REVIEW

Direct cerebral oxygenation monitoring—a systematic review of recent publications

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Abstract This review has been compiled to assess publications related to the clinical application of direct cerebral tissue oxygenation (PtiO$_2$) monitoring published in international, peer-reviewed scientific journals. Its goal was to extract relevant, i.e. positive and negative information on indications, clinical application, safety issues and impact on clinical situations as well as treatment strategies in neurosurgery, neurosurgical anaesthesiology, neurosurgical intensive care, neurology and related specialties. For completeness' sake it also presents some related basic science research. PtiO$_2$ monitoring technology is a safe and valuable cerebral monitoring device in neurocritical care. Although a randomized outcome study is not available its clinical utility has repeatedly been clearly confirmed because it adds a monitoring parameter, independent from established cerebral monitoring devices. It offers new insights into cerebral physiology and pathophysiology. Pathologic values have been established in peer-reviewed research, which are not only relevant to outcome but are treatable. The benefits clearly outweigh the risks, which remains unchallenged in all publications retrieved. It is particularly attractive because it offers continuous, real-time data and is available at the bedside.

Keywords Review · Cerebral oxygenation · Licox · Neurotrend · Cerebral partial pressure of oxygen · Brain tissue oxygenation

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Methods

This review is based on a systematic "MEDLINE" literature search using the following search terms: "licox", "neuro-trend", "brain tissue oxygenation", "cerebral oxygenation" and "cerebral partial pressure of oxygen". Only a few publications were not retrieved using this technique. They were, however, identified through personal communication with scientists in the field and meeting proceedings. This strategy provided sufficient certainty that relevant papers have not been missed. We excluded published or unpublished meeting abstracts or proceedings for this review. To address relevant matters, related to specific PtiO$_2$ issues, we have included a few papers published in supplements only when no other peer-reviewed information was available.

Results

The MEDLINE search provided over 1,400 matches, which were sorted and then scanned. For this review we restricted the literature search to peer-reviewed publications from 2004, 2005 and up to May 2006. Only relevant publications

and a few non-peer-reviewed publications published in supplements prior to 2004, which explicitly addressed or systematically examined the above issues, are included in this review and are listed in the reference section.

Indications and applications

Human

PtiO$_2$ monitoring technology is largely used in neurosurgical and neurologic intensive care. The majority of publications are based on analysis of data from patients suffering from severe traumatic brain injury (TBI), which indicates that this condition represents the largest field of clinical application [11, 13, 16, 32, 44, 47, 50, 59, 66, 68, 74]. It is also used in patients with multiple extracranial injuries and TBI [20]. The second largest group of publications comprises aneurysmal subarachnoid haemorrhage (SAH) [9, 18, 29, 31, 36, 60, 64–66, 68] (Fig. 1). PtiO$_2$ monitoring is also used intraoperatively during aneurysm surgery [33] and surgery of cerebral arteriovenous malformations [26] as well as during cerebral angiography [9]. A monitoring course of brain tissue oxygenation during cardiopulmonary resuscitation has been published on a case report basis [27].

Animal

Direct brain tissue oxygenation (PtiO$_2$) monitoring has also been used in animal models of spontaneous intracerebral haemorrhage [23] and malignant soft tissue tumours [4, 49]. In addition it is used to measure oxygen delivery to brain parenchyma in animal models [7, 10, 48]. It is also

used in animal models to study cerebral oxygenation during postasphyxial seizures [19] and transfusion protocols [21].

Clinical applications

The majority of publications come from Germany, Italy, Spain, The Netherlands, the UK and the USA [1, 2, 4–6, 12, 13, 16, 18, 22, 23, 25–27, 31, 38, 44, 49, 54, 55, 58–60, 62, 66, 68, 70, 71, 74]. There is one publication each from Australia [46], China [32], Singapore [47] and Switzerland [50].

