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# Monitoring brain tissue oxygen tension in brain-injured patients reveals hypoxic episodes in normal-appearing and in peri-focal tissue

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**Abstract** *Objective:* We compared brain tissue oxygen tension ($PtiO_2$) measured in peri-focal and in normal-appearing brain parenchyma on computerized tomography (CT) in patients following traumatic brain injury (TBI). *Design:* Prospective observational study. *Setting:* Neurointensive care unit. *Patients and participants:* Thirty-two consecutive TBI patients were subjected to $PtiO_2$ monitoring. *Interventions:* Peri-focal tissue was identified by the presence of a hypodense area of the contusion and/or within 1 cm from the core of the contusion. The position of the tip of the $PtiO_2$ probe was assessed at follow-up CT scan. *Measurements and results:* Mean $PtiO_2$ in the peri-contusional tissue was $19.7 \pm 2.1$ mmHg and was lower than $PtiO_2$ in normal-appearing tissue ($25.5 \pm 1.5$ mmHg, $p < 0.05$), despite a greater cerebral perfusion pressure (CPP) ($73.7 \pm 2.3$ mmHg vs. $67.4 \pm 1.4$ mmHg, $p < 0.05$). We observed both in peri-focal tissue and in normal-appearing tissue episodes of brain hypoxia ($PtiO_2 < 20$ mmHg for at least 10 min), whose median duration was longer in peri-focal tissue than in normal-appearing tissue (51% vs. 34% of monitoring time, $p < 0.01$). In peri-focal tissue, we observed a progressive $PtiO_2$ increase from pathologic to normal values ($p < 0.01$). *Conclusions:* Multiple episodes of brain hypoxia occurred over the first 5 days following severe TBI. $PtiO_2$ was lower in peri-contusional tissue than in normal-appearing tissue. In peri-contusional tissue, a progressive increase of $PtiO_2$ from pathologic to normal values was observed over time, suggestive of an improvement at microcirculatory level.

**Keywords** Traumatic brain injury · Brain oxygenation · Brain hypoxia · $PtiO_2$ · Secondary insults · Pathophysiology

## Introduction

Severe traumatic brain injury (TBI) is the leading cause of death in young adults in developed countries and leads to significant disability and breakdown of personal relationships in survivors, resulting in an enormous cost to society [1]. To date, TBI management is based on prompt diagnosis and removal of intracranial mass lesions and avoidance/treatment of intracranial and systemic insults [2].

Global and regional cerebral ischemia/hypoperfusion have been observed in animal models of TBI, in brain-injured patients and following analysis of post-mortem tissue [3–5]. Measures taken to insure adequate cerebral oxygenation are therefore of paramount importance in the management of TBI. The evaluation of brain oxygenation in TBI patients has been traditionally performed using measurements of jugular bulb hemoglobin oxygen saturation ($SjO_2$) and evaluation of arterio–jugular oxygen difference ($AjDO_2$), which permit the identification of global cerebral ischemia. However, regional cerebral ischemia has been reported during the first 24 h post injury following TBI despite the presence

of normal $SjO_2$ saturation and $AjDO_2$, with potential deleterious effects on the final outcome of these patients [6].

The measurement of cerebral blood flow (CBF), oxygen extraction fraction (OEF), brain oxygenation and cerebral metabolic rate of oxygen ($CMRO_2$) can be performed using positron emission tomography (PET), which provides information on global and regional brain oxygenation following TBI [7–10]. However, this monitoring technique can be performed only in selected centers and it has the limitation of offering only a snapshot of brain perfusion, while the evaluation of brain at risk for hypoxia ideally requires a continuous method of monitoring.

