the fraction of inspired oxygen (FiO₂) or for brain tissue oxygen tensions (PtiO₂).

Measurements of PtiO₂, using various commercially available sensors, can provide a continuous assessment of brain oxygenation and microdialysis enables monitoring of brain energy metabolites including lactate concentration. The role of intracerebral lactate after head injury has been much debated recently [5]. It has been hypothesized that lactate constitutes the preferred substrate over glucose in neurons, especially in times of increased metabolism [30–32, 55–57]. This is because neurons use lactate by converting it to pyruvate which then enters the mitochondrial Krebs-cycle to produce ATP [5], as long as mitochondria are functioning

[14, 58]. Thus, an increased lactate level may have a dual significance: it may be either a sign of anaerobic metabolism, or of hyperglycolysis independent of aerobic conditions.

Although an FiO_2 of 0.4 is usually employed in intubated and mechanically ventilated patients to maintain 100% oxygen blood saturation, higher values have been proposed. A number of groups have analyzed the relation between arterial oxygen tension (ABGAO₂) and PtiO₂ in patients with severe head injury [3, 37, 52] and Menzel *et al.* reported that, by increasing ABGAO₂ through ventilatory oxygen enhancement, PtiO₂ was elevated also [35].

WE hypothesized that, by increasing FiO_2 from 0.4 to 1.0, PtiO₂ would be improved and that this might influence brain metabolism as reflected in measurements of glucose and lactate production. We report studies aimed to test this hypothesis through observation of the effects of increasing FiO_2 to 1.0 for 6 hours in a group of severely head injury patients. The studies were made in the first day after injury, as soon as possible after stabilization of the monitoring sensors and we also analyzed the relationship between CPP and PtiO₂.

Materials and methods

A total of 20 patients who had suffered a severe head injury, with a Glasgow coma score ≤ 8 , were included in the study. The study protocol was approved by the local Ethics Committee for Human Research. Informed consent was obtained from the families of the patients. All patients were directly referred to our centre either by helicopter or by ambulance in the first 3 hours after trauma, were intubated, sedated and treated to relax muscles. At the time of admission patients were ventilated with FiO_2 1.0. A cranial CT scan was performed as soon as possible. A patient who was not expected to survive the next 24 hours was excluded from this study, but was treated according to our standard protocol. If an emergency operation was not required, cranial bolts for measurement of PtiO₂, ICP and a brain microdialysis catheter were introduced. If a patient required an emergency operation, the sensors were placed in the operating theatre after closure of the skin. A run-in-time with the Licox sensor and the microdialysis sensor of between one to two hours after insertion was allowed before collection of data for analysis. For data monitoring, a mobile intensive care HP[®] monitor was upgraded with an interface for the multi-modality-monitor MMM (Licox[®] GMS, Germany). After the study period, the data were downloaded onto a computer. Microsoft[®] Access and Excel programs were used for data storage and processing. The indices collected were mean arterial blood pressure (MABP), end-tidal CO₂ (EtCO₂), CPP, ICP, PtiO₂, core temperature and heart rate.

Oxygen challenge period in the first 24 hours after injury (period A)

The 6 hour "oxygen challenge test" was started as soon as the "run-in-time" for the sensors was over. The patient was ventilated with an FiO_2 of 1.0; thereafter, FiO_2 was gradually reduced to the usual values (0.4) according to standard management.

Period following oxygen challenge (period B)

For comparison we used the 6 hour period immediately following the oxygen challenge period A and named it period B. Data collection was not different to Period A.

Baseline FiO_2

FiO_2 values before to Period A were around 0.6. After the oxygen challenge Period A, FiO_2 was reduced to 0.6 and from there stepwise to baseline values (FiO_2 0.3–0.4) that depended on the patient's condition.

Bolts and ICP sensor

A commercially available intraparenchymal ICP transducer (Integra[®] Neurosciences, Camino, San Diego, California, USA) was used and fixed to the frontal skull.

Licox

For measurement of the oxygen tension in brain tissue, the Licox oxygen sensor with a 13 mm² sensitive area (Licox, Integra[®] Neurosciences) was used in each of the 20 patients. The sensor was introduced, along with a microdialysis catheter, into a separate burr hole. The data were collected online through the Licox Multimodal Monitor MMM. The sensor was placed in the frontal area, in an area of brain judged by the first CT not to be contused.