PtiO$_2$ monitoring is almost exclusively used in combination with other cerebral non-invasive and invasive monitoring modalities, in particular intracranial pressure (ICP) monitoring [22, 29, 51, 65, 66], cerebral perfusion pressure monitoring [35, 38, 46, 47], jugular venous saturation (JvDO$_2$) monitoring [70], cerebral microdialysis [8, 11, 36, 56, 57, 61], cerebral blood flow velocity measured by transcranial Doppler ultrasound (TCD) [38, 74], regional cerebral blood flow measurements (rCBF) [31], near infrared spectroscopy (NIRS) [6] and intracranial temperature measurements [32].

Oxygen monitoring technologies

Two monitoring devices are currently available, "Licox" and "Neurotrend" technology. Licox is manufactured by GMS-Integra (Kiel-Mielkendorf, Germany). Neurotrend is manufactured by Codman (Raynham, MA, USA).

The Neurotrend probe uses optical sensors. Measurements are obtained through a dye which is connected to a fiberoptic cable. The properties of the dye change along

Fig. 1 This figure shows a patient suffering from aneurysmal subarachnoid haemorrhage. The small PtiO$_2$ catheter is visible in the right-sided cerebral white matter, contralateral to the larger external ventricular drain. This scan was obtained after decreasing PtiO$_2$ values with normal ICP values noted. Shortly thereafter the patient suffered a large right-sided cerebral infarct. Early signs of right-sided ischaemia can be appreciated
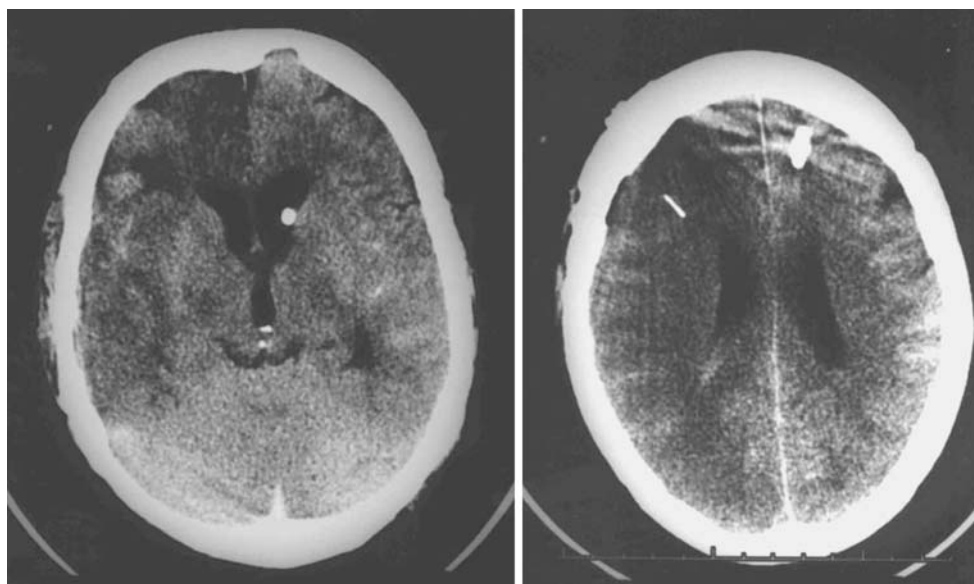
with gas concentrations and pH of adjacent tissues, which in turn reflects tissue partial pressure of oxygen. The Neurotrend probe contains four sensors; it measures $PtiO_2$, $PtiCO_2$, tissue pH and tissue temperature. Its sampling area is around 2 mm^2.

The Licox probe uses a polarographic cell in which oxygen diffuses from the tissue through the catheter polyethylene wall into its inner electrolyte chamber. Oxygen is transformed at the electrode where it determines an electrical current. The electrical current reflects tissue $PtiO_2$. Its sampling area is around 14 mm^2, seven times the size of the Neurotrend probe.