Brain tissue oxygen tension ($PtiO_2$), the measurement of the mean tissue $O_2$ tension over a volume of a few cubic millimeters that contains extracellular fluid, capillaries, cells, and axons, can be measured using sensors placed directly into the brain parenchyma [11]. $PtiO_2$ represents a balance between $O_2$ delivery ($DO_2$) to the brain and its consumption. Advantages of this technique include the ability to detect changes in regional brain oxygenation that would otherwise be missed by measuring $SjO_2$ [12] and its ability to provide data continuously over long periods during the critically acute post-traumatic period. Following TBI, a relationship has been established between outcome and $PtiO_2$ levels and/or $PtiO_2$ reactivity to hyperoxia [13–17]. However, a debate still exists on whether this technique should be employed in apparently undamaged brain parenchyma (normal-appearing regional monitoring, reflective of global oxygenation), or preferably in the penumbral zone of contusions/infarctions (peri-focal regional monitoring), with the objective of monitoring vulnerable regions. In this study, we describe and compare the $PtiO_2$ measured in undamaged and in peri-focal brain parenchyma of patients following TBI.

## Materials and methods

### Patient population

The study was approved by the Local Research Ethics Committee of the Ospedale Maggiore Policlinico, Milan. Inclusion criteria were:

- Age over 15 years
- Severe TBI requiring mechanical ventilation
- CT scan evidence of cerebral traumatic lesions
- ICP monitoring
- Informed consent from the next of kin

Evidence of coagulopathy was an exclusion criterion. Patients ($n = 32$) admitted to our neurosurgical ICU following TBI were enrolled as subjects in this study.

### Clinical management

Consecutive patients were admitted to ICU after initial stabilization or surgical evacuation of an intracranial hematoma. Management goals included arterial tissue oxygen tension ($PaO_2$) > 100 mmHg, mean arterial pressure (MAP) > 90 mmHg, ICP < 20 mmHg, with CPP > 60 mmHg, in accordance with established guidelines for the management of severe head injury [2]. CPP was calculated as the difference between MAP and ICP with transducers calibrated to zero at the foramen of Monro. ICP was measured with intraventricular catheters in 4 patients, intraparenchymal catheters in 14 and subdural catheters in 14. All patients had a jugular bulb catheter to allow for determination of $SjO_2$ saturation and calculation of $AjDO_2$ differences according to the following formula: $AjDO_2$ = [(arterial saturation of $O_2$–jugular saturation of $O_2$)*hemoglobin grams*1.34]+[(arterial $PO_2$–jugular $PO_2$ mmHg)*0.003]. The internal jugular vein was cannulated ipsilaterally to the more damaged hemisphere. The tip was positioned at the jugular superior bulb and correct placement of the catheter was confirmed by skull X-ray.

### Brain $PtiO_2$ monitoring

Brain $PtiO_2$ was continuously measured using a polarographic Clark-type microcatheter (Licox, Kiel, Germany) or a multiparameter sensor (Neurotrend Cerebral Tissue Monitoring System; Codman, Bracknell, UK). Patients underwent insertion of the $PtiO_2$ probe in the operating room either under direct vision after neurosurgical interventions, otherwise through a burr hole. In patients with cerebral contusions detected by computed tomography (CT), our objective was to insert the probe within the hypodense area around the core of the contusion. $PtiO_2$ monitoring commenced after radiological identification of contusion with a surrounding hypodense area. In patients with diffuse injury and no visible contusions on CT scan, the $PtiO_2$ probe was inserted concomitant with the placement of the probe for ICP monitoring. A postoperative CT scan was performed to determine the proper position of the sensor. (Our standard protocol consists of scans at 5-mm intervals in the posterior fossa and 10-mm intervals in the supratentorial space. We used 5-mm slice intervals in the supratentorial space too in cases in which we needed to clarify the position of the probe tip.) Monitoring of $PtiO_2$ in peri-focal tissue was defined by the presence of the tip of the probe in the hypodense area of the contusion (as seen on CT scan) and/or within 1 cm from the core of the contusion, since this tissue recapitulates a penumbra-like condition as recently shown by measuring regional CBF [18]. One centimeter away apart from the contusion core and outside the hypodense peri-contusional tissue, the CBF is above the ischemic threshold and comparable to

normal-appearing control tissue [18]. The measurement of the distance between $PtiO_2$ probe and the core of the contusion was performed using the Osiris imaging software (Digital Imaging Unit, University Hospital of Geneva, Switzerland). Brain $PtiO_2$ was allowed to stabilize for 2 h after insertion of the probe. When Licox was used, $PtiO_2$ was corrected by the temperature.

