

Systematic and Comprehensive Literature Review of Publications on Direct Cerebral Oxygenation Monitoring

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Abstract: This review has been compiled to assess publications related to the clinical application of direct cerebral tissue oxygenation (pbtO₂) monitoring published in international, peer-reviewed scientific journals, or major meeting reports published as journal supplements. 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 related basic science research and case reports. This review is an update of its previous edition published elsewhere in 2007. This review reflects publications from 2004 to 2012. Only relevant publications prior to 2004, which explicitly addressed or systematically examined the above issues, are included in this review and are listed in the reference section. Based on 349 citations it is the most comprehensive review available on direct cerebral oxygen monitoring to this date.

Keywords: Review, cerebral oxygenation, raumedic, licox, neurotrend, cerebral partial pressure of oxygen, brain tissue oxygenation.

METHODS

This review is based on a systematic "Medline" literature search using the following search terms: licox, neurotrend, neurovent, raumedic, brain tissue oxygen, brain tissue oxygenation, cerebral oxygenation, cerebral tissue oxygen, cerebral partial pressure of oxygen, btO₂, ptiO₂, pti(O)₂, ptiO(2), pbrO₂, PBr(O₂), P(bt)O(2), P(br)O(2), PbrO(2), BTpO₂, tP(O₂), PbO₂, PbtO₂, Ppto, PbtO(2).

Only few publications were not retrieved using this technique. They were, however, identified through personal communication with scientists in the field, meeting proceedings and reviewer assignments. This strategy provided sufficient certainty that relevant papers have not been missed. Unpublished meeting abstracts and published conference proceedings were excluded for this review except for few which provided comparative studies between different probes. To address relevant matters, related to specific pbtO₂ issues, selected non-peer reviewed papers published in supplements were also used only when no other peer-reviewed information was available.

RESULTS

This review is based on a previous review [1]. It is currently based on 349 papers, 274 more papers compared to its previous version in 2007, which warrants the update.

Indications and Applications

Human

PbtO₂ monitoring technology is largely used in neurosurgical and neurologic intensive care. The majority of publications are based on analysis of data from adult patients suffering from severe traumatic brain injury (TBI), which indicates that this condition represents the largest field of clinical application [2-22]. It is also used in patients with multiple extracranial injuries and TBI, so called "polytraumatized patients" [23]. It is also used in children [24-40].

The second largest group of publications comprises aneurysmal subarachnoid hemorrhage (SAH) [6, 7, 41-59].

PbtO₂ monitoring technology is also used intraoperatively during aneurysm surgery [45, 52, 60-64], during surgery of cerebral arterio-venous malformation [60, 65, 66], functional stereotaxy [67], and during cerebral angiography [68]. It has also been used in patients with spontaneous intraparenchymal hemorrhage [69-76], ischemic stroke in children and adults [36, 71, 77], severe haemorrhagic stroke [78], and in silent infarcts after subarachnoid hemorrhage [79].

Case Reports

A pbtO₂ monitoring course during cardiopulmonary resuscitation [80], and a course of Vein of Labbe thrombosis [81] have been published as case reports. One case report presents the effects of high-dose inhaled aerosolized prostacyclin therapy for acute lung injury on cerebral

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oxygenation [82]. A case report describes a carotid dissection during angioplasty for cerebral vasospasm with pbtO₂ monitoring in situ [43]. Hypoxic brain damage management after cardiac arrest in a child with catecholamine-induced cardiac arrhythmia using pbtO₂ monitoring has been presented [29]. One paper reports on pbtO₂ monitoring in 2 pediatric cases with tuberculous meningitis [31]. One paper reports its utility in a case where decompressive hemicraniectomy was guided by pbtO₂ monitoring in a patient with bacterial meningitis [83], a similar case was reported in a patient after brain gunshot [84].

Other case reports include a patient with aneurysmal subarachnoid hemorrhage associated with aortic coarctation [85], status epilepticus-induced hyperemia and brain tissue hypoxia after cardiac arrest [76], and pulmonary embolus from acute superior sagittal sinus thrombosis secondary to skull fracture [86].

PbtO₂ monitoring technology has also been used in brain tumor surgery [71, 73, 87, 88], and for continued postoperative monitoring in awake patients [89]. It has also been used for Normal Pressure Hydrocephalus management in awake patients [90, 91]. One study reports that pbtO₂ monitoring has been used in ventricular infusion studies on 33 patients suspected of idiopathic normal pressure hydrocephalus (iNPH), benign intracranial hypertension (BIH) or occlusive hydrocephalus (HOC) in order to confirm shunt indications [92].

It has also been used for diagnosis of idiopathic intracranial hypertension with measurements in an awake patient [93]. This case report is noteworthy because it demonstrates that the technology can be safely used in subjects undergoing physical exercise (running, cycling). It also demonstrated cortical hyperoxygenation in a human breathing natural air without oxygen supplementation [93]. Brain tissue oxygenation-guided management of diabetic ketoacidosis induced cerebral edema has also been reported in two paediatric cases [40]. One paper reports on “threshold-based brain oxygen monitoring for seizure detection” after SAH and TBI [94].

This technology has also been used to study the effects of anaesthetic agents [95, 96] as well as the effects of hypo – and hyperthermia on cerebral oxygenation [97-99].

Last but not least pbtO₂ monitoring has been subject to the “Development and validation of an integrated computational model of cerebral blood flow and oxygenation” with a subsequent report on “Modeling the causes of variation in brain tissue oxygenation” [100, 101].