The Neurotrend probe yields lower values compared to the Licox probe. This is a difference due to the probe's monitoring techniques, which users must be aware of. It does not indicate measurement validity. Comparative studies are presented further on in the paper.

Catheter placement and sampling size

Catheters are generally placed in the right frontal lobe white matter in diffuse brain injury, or on the affected side in a hemispheric injury, and by and at large remain in situ for as long as ICP measurements are required [43, 73]. Although it is a local measurement, restricted to a small cerebral volume, its utility for reflecting hemispheric conditions has been demonstrated in studies where $PtiO_2$ measurements were correlated with cerebral arteriovenous oxygen difference ($AVDO_2$) and cerebral blood flow (CBF) measurements. Not only did they show a strong correlation but they also showed that $PtiO_2$ measurements did pick up more ischaemic events than the global measurement [37, 52, 53].

The metabolic heterogeneity of different tissue types is well known because it affects sampling size considerations. It is important to factor in the heterogeneous nature of the brain when interpreting oximetry data. Early experiments on rats have demonstrated the differing $PtiO_2$ within the cortex depending on the depth of probe placement [3]. It was proposed that the differing base levels relate to the metabolism, microcirculation and overall microstructure of each environment. Furthermore, depending on the probe's relationship to the arterial microvessels, a gradient within the tissues can exist with oxygen levels decreasing over the space from arterial to venous circulation. The microenvironment is influenced by the cerebral blood flow velocity of each microenvironment, with low velocities showing the highest variability in terms of oxygenation differences [40].

This translates into a situation where spatial heterogeneity must be compensated for by a sufficiently large sensor sampling area to minimize the so-called random position error. This random position error will yield $PtiO_2$ levels anywhere from 15 to 40 mmHg if the O_2-sensitive area is limited to 1.4 mm in length. If the area is increased

to 5.0 mm, the range is reduced to values between 25 and 30.

Impact on clinical situations and treatment strategies

There are numerous and most interesting findings which have been derived from about 10 years of research using $PtiO_2$ technology. The following paragraphs summarize the important ones:

Normal $PtiO_2$ values based on Licox technology are around 25–30 mmHg, based on animal research [41]. This was confirmed in patients with normal ICP and CPP [15, 37].

A study published in 1998 using Licox technology demonstrated that the likelihood of death increased with increasing duration of time at or below a $PbtO_2$ of 15 mmHg (2.0 kPa) or with the occurrence of any $PbtO_2$ values of < or=6 mmHg (<or=0.8 kPa) [72]. This study shows that $PtiO_2$ technology has prognostic value in the treatment of patients with severe traumatic brain injury. This study has also helped to establish a generally accepted treatment threshold, which has been confirmed in other papers [9, 46].

Of interest is another paper, which has reported that "the presence of anaerobic cerebral metabolism probably depends on duration and severity of the hypoxic episode" [56]. This conclusion is relevant for clinical practice because it shows that (a) $PtiO_2$ technology detects short episodes of cerebral hypoxia which are not picked up by other monitoring modalities and (b) magnitude and duration of cerebral hypoxia have prognostic relevance. One study also reports on the positive correlation and prognostic value of $PtiO_2$ measurements and long-term neuropsychological outcome after severe traumatic brain injury [45].

A most recent study is of particular noteworthiness [67]. In a series of 53 TBI patients, 25 patients were treated using an ICP monitor alone while 28 patients had $PtiO_2$-directed care, with comparable ICP and CPP levels for each group. The mortality rate was 44% for the first group and 25% for the second group, which was statistically significant. Although they were not exactly matched for age, 44± 14 years for the ICP/CPP group vs 38±18 years for the $PtiO_2$ group, the outcome difference was significant ($p< 0.05$). They conclude that "the use of both ICP and brain tissue PO_2 monitors and therapy directed at brain tissue PO_2 is associated with reduced patient death following severe TBI [67].