### Data management

MAP, ICP and $PtiO_2$ data were transmitted from the monitor to a computer through an analog–digital (AD) converter (Mac Lab; World Precision Instruments Castle Hill, NSW, Australia) for storage and analysis. Artifacts caused by nursing interventions or by temporary disconnection of catheters because of transport were manually eliminated from the datasets. Episodes of brain hypoxia (lasting at least 10 min) were categorized as "moderate hypoxia" if $PtiO_2$ was in the range 10–19 mmHg or as severe hypoxia if $PtiO_2$ was $< 10$ mmHg [11, 14–16, 19–25].

### Statistical analysis

Data are presented as mean ± standard error of the mean. Data in the peri-focal and normal-appearing group were compared using a *t*-test. Non-parametric data are presented as median values and were compared using Mann–Whitney test. The incidence of episodes of brain hypoxia between the two groups was compared using the Fisher exact test. Trends of $PtiO_2$ and CPP over time were evaluated using an analysis of variance (ANOVA) for repeated measurements by a mixed procedure (SAS System, version 8; SAS Institute, Cary, NC). The variables $PtiO_2$ and CPP were modeled as linear functions of time (SAS System for Mixed Models, Cary, NC: SAS Institute, 1996). A difference with a probability of less than 0.05 was considered statistically significant.

## Results

### Patients' characteristics

Mean age was 37.5 ± 3.6 years (range 16–85 years) and 6 (19%) were female. The median post-resuscitation Glasgow coma score (GCS) was 5 (it was similar in the two groups); 81% of patients had an initial GCS ≤ 8. All patients had a GCS ≤ 8 at the time of $PtiO_2$ monitoring. According to the Marshall CT classification, 9 patients were classified as diffuse injury II (1 peri-focal group), 1 patient as diffuse injury III (normal-appearing group), 20 patients as evacuated mass lesions (14 peri-focal group) and 2 patients as non-evacuated mass lesions (normal-appearing group) [26].

### $PtiO_2$ monitoring in peri-focal versus normal-appearing tissue

A total of 34 probes were placed intracranially to monitor $PtiO_2$. Two patients received two probes, (one for repositioning and the second because the first probe stopped working properly). Fifteen of the 34 probes were placed directly in the area adjacent to a focal lesion. Monitoring of $PtiO_2$ began on day 3 post injury in the peri-focal tissue "group" and day 2 post injury in the normal-appearing tissue "group", continuing for 71 ± 8.7 h and 85 ± 8.5 h ($p = 0.2$), respectively.

Mean $PtiO_2$ in peri-focal tissue was 19.7 ± 2.1 mmHg, significantly lower than in normal-appearing tissue (25.5 ± 1.5 mmHg, $p < 0.05$; Fig. 1) despite higher CPP (73.7 ± 2.3 mmHg vs. 67.4 ± 1.4 mmHg, $p < 0.05$). No additional differences were observed in other variables that could have influenced the $PtiO_2$ as shown in Table 1.

### Incidence of brain hypoxia

Brain hypoxia ($PtiO_2 < 20$ mmHg) was observed when $PtiO_2$ was measured in both peri-focal and normal-appearing tissue. The duration of cerebral hypoxia in peri-focal tissue (51% of monitoring time) was significantly greater than that observed in normal-appearing tissue (34%, $p < 0.01$; Fig. 2). The median duration of hyp-