Microdialysis

A custom microdialysis probe (CMA[®], Sweden), with a molecular mass cut-off level of 20 kDa, was used along with the Licox probe. The microdialysis probe was perfused using a CMA microdialysis pump with saline at a flow rate of 0.5 $\mu\text{l}/\text{min}$. Samples were collected every hour. The samples were then frozen for later analysis for glucose and lactate using an automated enzymatic assay with the YSI 2700 (Yellow Springs[®], USA). At the end of the study, the microdialysis probes were collected and inspected for leakage and kept for measurement of the in vitro recovery rates for glucose and lactate. A sample volume of 25 μl in total was needed for the analysis for glucose and lactate with the YSI 2700.

Data collection and storage

The data were collected online using a Hewlett Packard[®] ICU Monitor mounted on a mobile unit and upgraded with an interface to enable connection to the Licox[®] MMM. The data were downloaded on to an Acer[®] Notebook at a frequency of 2 per minute. For the 20 patients, 160812 separate data points were collected; these represented a total of 80406 minutes of monitoring. Data were stored in a Microsoft[®] Access database.

Statistical analysis

To assess correlations between FiO_2 , ABGAO₂ and CPP versus PtiO₂, we calculated the r-values for each patient the 24 h observation period. Thereafter, a one sample t-test was run over the r-values to calculate the significance. To analyze the 2 observation periods A and B for FiO_2 and ABGAO₂ versus PtiO₂, the means of the 6 hour oxygen challenge period (A) and of the 6 hours after the oxygen challenge period (B) were calculated for each patient. A paired t-test over the mean values of all patients was run to assess the significances of any differences. For calculation of the peak correlation analysis between CPP and PtiO₂ in all patients, Lorentzian peak regression analysis was used [33]. To determine

the significance of any differences in lactate during the two observations periods (A and B), an ANOVA test was used. For all results the threshold of significance was set at a p-value of 0.05. The calculations were done using Sigma Plot 2001[®], SPSS[®] and Statistica[®].

Results

A total of 20 patients suffering from severe head injury were studied, 13 males (40 ± 16 years) and 7 females (37 ± 20 years). The average initial Glasgow Coma Score was 6. The demographic data are summarized in Table 1. The intracerebral sensors (Licox and ICP) were placed in 17 cases on the right frontal side and in 3 cases on the left

frontal side. Microdialysis was placed in 19 patients; the samples were used for analysis in 15 patients. In 2 cases the dialysate showed a red discoloration indicating the sensor was ruptured, the samples were discarded. Five patients required immediate surgery.

Fraction of inspired oxygen and arterial blood gas oxygen versus PtiO₂

FiO₂ and PtiO₂ were significantly positively correlated (p < 0.0001) (t-test over the r-values from the correlation of all patients in the first 24 hours (Fig. 1a). A similar

Table 1. Demographic data. Probe placement refers to the location of the ICP, PtiO₂ and microdialysis sensors

Patient	Age	Sex	Initial GCS	Probe placement	Injury type	Emergency op.
1	25	male	4	right frontal	DIA	0
2	56	male	6	right frontal	SDH and DIA	1
3	24	female	3	right frontal	DIA	0
4	59	male	6	right frontal	DIA	0
5	21	female	9	right frontal	DIA	0
6	28	male	6	right frontal	DIA	0
7	69	male	4	right frontal	DIA bifronto-basal	0
8	17	male	6	right frontal	DIA	0
9	53	male	9	right frontal	EDH and DIA	1
10	22	female	9	right frontal	DIA	0
11	73	female	8	right frontal	DIA	0
12	51	male	9	right frontal	SDH and DIA	2
13	21	male	3	right frontal	DIA	0
14	48	female	10	left frontal	DIA	0
15	25	male	4	right frontal	DIA	0
16	22	female	7	right frontal	DIA	0
17	41	male	6	left frontal	SDH and DIA	1
18	54	female	3	right frontal	SDH and DIA	1
19	28	male	3	left frontal	DIA	0
20	48	male	8	right frontal	DIA	0

DIA Diffuse axonal Injury, SDH Subdural hematoma, EDH Epidural hematoma.