In 1996 and 2004 studies have addressed a long and much debated issue in neurocritical care: the role of hyperventilation for controlling intracranial hypertension. Hyperventilation constricts cerebral blood vessels, which in turn can cause hypoperfusion and ischaemia and lead to exacerbation of brain swelling. $PtiO_2$ technology has the potential to guide the degree of hyperventilation because of

its ability to indicate states of hypoperfusion and impending ischaemia [5, 12, 15]. This utility has also been demonstrated intraoperatively: "PtiO$_2$ monitoring has a high reliability in the detection of intraoperative tissue hypoxia" [26]. Similar recommendations have previously been reported [62]. One paper, however, reports that in 3 of 17 TBI patients they noted an increase of PtiO$_2$ on hyperventilation, which they called a "paradox reaction" [14]. This pattern was only seen in the early phase between days 0 and 3 after injury. It may represent flow-metabolic uncoupling, and it stresses the utility of multimodality monitoring for which other parameters are used as well.

PtiO$_2$ technology has been used to address another much and long debated issue in neurocritical care: the role of head elevation. A study in 2004 using PtiO$_2$ measurements has demonstrated that "routine nursing of patients with severe head injury at 30 degrees of head elevation within 24 hours after trauma leads to a consistent reduction of ICP (statistically significant) and an improvement in CPP (although not statistically significant) without concomitant deleterious changes in cerebral oxygenation" [47].

Two studies have recently addressed the utility of PtiO$_2$ technology for timing of decompressive hemicraniectomy (DCH) in severe brain swelling [51, 68]. It has been shown that not only absolute PtiO$_2$ values should be considered for the indication of DCH but also magnitude and the time course of monitoring trends [68]. Another study has concluded that "...ptiO(2) monitoring could be an important tool for timing craniectomy in the future" [51]. The effects of DCH, which represents a very invasive treatment option and which is considered an ultimate surgical treatment option, has also been studied: "DCH in the treatment of severe brain injury is associated with a significant improvement in brain oxygenation" [66]. In another, however small, series of patients it was pointed out that despite a rapid PtiO$_2$ increase and ICP reduction from critical to normal values "the patients' clinical status remained poor with two in a persistent vegetative state and one dead" [29]. This is in keeping with the long-standing and unresolved debate about the utility of DCH and its particular regard to outcome.

Two papers have addressed other long and much debated issues in neurocritical care: the effects of commonly used drugs in neurocritical care: nimodipine and mannitol. A paper published in 2005 has reported that "...although nimodipine use is associated with improved outcome following SAH, in some patients it can temporarily reduce brain tissue PO2" [65]. This report will again spark the academic discussion about whether nimodipine should be used in patients suffering from aneurysmal subarachnoid haemorrhage. The most valuable conclusion for daily neurocritical care practice which can be extracted from this study is that using PtiO$_2$ technology will identify those

patients in whom nimodipine has a negative effect [22]. With regard to mannitol it has been shown that although mannitol reduces ICP it has little effect on PtiO$_2$. This is rather unexpected because it is expected that ICP reduction will improve PtiO$_2$. The important clinical conclusion from this finding is that PtiO$_2$ technology should be used in addition to ICP monitoring as the two monitoring parameters are not ultimately linked.

Vasopressors are commonly used in neurocritical care. There is currently debate whether dopamine or noradrenaline should be preferred. PtiO$_2$ monitoring has been used to study the effects of both drugs in comparative studies. The authors report that "... CPP augmentation with norepinephrine, but not with dopamine, resulted in a significant reduction in arterial-venous oxygen difference (37±11 vs 33±12 ml/l) and a significant increase in brain tissue oxygen (2.6±1.1 vs 3.0±1.1 kPa). The CPP intervention did not significantly affect intracranial pressure. There were no significant differences between norepinephrine and dopamine on cerebral oxygenation or metabolism either at baseline or following a CPP intervention; however, the response to a CPP intervention with dopamine seemed to be more variable than the response achieved with norepinephrine" [35].