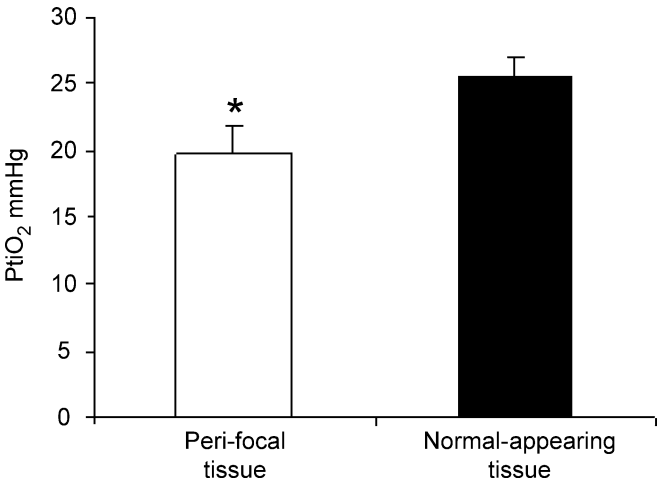


**Fig. 1** $PtiO_2$ in peri-focal versus normal-appearing tissue. Mean $PtiO_2$ in peri-focal tissue was significantly lower than $PtiO_2$ in normal-appearing tissue. Data are presented as mean ± standard error of the mean. * $p < 0.05$

**Table 1** Physiological data in peri-focal group and in normal-appearing tissue group

| | Peri-focal regional monitoring | Normal-appearing regional monitoring | *p* value |
|---|---|---|---|
| ICP (mmHg) | $15.9 \pm 0.9$ | $15.3 \pm 0.8$ | 0.6 |
| CPP (mmHg) | $73.7 \pm 2.3$ | $67.4 \pm 1.4$ | 0.02 |
| $PaO_2$ (mmHg) | $143.3 \pm 4.5$ | $132.1 \pm 4.3$ | 0.09 |
| $PaCO_2$ (mmHg) | $28.8 \pm 0.9$ | $30.7 \pm 0.9$ | 0.1 |
| $SjO_2$ (%) | $71 \pm 0.2$ | $67 \pm 0.1$ | 0.1 |
| $AjDO_2$ (vol%) | $3.7 \pm 0.2$ | $4.2 \pm 0.2$ | 0.08 |
| Hb (g/100 ml) | $9.3 \pm 0.2$ | $9.9 \pm 0.2$ | 0.06 |
| T° | $37.5 \pm 0.2$ | $37.5 \pm 0.1$ | 0.9 |

$PaO_2$, $PaCO_2$, $SjO_2$, $AjDO_2$, Hb and T° were collected twice a day at 8 a.m. and 8 p.m. and stored electronically in an Excel spreadsheet. Values in the table represent the mean values calculated during $PtiO_2$ monitoring time.
*ICP*, intracranial pressure; *CPP*, cerebral perfusion pressure. ICP and CPP values represent the mean values recorded during $PtiO_2$ monitoring time (obtained averaging the mean ICP and CPP related to each probe).
*$SjO_2$*, oxygen saturation measured in bulb of internal jugular vein; *$AjDO_2$*, arterio–jugular oxygen difference; *Hb*, hemoglobin; *T°*, external temperature

**Table 2** Duration of episodes of moderate and severe brain hypoxia in peri-focal and in normal-appearing tissue

| | Peri-focal regional monitoring | Normal-appearing regional monitoring | *p* value |
|---|---|---|---|
| Moderate hypoxia | | | |
| Duration of episodes (minutes, median) | 64 | 50 | $< 0.01$ |
| Total time of moderate hypoxia, minutes (range) | 24049 (10–2927) | 22544 (10–1157) | |
| Percentage of monitoring | 34% | 23% | $< 0.01$ |
| Severe hypoxia | | | |
| Duration of episodes (minutes, median) | 64 | 39 | $< 0.05$ |
| Total time of severe brain hypoxia, minutes (range) | 11651 (10–2032) | 10402 (10–1186) | |
| Percentage of monitoring | 17% | 11% | $< 0.01$ |

oxic episodes of moderate severity ($PtiO_2$ 10–19 mmHg) was significantly longer in the peri-focal tissue compared to the normal-appearing tissue, ($p < 0.01$; Table 2). We observed 75 episodes of severe brain hypoxia, where $PtiO_2$ sank to less than 10 mmHg, in the peri-focal tissue and 102 episodes in the normal-appearing tissue; however the median duration of these episodes and the total time of severe brain hypoxia were significantly longer in the peri-focal tissue than in the normal-appearing tissue ($p < 0.05$; Table 2).