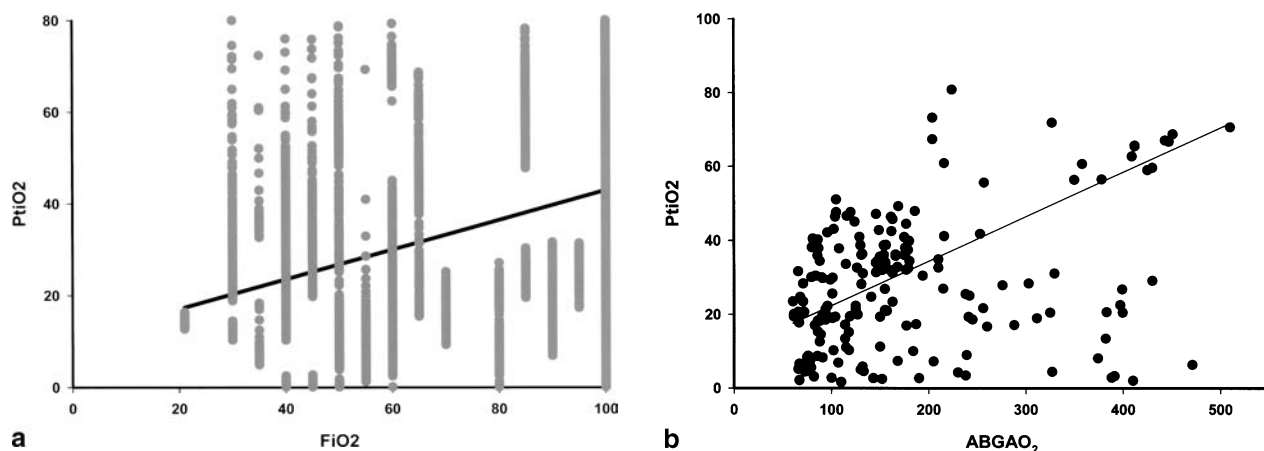


Fig. 1. (a) Combined regression analysis between FiO₂ and PtiO₂ of all patients after TBI. Test t-test over the r-values of each patient showed a significance of p < 0.0001. (b) Combined regression analysis between ABGAO₂ and PtiO₂ of all patients after TBI (r = 0.5). The t-test on the r-values of each patients showed a significance of p < 0.0001

significant positive correlation between ABGAO₂ and PtiO₂ was observed ($p < 0.0001$). The r -value of the combined data of all patients in one plot is $r = 0.5$, as shown in Fig. 1b.

Of a sub-group of 6 patients with low PtiO₂ (< 10 mmHg) and high ABGAO₂ and FiO₂ (1.0) during monitoring (Figs. 1a and 1b), 4 died in ICU. The other 2 patients had low PtiO₂ levels from the start and reacted more slowly to an increase in FiO₂. The Licox probes were in the vicinity of haemorrhagic contusions in these cases.

The stability of PtiO₂ over the Period A is shown as the percentage change over the 6 hours in relation to the values of the first 10 minutes of Period A (Fig. 2).

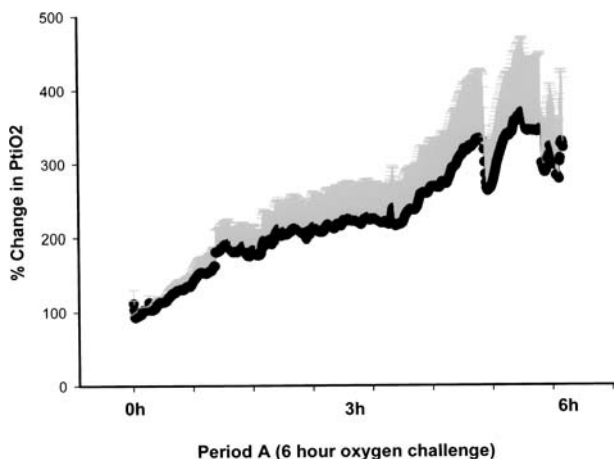


Fig. 2. Mean percentage increase in PtiO₂ (+SEM) during the Period A (FiO₂ 1.0) of all 20 patients. The reference is the first 10 minutes of Period A