The effects of another commonly used sedative in neurocritical care, propofol, have also been studies using PtiO$_2$ monitoring. Rather unexpectedly they found that burst suppression induced by propofol has no effect on cerebral oxygenation [34].

The fraction of inspired oxygen (FiO$_2$) obviously affects cerebral PtiO$_2$ levels. One study has recently addressed this issue, which is important in the interpretation of measured PtiO$_2$ values [42]. The authors report a PtiO$_2$ increase from a baseline of 30±5 mmHg to 147±36 mmHg when the FiO$_2$ was increased from individual baseline values to 100%. When it was decreased to 0.6 FiO$_2$, PtiO$_2$ fell to 63± 6 mmHg. Another study of 52 TBI patients showed that normobaric hyperoxia treatment resulted in a significant improvement in biochemical cerebral markers [69]. Using simultaneous cerebral microdialysis they report increased glucose levels with significantly decreased glutamate and lactate levels. They also report lactate/glucose and lactate/pyruvate ratio decreases at comparable CPP levels. Outcome in the normobaric hyperoxia treatment group was improved. They concluded that: "...normobaric hyperoxia in patients with severe TBI improves the indices of brain oxidative metabolism. Based on these data further mechanistic studies and a prospective randomized controlled trial are warranted" [69].

The effects of packed red blood cell transfusion (RBCT) on brain tissue partial pressure of oxygen has also been studied. The authors report a graded response of local cerebral oxygenation in a combined group of TBI and SAH

patients [63]. In 74% of patients they observed a $PtiO_2$ increase but did not provide a suitable explanation why it fell in 26% of patients. Cerebral perfusion pressure, SaO_2, and FiO_2 were similar before and after RBCT.

One study reports on the utility of $PtiO_2$ monitoring during cerebral angiography [9]. In their series of 14 patients, 4 patients showed a linear $PtiO_2$ decrease which indicated cerebral hypoxia without ICP elevation when the cerebral catheter was advanced through cervical vessels. They also report significant correlations between severe intracranial angiographic arterial caliber reduction and reduced $PtiO_2$ values, which was also reflected in an increased number of ischaemic lesions on computed tomography (CT) imaging [9].

More complex physiological matters, which have attracted much attention in neurocritical care, have also been addressed using $PtiO_2$ technology: the role of cerebral autoregulation monitoring, i.e. the link between the mechanism of cerebral vascular regulation and cerebral oxygenation regulation. So far four studies have shown that the mechanisms are closely linked [24, 28, 38, 64]. One study has concluded that "assessment of ptiO2-autoregulation gives valuable information on which patient will benefit from an increase in CPP and which CPP should be achieved to do so" [64]. This finding is in keeping with the suggestion that CPP elevation may be beneficial for ICP control and $PtiO_2$ management in selected patients after TBI, those with intact cerebral autoregulation [24, 39].

Safety issues and technical considerations

We retrieved three papers which have systematically addressed technical issues related to using $PtiO_2$ technology [16, 17, 25]. It is assumed that the reader is familiar with the insertion of intracranial monitors using bolt or tunnelling techniques. Both Licox and Neurotrend sensors can be introduced using these techniques, which have been used for over 20 years for ICP monitoring.