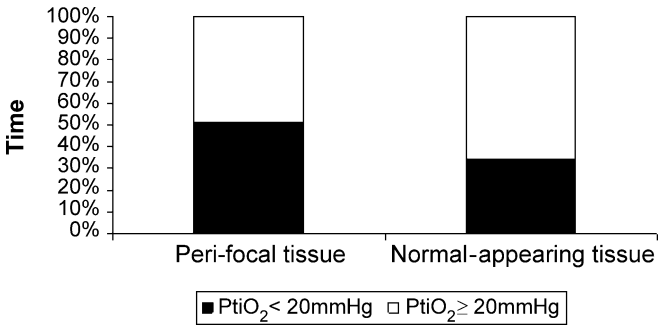


**Fig. 2** Duration of brain hypoxia in peri-focal and normal-appearing tissue. Brain hypoxia ($PtiO_2 < 20$ mmHg) was observed 51% and 34% of the time in the peri-focal and normal-appearing tissue respectively ($p < 0.01$)

*Brain hypoxia in the peri-focal tissue*

In the peri-focal tissue, no significant relationship was observed between $PtiO_2$ and CPP, $PaO_2$, $PaCO_2$ or Hb. Interestingly, CPP was $< 60$ mmHg in only 4.8% of the cases, suggesting that only in a minority of episodes was global hypoperfusion associated with regional brain hypoxia. Moderately hypoxic episodes (mean $PtiO_2$ $14.5 \pm 0.2$ mmHg) and severely hypoxic episodes (mean $PtiO_2$ $7.2 \pm 0.2$ mmHg) were associated with similar values of CPP ($75.9 \pm 1$ mmHg and $73.1 \pm 1.6$ mmHg respectively, $p =$ ns), $PaO_2$ ($156 \pm 2.6$ mmHg and $151 \pm 3.7$ mmHg, $p =$ ns), $PaCO_2$ ($28.8 \pm 0.9$ mmHg and $28 \pm 0.5$ mmHg, $p =$ ns) and Hb ($9.2 \pm 0.1$ g/100 ml and $9 \pm 0.1$ g/100 ml, $p =$ ns). Parameters of global cerebral oxygenation were not suggestive of regional brain hypoxia since during moderate versus severe hypoxia

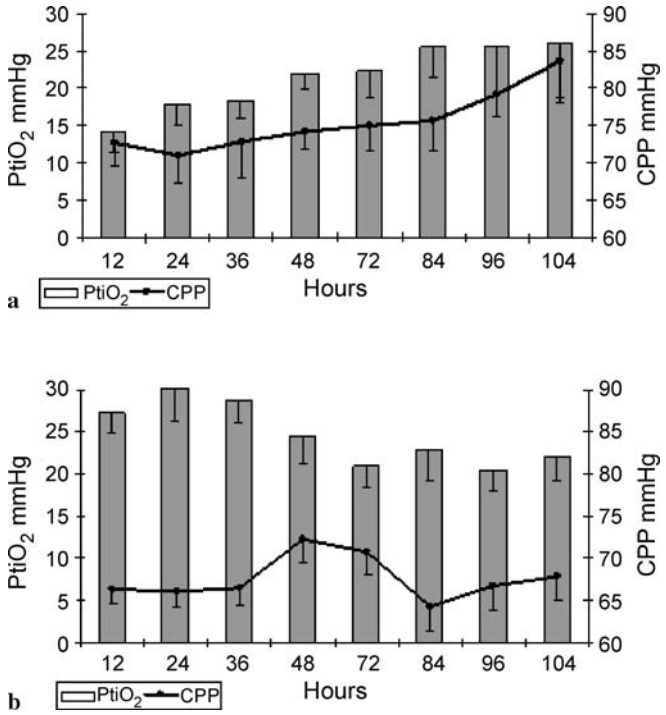


**Fig. 3** $PtiO_2$ over time in peri-focal and normal-appearing tissue. In peri-focal tissue we observed a progressive $PtiO_2$ increase over time from pathologic values to normal values ($p = 0.01$) with no significant change in CPP ($p = 0.28$; **a**). In normal-appearing tissue we did not observe any trend during the monitoring either for $PtiO_2$ ($p = 0.18$) and for CPP ($p = 0.34$; **b**). Data are presented as mean of 12 h of monitoring ("studies") ± standard error of the mean

$AjDO_2$ was 3.3 ± 0.1 vol. % and 3.2 ± 0.18 vol. %, respectively ($p$ = ns).