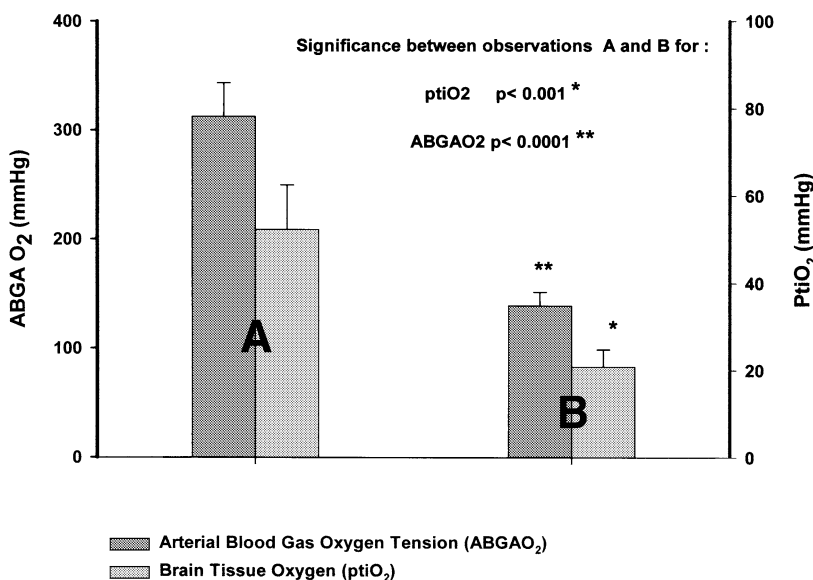


Fig. 3. Oxygen challenge (period A) and comparison of ABGAO₂ and PtiO₂ in the subsequent period B, ABGAO₂ and PtiO₂ were significantly higher in A than in B

6 hour oxygen challenge and PtiO₂–ABGAO₂

PtiO₂ was significantly higher ($p < 0.001$) during period A (52.3 ± 10.1) as compared to period B (20.7 ± 3.9). ABGAO₂ was similarly higher during period A ($p < 0.0001$) (Fig. 3).

Analysis of cerebral perfusion pressure versus PtiO₂

The analysis of cerebral perfusion pressure versus PtiO₂ showed a significant positive correlation ($p < 0.001$) (t-test of the r -values of all patients). Analyzing all patients together in one plot with a Lorentzian peak correlation analysis, demonstrated a peak of PtiO₂ at a CPP of 78 mmHg (Fig. 4).

The 6 hour oxygen challenge brain microdialysate glucose and lactate dynamics

The dialysate lactate values during period A were significantly lower ($p = 0.015$) than during period B (ANOVA Test) (Fig. 5). Analysis of dialysate glucose levels did not show significant difference (Fig. 6).

The mean values and standard deviations of the values of MABP, ICP, CPP and EtCO₂ during periods A and B are listed in Table 2.

Relationship between EtCO₂ and arterial blood gas oxygen values

The online measured EtCO₂ values were 8.1 mmHg lower than the directly measured arterial blood gas oxygen tensions ($n = 1365$), confirming that the patients

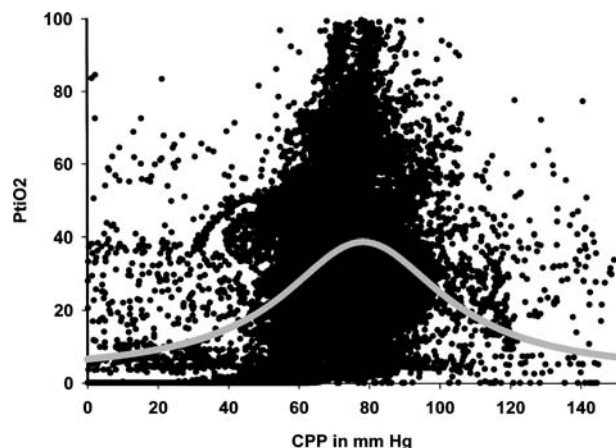


Fig. 4. Lorentzian peak correlation analysis between CPP and PtiO₂ of all patients in one plot, showing a peak in best PtiO₂ at a CPP value of 78 mmHg

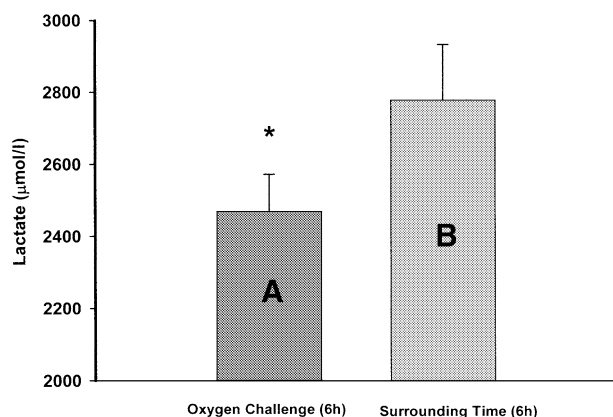


Fig. 5. Bar plot comparing dialysate lactate during the oxygen challenge period and the subsequent time when dialysate lactate was higher ($p = 0.015$)