In 1998 a comprehensive study addressed technical considerations and safety issues; 118 Licox catheters, which were used in 101 patients, were assessed [16]. This paper includes findings of a previous publication based on an assessment of 73 catheters [17]. The results are as follows:

1. Small iatrogenic haematomas were observed for two patients (1.7%). This number compares favourably to what has been published for similar monitoring devices, e.g. intraparenchymal intracranial pressure monitoring. This number is much smaller than what has been published for external ventricular drains which are widely for treatment of TBI patients.
2. No infection occurred after 6.7 ± 3.9 days. This number compares to what has been published (see 1 above)

3. The technical complication (dislocation or defect) rate was 13.6%. This figure is higher than what has been published (see 1 above). It does, however, not translate into patients' harm because it relates to technical malfunction. Such technical complications incur increased expenses because a fresh sensor is required.
4. The mean adaptation time was 79.0 ± 51.7 min. This number relates to this particular monitoring technology.
5. The greatest PO_2 display errors were measured during the first 4 days of continuous monitoring. There are no comparable data to further comment on this number.
6. The maximal probe display error was $1.07 \pm 2.14\%$, tested at temperatures between 22 and 37° C and tested at oxygen pressures of 0, 44 and 150 mmHg. This number is low and is irrelevant for daily clinical practice.
7. The zero display error was -0.21 ± 0.25 mmHg. This number is low and is irrelevant for daily clinical practice.
8. Excluding the first 1 h after insertion, data are reliable, with almost 100% good data quality.

Formal comparison between sensors

In vitro accuracy, long-term drift and response time were addressed in a paper published in 2005 [25]. This paper also compared Licox and Neurotrend. The authors conclude that (1) both systems measure oxygen tension sufficiently, (2) Licox technology measures more accurately than Neurotrend, (3) Neurotrend sensors read significantly lower $PtiO_2$ in 1% O_2, (4) Neurotrend sensors show an increasing deviation with higher oxygen concentrations which was due to 2 of 12 probes and (5) a slight drift towards lower oxygen tension readings for both sensors, but more pronounced for the Neurotrend, does not impair long-term use.

Similar work was presented, although in a non-peer-reviewed paper, restricted to seven patients in whom $PtiO_2$ was measured simultaneously using Licox and Neurotrend probes [30]. The authors report that $PtiO_2$ measured with Neurotrend was approximately 7 mmHg lower compared to Licox measurements. They also report that only one Neurotrend sensor worked properly during the entire monitoring period and one did not work at all. They report no malfunction with a Licox sensor. Another group reports calibration-related problems with the Neurotrend probe in 4 of 14 monitored patients [9].

We did not find any negative reports about $PtiO_2$ technology. We did not retrieve any reports which report serious complications using $PtiO_2$ technology. We did not retrieve any reports which have challenged the risk-benefit

ratio of PtiO$_2$ technology. There are no reports that persons involved in direct care of the patients have been harmed or injured while using PtiO$_2$ technology.

Critical appraisal

All evidence stresses the utility of this parameter for optimizing cerebral oxygenation in neurosurgical and neurologic critical care. All but one paper have failed to demonstrate that using this technology improves outcome. The outcome improvement was only reflected in a mortality reduction [67].

Although PtiO$_2$ is an independent parameter which can predict the development of delayed cerebral ischaemia, there are episodes where it will fail to do so or where response patterns of apparently interconnected cerebral parameters do not follow the expected directions [36]. This fact once again stresses the utility of a multiparameter approach.

Conclusions

Based on this review it is concluded that PtiO$_2$ technology is a safe and valuable cerebral monitoring device in neurocritical care. Its clinical utility has repeatedly been clearly confirmed because it adds a monitoring parameter, independent from established cerebral monitoring devices. It offers new insights into cerebral physiology and pathophysiology. Pathologic values have been established in peer-reviewed research, which are not only relevant to outcome but are treatable. The benefits clearly outweigh the risks, which remains unchallenged in all publications retrieved. It is particularly attractive because it offers continuous, real-time data and is available at the bedside.

This summary has been confirmed in virtually all studies retrieved, exemplified by two conclusions quoted here. The authors conclude that "...P(ti)O2 monitoring is a safe and reliable technique for monitoring cerebral oxygenation" [16]. A more recent study has once again confirmed this statement. "Cerebral oxymetry is confirmed safe in the patient with multiple injuries with TBI" [20]. PtiO$_2$ monitoring might even have the potential to improve outcome [67].