*Brain hypoxia in normal-appearing tissue*

Also in normal-appearing tissue, no relationship was observed between $PtiO_2$ and CPP, $PaO_2$, $PaCO_2$ and Hb. Reduced CPP (< 60 mmHg) was observed in 17% of the cases, which was a significantly greater proportion than in the peri-focal tissue ($p < 0.01$). Moderately hypoxic episodes (mean $PtiO_2$ 14.7 ± 0.2 mmHg) and severely hypoxic episodes (mean $PtiO_2$ 7.5 ± 0.13 mmHg) showed similar values for $PaO_2$ (133 ± 1.7 mmHg and 134 ± 2.6 mmHg, $p$ = ns) and Hb (10.1 ± 0.06 g/100 ml and 10 ± 0.08 g/100 ml, $p$ = ns). In contrast, CPP during severe brain hypoxia in the normal-appearing tissue (76.2 ± 1.8 mmHg) was significantly greater than that observed during moderate hypoxia (72 ± 1 mmHg, $p < 0.05$). Moreover, we observed a significantly greater $PaCO_2$ during severe hypoxia (32.7 ± 0.4 mmHg) than during moderate hypoxia (31 ± 0.3 mmHg, $p < 0.01$). $AjDO_2$ values were similar during episodes of severe and moderate hypoxia (4.5 ± 0.08 vol. % and 4.8 ± 0.14 vol. % respectively, $p = 0.08$).

$PtiO_2$ over time in peri-focal and normal-appearing tissue

In peri-focal tissue, a progressive elevation in $PtiO_2$ was observed over time during the first 4 days of monitoring ($p = 0.01$). Brain oxygenation was < 20 mmHg during the first 36 h, then progressively rose and stabilized during the subsequent 2 days. During the first 12 h of monitoring, $PtiO_2$ was < 20 mmHg in 11 patients and rose to normal values in 7 of them. In contrast, we observed only a slight increase in CPP during the same period ($p = 0.28$, Fig. 3a). In the normal-appearing tissue, the average $PtiO_2$ was normal during the first 4 days of ICU monitoring (range 20.4 ± 2.6 mmHg to 30.2 ± 3.9 mmHg, Fig. 3b).

## Discussion

In the present study we observed that (1) $PtiO_2$ is lower in the peri-contusional tissue than in normal-appearing tissue despite a significantly greater CPP; (2) episodes of regional brain hypoxia (undetected by measures of global cerebral oxygenation) occur both in normal-appearing and in peri-contusional tissue; (3) in peri-contusional tissue, a progressive $PtiO_2$ increase from pathologic to normal values occurs over time, suggestive of an improvement at the microcirculatory level.

A debate exists on whether $PtiO_2$ should be monitored in apparently undamaged brain parenchyma, or in the penumbral zone of contusions [27], with the objective of detecting brain hypoxia in vulnerable regions that may be overlooked by the monitoring of global cerebral oxygenation [6]. In our study, peri-focal $PtiO_2$ was significantly lower than $PtiO_2$ measured in normal-appearing tissue. Oxygen transport to the brain depends on the respiratory and circulatory systems and on local vascular factors. Oxygen is transported from alveolar air to blood and from blood to peripheral tissues and finally to the mitochondria via diffusion steps. At the microvascular level, oxygen diffusion is mostly dependent on the tension gradient between vessels and tissue and is inversely related to the diffusion distance [25]. The two groups in our study were similar in terms of blood oxygen content and $PaCO_2$, and it is unlikely that the significantly greater CPP (73.7 ± 2.3 mmHg vs. 67.4 ± 1.4 mmHg) would translate into an increased global CBF (assuming preserved pressure autoregulation). Electron-microscopic analysis of contused brain tissue removed during neurosurgical procedures in patients following TBI has shown glial swelling with narrowing of blood vessels whose lumen might be occluded by circulating leukocytes/red blood cells and microthrombi [21, 28, 29], suggesting that a reduced

regional CBF and a relative reduction of vessels/capillary density within the hypodense area of a cerebral contusion might be responsible for the reduced local oxygen delivery and diffusion, leading to the lower $PtiO_2$ in peri-focal tissue.