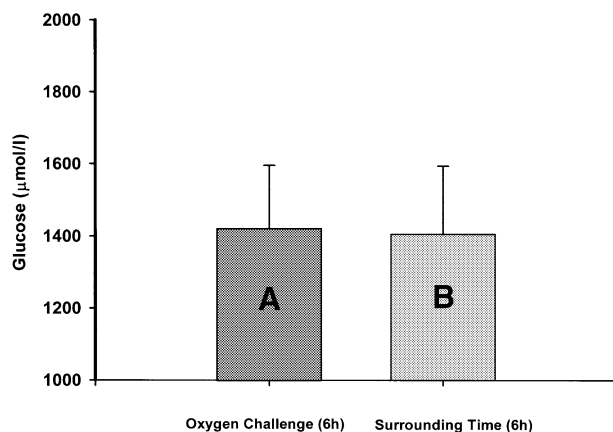


Fig. 6. Bar plot comparing dialysate glucose during the oxygen challenge period and the subsequent time

Table 2. Hemodynamic data (mean values and the standard deviations) during Period A and Period B

	A		B	
	Mean	SD	Mean	SD
MAP	86.4	14.8	81.4	14.0
ICP	17.2	15.4	18.3	17.5
CPP	69.3	14.9	63.1	18.5
PECO ₂	26.9	4.1	28.2	3.9

n = 17104.

MABP Mean arterial blood pressure; ICP intracranial pressure; CPP cerebral perfusion pressure; EtCO₂ end tidal CO₂.

were moderately hyperventilated according to our guidelines (Table 2).

Discussion

Our study demonstrates that an increase in FiO₂ can lead to a significant increase in arterial blood gas oxygen tensions (ABGAO₂) and brain tissue oxygen tensions (PtiO₂) in recently head injured patients. Furthermore, increasing FiO₂, and hence increasing PtiO₂, was associated with a decreased brain microdialysis lactate, without a change in brain microdialysis glucose. CPP was positively correlated with PtiO₂ with a peak at a CPP-value of 78 mmHg.

General considerations

This study was performed prospectively, excluding patients unlikely to survive the first 24 hours. This is one reason that fewer patients with very low PtiO₂ values were included, as compared to those reported in other studies of similar severely head injured patients [3, 69]. In our study, each patient was their own control for the microdialysis results. We chose this design of study because baseline values for microdialysis, glucose and lactate differ in different patients with a severe head injury, as a result of different types of injury. To reduce these effects, microdialysis sensors and oxygen sensors were placed in non-contused areas. However, contusions sometimes develop after a delay and the use of multiple probe placement has been proposed to gain a more global view of changes in brain metabolism [25, 60].

The sequence of observations, i.e. Period A to Period B, is likely to have influenced our findings. FiO₂ was decreased only after the oxygen challenge so that the difference in brain tissue microdialysis lactate values might have been greater between Period A and Period B. We plan to expand the present protocol and study a

“real” control group, in which there is no oxygen enhancement.

Two different probes are in clinical use to measure brain tissue oxygen tensions: the Clark type electrode as used in the Licox[®] and, previously, Paratrend[®] probes, and an optical system as used in the Neurotrend[®]. Different dynamics of oxygen measurement and different effects of increasing FiO₂ have been described for the two systems, and studies testing the sensors simultaneously are ongoing [46, 22].

Fraction of inspired oxygen and brain tissue oxygen

There are reports of a positive correlation between values of PtiO₂ and of different induced arterial oxygen tensions [29, 37, 66, 70]. Thus, Van Santbrink *et al.* and Menzel *et al.* described an increasing brain tissue oxygen in patients with severe head injury in response to increasing arterial oxygen tensions [36, 66]. Differences in baseline values of PtiO₂ and in how these respond to increased arterial oxygen tensions may result from the use of different oxygen sensors placed at different depths and in different areas of the brain. In our study the sensor was placed at the same depth, in relation to the bolt system, in each patient.