Yet this technology represents an invasive cerebral monitoring modality which requires cranial access. It should only be used in units which have experience with comparable monitoring devices, e.g. intracranial pressure monitoring. It appears helpful to establish guidelines for safe practice which have recently been suggested [75].

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Comments

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Brain tissue oxygenation, as demonstrated in this complete systematic review by Lang et al., is a promising technology. I agree that it offers continuous, real-time data and is available at the bedside safely. The rapid correlation between the indicated treatment and the regional response allowed by the devices is stimulating.

Beyond the applications updated in the review there is a potential use in early brain death diagnosis that should be borne in mind as a matter of research. Estimation of the best cerebral perfusion pressure and hyperventilation therapy control are, in my opinion, among the most important applications.

Nevertheless, there are some important issues to highlight regarding this technology. The Neurotrend device has been dropped off the market by Codman, Johnson and Johnson, so Licox is the only device available. There are no papers assessing sensitivity, specificity, positive and negative value as well as positive or negative likelihood ratio and pre- or post-test odds for the method as a prognostic or diagnostic tool, according to the principles of evidence-based medicine. There are also controversies on which region should be monitored: non-injured tissue, penumbra area or injured tissue, as well as which are the normal values or the pathologic threshold. Another controversy is the one that confronts regional vs global monitoring systems.

Even though well conducted and serious, most of the research has been done in Germany where the Gesellschaft für Medizinische Sondentechnik (GMS) developed the polarographic cell device, as is noted in the review references.

In view of these critical considerations that should be taken into account, brain tissue oxygenation should be considered a new star in the neurocritical monitoring constellation in which none is more important than the other and all of them are still looking for their right place.

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In their paper the authors review the development and clinical application of the registration of cerebral oxygenation (PtiO$_2$). They reviewed the pertinent literature from 2004 to 2006 with the aim of collecting the relevant information on clinical applicability, safety issues and clinical usefulness. All in all 1,400 publications were scanned. Mostly PtiO$_2$ monitoring was used in traumatic brain injury (TBI) followed by subarachnoid hemorrhage. Less commonly it was used intraoperatively during cerebrovascular surgery. Other rarer applications, like during cardiopulmonary resuscitation or cerebral angiography, are included in the review. The authors report that PtiO$_2$ monitoring is mostly used clinically in conjunction with additional cerebral monitoring devices like intracranial pressure (ICP) monitoring, jugular venous saturation monitoring, cerebral microdialysis and near infrared spectroscopy, just to name a few. Two different devices are on the market based on different technology and giving slightly different data. The main results of this review are that this methodology is safe and has an impact on clinical treatment of the above-mentioned patient groups. A safety range of tissue oxygen levels could be established, below that the outcome of the studied patients was significantly worse. Thus PtiO$_2$ monitoring has a prognostic value. Negative effects of hyperventilation were detected and it was applied more safely as hypoxic cerebral oxygen levels were avoided. The indication for decompressive craniectomy in severe brain swelling could be guided by cerebral oxygen monitoring more safely. PtiO$_2$ has also been proven useful in monitoring the use of vasoactive drugs given in neurocritical care as well as in elucidating effects of nimodipine and mannitol. There were no severe side effects using PtiO$_2$ in patients. Both available probes measure oxygen tension sufficiently. However, the Licox technology seems to be more accurate than the Neurotrend monitor. The often quoted disadvantage of the "locality" of the measuring devices—they measure an area of a few cubic millimeters—could be alleviated by several publications. These could show that there is a certain random positioning error. On the other hand these local measurements correlated well with more global methods like cerebral blood flow. The authors conclude that PtiO$_2$ monitoring is safe, clinically useful, and it improves the treatment of ICU patients. They favor, however, a multiparameter approach, meaning that other "brain" parameters should be monitored in addition. All in all this is a very informative study giving relevant and up-to-date information about this important monitoring technique.