To date, some uncertainty remains concerning the critical $PtiO_2$ threshold, because different studies have utilized different probes (Licox, Paratrend and Neurotrend) placed in different locations (gray versus white matter) and because the threshold and duration of hypoxia associated with irreversible damage to the CNS has not been clarified. Since proposed thresholds have ranged from 5 mmHg to 20 mmHg using the Licox and the Neurotrend [11, 14–16, 20–25, 30], we defined moderate brain hypoxia as a $PtiO_2$ in the range 10–19 mmHg and severe brain hypoxia as $PtiO_2 < 10$ mmHg. In our patients brain hypoxia occurred in normal-appearing tissue and in peri-focal tissue, where it persisted for a longer time. Kiening et al. showed that the hypoxic $SjO_2$ threshold of 50% corresponded to a $PtiO_2$ of 8.5 mmHg, and indicated a CPP cut-off of 60 mmHg at which $SjO_2$ and $PtiO_2$ were shown to be sufficient [20]. In our study we observed that a normal $SjO_2$ does not exclude regional brain hypoxia, suggesting that $PtiO_2$ monitoring should be performed in addition to $SjO_2$ measurements. We attempted to relate hypoxic episodes with intracranial/systemic complications but we could not find any relationship between brain hypoxia and hypotension, hypoxemia, anemia or hypocapnia, suggesting that in order to understand the pathophysiology of $PtiO_2$ we should move from a focus on macrocirculation to microcirculation and that local $O_2$ diffusion alterations from blood vessels to the tissue are likely to be the major determinant of the observed pathologic $PtiO_2$ [21, 31].

Although van den Brink et al. observed that $PtiO_2$ monitored in normal-appearing tissue was pathologic in about 50% of comatose TBI patients during the first 12–24 h post injury and then increased to normal levels for 5 days post injury [15], we did not observe any significant trend in $PtiO_2$ over time in normal-appearing tissue. A possible explanation of these difference is that van den Brink and colleagues initiated $PtiO_2$ monitoring within the first 12 h post injury while our study commenced on the 2nd day post injury, when global CBF is likely to be restored [10]. In contrast, in peri-focal tissue we observed a progressive $PtiO_2$ improvement that was not linked to a similar CPP trend, suggesting that this improvement might be the result of changes at microvascular level [32], such as local vasodilation, edema reduction, and lysis of microthrombosis.

Our study has limitations: Since we could not measure the CBF, our data interpretation is largely hypothetical. Additionally, our evaluation of peri-focal tissue was strictly based on a morphological evaluation. Since we used two different catheters, we evaluated whether the observed difference in peri-focal and normal-appearing groups could be due to the different technology. Neurotrend (which underestimates $PtiO_2$ compared to Licox [33]) was used only in normal-appearing tissue, where $PtiO_2$ values were higher; therefore, catheter location was the determinant of the results of the study (data not shown).

In our study $PtiO_2$ monitoring and comparison between normal-appearing and peri-focal tissue was performed in different patients starting respectively on day 2 and day 3 post-injury. Ideally, the comparison of $PtiO_2$ in "normal" and peri-contusional brain would be to monitor the two areas in the same patient. However, because of the invasive nature of this technology, we consider the insertion of two probes unethical.

Our findings confirm that $PtiO_2$ provides information not disclosed by other monitoring modalities, such as CPP or $AjDO_2$, and critically dependent on the position of the probe. Unsuspected transient episodes of brain hypoxia have been detected both in contused and normal-appearing tissue. The consequences of these episodes on long-term outcome require further investigation.

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