Low brain tissue oxygen tensions have been associated with poor outcome (PtiO₂ < 20 mmHg) and fatal outcomes (PtiO₂ < 10 mmHg) [3, 16]. Van den Brink *et al.* [65] reported low PtiO₂ in 57% of patients with severe head injury despite full treatment. Our demonstration that, if PtiO₂ values remain low, despite an oxygen challenge (FiO₂ 1.0), most patients died, may help to identify very severe injury. On the other hand, it has also been demonstrated that a marked increase in brain tissue oxygen after inducing FiO₂ 1.0 can be associated with a poor outcome [35, 66]. This has been linked to impaired cerebral vasoreactivity. Normally arterial hyperoxia causes vasoconstriction and there is about a 20% reduction of CBF when ventilation with FiO₂ 1.0 is used, as long as vasoreactivity is maintained [48]. This suggests that an oxygen reactivity challenge might help to identify patients who might benefit from early increased oxygen ventilation, but more data are needed.

Microdialysis glucose and lactate

There is evidence from studies using microdialysis that neuroexcitatory induced hyperglycolysis occurs

after experimental head injury [11–13]. Glutamate released by neurons after injury is taken up by astrocytes and Pellerin and Magestretti hypothesized that this drives glycolysis. This may relate to the hyper glycolysis observed with PET in patients suffering severe head injury [4, 45] and in accord with findings with microdialysis of increased glutamate and lactate and reduced glucose [9, 18]. This neuroexcitotoxic response occurs very soon after injury and may be missed in the clinical circumstances. Menzel *et al.* performed studies in a similar time period after severe head injury but placed less emphasis on an immediate start and included a hyperoxygenation challenge [36]. Lactate levels in the microdialysis fluid were reduced during the oxygen challenge period, and glucose showed a trend to lower values. Overall the values they observed with microdialysis were lower than the values reported in our study. This difference may be caused by the different microdialysis flow rates used, 2.0 µl/min versus 0.5 µl/min in ours. Rossi and Stocchetti previously commented that the reduction in lactate reported by Menzel *et al.* may be due either to an improvement in aerobic glucose metabolism or simply to a lower oxygen availability as a result of reduction in cerebral blood flow following an increase in arterial blood gas oxygen [50]. However we found no change in glucose levels during the oxygen challenge which suggests an improvement in cerebral glucose utilization. Analysis of pyruvate levels in relation to those of the excitatory transmitter glutamate might elucidate this topic.

Cerebral perfusion pressure and brain tissue oxygen

As discussed above, the mismatch between cerebral perfusion [7] and metabolic need [4] after TBI can lead to ischaemia, resulting in brain swelling and poor outcome. Prolonged hyperventilation (PaCO₂ < 25 mmHg) has been shown to be associated with a worse outcome and should be used only with additional monitoring of blood flow or oxygenation [21, 53, 54, 65] for which CPP is the best available method. The EBIC Guidelines propose that CPP is maintained between 60–70 mmHg, whereas the ABIC Guidelines support slightly higher values, above 70 mmHg [28, 43]. As definitive evidence is lacking, firm recommendations cannot be made. In our study, CPP was positively correlated with PtiO₂ and the Lorentzian peak correlation analysis demonstrated a peak of PtiO₂ at a CPP value around 78 mmHg. This observation supports the view that CPP

should be maintained over 70 mmHg. However, CPP should not be elevated excessively because the blood brain barrier may be disrupted, which could result in brain edema. Based upon studies of cerebral autoregulation, Czosnyka *et al.* reported a similar value of optimal CPP of around 80 mmHg [15, 61] with higher values possibly disrupting cerebral autoregulation. However interpretation of the results of this Lorentzian peak correlation analysis does not permit conclusions about a definite threshold level for clinical circumstances.

Several studies have analyzed the relation between CPP and PtiO₂. In an experimental study using a swine model, brain PtiO₂ reflected changes in CPP or CBF [49]. In one clinical study of patients with *mild* to severe head injury, low PtiO₂ could not be predicted on the basis of CPP alone [51], but in another, Bardt *et al.* reported low PtiO₂ values in relation with low CPP values in patients with severe head injury [3]. Stocchetti *et al.* and Bruzzone *et al.* described a relation between CPP and PtiO₂ in areas with disrupted autoregulation in patients with severe head injury and subarachnoid haemorrhage [8, 62]. Taken together, these results suggest that PtiO₂ may be influenced by CPP, independently of tissue demand. This effect may be especially important when autoregulation is disrupted but may have an upper limit after which autoregulation breakthrough may dominate. Measuring the pressure reactivity index online as an index of the state of autoregulation [6], may be helpful in differentiating between patients who can benefit from a more forced CPP therapy, from those for whom therapy aimed at an improvement of blood brain barrier integrity is more appropriate.

Free radicals

Enhanced free radical production is a major concern of prolonged oxygen therapy and has been demonstrated in ischaemia reperfusion [10, 40, 44] or fluid percussion models [20, 44]. However, the concern is probably not justified, because many studies show no elevation of free radical production following oxygen enhancement [1, 17, 39, 42, 44]. Clinical trials with free radical scavengers such as PEG-SOD and tirilazad-mesylate have neither proved nor disapproved a role for free radicals in head injury [34, 68]. Potentially irreversible lung injury has been described by using an FiO₂ of 1.0 24 to 36 hours [2] and these regimens therefore should be avoided [59, 63, 64].

Conclusion

Increasing the fraction of inspired oxygen (FiO₂) is a simple manoeuvre and seems to influence brain metabolism, as shown by the reduction in brain microdialysis lactate. Either alone or in combination with therapies aimed at optimising CPP and/or reestablishment of the blood brain barrier, it may minimize secondary injury following severe head injury. Experimental studies, using standardized trauma models are needed along with multicenter, prospective, randomized, clinical studies with analysis of outcome.

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Comment

This prospective observation cohort study, conducted on 20 patients with severe head injury describes the effects of increasing FiO₂ on brain tissue PtiO₂, lactate and glucose concentrations in microdialysate of the brain and further describes the relation between CPP and brain tissue PtiO₂. Monitoring of brain tissue oxygen tension and microdialysis were introduced into clinical practice approximately 10 years ago. Microdialysis has remained mainly confined to research settings, but the technique of brain tissue oxygen monitoring has, partly because of its simplicity, gained wide acceptance in neuro intensive care and is now routinely employed in many centers. Studies in TBI have shown a frequent occurrence of low values of PtiO₂ in the initial 12 to 24 hours and the occurrence of such values is related to poorer outcome. We are now at the turning point where results of this currently accepted monitoring technique can be translated into improved therapeutic strategies, aiming at increasing the chances for better outcome in individual patients. This manuscript represents a significant step forward in this direction. The authors convincingly demonstrate that increasing FiO₂ improves brain tissue oxygen tension. They further show that during the oxygen challenge period of 6 hours lactate levels are lower in microdialysate of the brain than in the following period. These observations would support the concept for improving cerebral oxygenation following severe head injury by simply increasing FiO₂. There remain however many clinical and also basic questions which need to be answered before this approach should be routinely adopted in neuro-intensive care. Somewhat unfortunately this manuscript focuses on means and averages in the population described. This approach for goes opportunities for individualized targeted management based on multimodality monitoring. It may well be that for instance the slope of diffusion of oxygen between the arterial circulation and the brain tissue may be relevant. The authors for instance described that in patients in whom low PtiO₂ was not increased on elevating FiO₂ fatal outcome occurred in 4 out of 6 cases; presumably in the other 2 cases in which this phenomenon was observed, the local values were influenced by the presence of hemorrhage contusions. This observation highlights the limitations and potential pitfalls of a regional technique. It should further be recognized that measured values of PtiO₂ with the technique employed represent average values from the recruitment area surrounding the probe. This recruitment area is determined by the number, spatial distribution and diameter of local vessels contributing to tissue perfusion. In this regard equal

attention should be paid to improving local microcirculation as well as it to improving FiO₂. The observation from the Lorentzian analysis showing a peak of PtiO₂ at a CPP of 78 mmHg is of interest and would support the concept of maintaining CPP between 70 and 80 mmHg. However here again the limitations of analysis of averages is pertinent and hopefully in the future more targeted values in individual patients can be determined by results of multimodality monitoring.

Although the authors correctly state that prospective randomised clinical studies will be required to demonstrate clinical efficacy of oxygen targeted management in head injury I doubt whether such will be achievable and is in fact even necessary. Personally I would

be quite happy if functional studies such as fMRI or PET studies would show positive effects of oxygen targeted management on cerebral function.

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