Animal

The numbers of animal studies, which are designed to support and further investigate clinical pbtO₂ applications in trauma, resuscitation models and the effects of various drugs have once again increased since the previous edition of this report [12, 23, 102-141]. It is used to measure oxygen delivery to brain parenchyma in animal models [111, 113, 115, 133, 135, 142-151]. The utility in traumatic brain injury and severe uncontrolled haemorrhage with short delay pre-hospital resuscitation was examined in a swine model [152].

Animal models have also been used for comparative studies using different cerebral monitoring applications, e.g. near-infrared spectroscopy [153], ICP [154], muscle tissue oxygen, CBF [145], and cerebral microdialysis [155].

PbtO₂ monitoring has also been used in animal models of spontaneous intracerebral hemorrhage [110, 156], malignant soft tissue tumors [157, 158], ischemic stroke [159], in experimental subarachnoid hemorrhage [160], in a swine model of pediatric traumatic brain injury [161], a rodent model of penetrating ballistic-like brain injury [162], in a rodent model of acclimation and deacclimation to hypoxia [163], in a standardized experimental brain death model [164], in experimental anhepatic liver failure [165, 166], an in potassium-induced cortical spreading depression [167].

One animal study reports on comparative monitoring with one Licox probe inserted into a glioblastoma multiforme [C6 glioma rat model] and a contralateral cerebral hemisphere [103].

It is also used in animal models to study cerebral oxygenation during postasphyxial seizures [116]; transfusion protocols [118], Erythropoitin administration [148], circulatory recovery [106], evoked neural stimulation [151], hibernation [105]; and cerebral blood flow, electrocorticographic activity after hypoxia [107]. PbtO₂ measurements have also been performed in isolated rodent intestinal tissue with a special focus on “possible pitfalls in the interpretation of microcirculatory measurements” [168].

Spinal cord intraparenchymal and subdural CSF monitoring in a traumatic spinal cord injury model has been reported [169] and last but not least feasibility and various aspects of “a fully implantable telemetry system for the chronic monitoring of brain tissue oxygen in freely moving rats” have been published [170].

Clinical Applications

PbtO₂ monitoring technology is increasingly used, which is reflected by a growing number of original publications. The majority of publications come [in alphabetical order] from Germany, Italy, Spain, The Netherlands, the UK, and the USA [5-8, 12-14, 24, 25, 47, 48, 52, 54, 55, 65, 80, 81, 88, 89, 91, 110, 112, 128, 158, 171-196, 197, 311].

There are publications also from Australia [38, 198-200], Austria [53, 85], Brazil [58], Canada [93, 118, 132, 135, 139], China [9, 201, 202], Croatia [203], the Czech Republic [204], Denmark [134]; Finland [134], France [43, 77, 114, 205, 206], Greece [207], Hungary [141], India [208], Japan [140, 146, 167, 209], Portugal [64]; Russia [210, 211], Singapore [2, 4, 10, 16, 74, 212, 213]; Serbia [214]; South Africa [26, 28, 35], South Korea [127], Sweden [90, 134, 215], Switzerland [11, 216, 217], and Taiwan [218].

PbtO₂ monitoring is almost exclusively used in combination with other cerebral non-invasive and invasive monitoring modalities, in particular intracranial pressure [ICP] monitoring [4, 6, 17, 22, 24, 26, 32, 33, 50, 51, 53, 55, 72, 81, 88, 202, 91, 130, 176, 187, 203, 206, 219-223], cerebral perfusion pressure (CPP) monitoring [3, 4, 10, 25, 178, 187, 198, 224-226], jugular venous saturation (JvDO₂) monitoring [184, 190, 206, 227, 228], cerebral microdialysis [17, 74, 83, 114, 117, 186, 193, 196, 205, 207, 212, 227, 229-238], cerebro spinal fluid (CSF) chemistry [239],

cerebral blood flow velocity (CBFV) measured by transcranial Doppler ultrasound (TCD) [8, 30, 88 202, 178, 237], regional cerebral blood flow measurements (rCBF) [47, 240-242], near infrared spectroscopy (NIRS) [15, 123, 179, 190, 243], intracranial temperature measurements [9, 97, 99, 141], oxygen-15 positron emission tomography (15O-PET) [230], continuous surface electroencephalogram [94], and cortical spreading depolarizations (CSD) monitoring using subdural electrocorticography (ECoG) strip electrodes [244].

Oxygen Monitoring Technologies

Six monitoring devices are found in the literature, "Licox", "Neurotrend", "Neurovent-PTO", "MPBS", "Foxy AL-300", and a probe called "PO2-100DW".

Licox is manufactured by GMS-Integra, (Kiel-Mielkendorf, Germany). Neurotrend is manufactured by Codman, Johnson & Johnson (Raynham, MA, USA). Neurovent is manufactured by Raumedic (Münchberg, Germany). MPBS is manufactured by Oxford Optronix [Oxford, UK]. Foxy AL-300 is manufactured by Ocean Optics (Dunedin, FL, USA). The "PO2-100DW" is manufactured by Inter Medical Co. Ltd. (Nagoya, Japan).

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 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 pbtO₂, ptiCO₂, tissue pH, and tissue temperature. Its sampling area is around 2mm².

The Licox probe uses a polarographic ("Clark") 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 pbtO₂. Its sampling area, depending of the type of oxygen sensor, is around 13mm² to 18 mm².

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.

The "Neurovent-PTO" is a sensor which measures pbtO₂, ICP and brain temperature. The pbtO₂ measurement principle is based on exciting a fluorescent dye with light. PbtO₂ is calculated from the fading properties of the fluorescent dye, so called "luminescence quenching". Its sampling area is around 22mm² [71].

The Oxford Optronix and the Foxy-ptiO₂ sensor also use the "luminescence quenching" technique. The Oxford Optronix sensor, referred to as "multi-parametric brain sensor" [MPBS] also measures laser-Doppler based cerebral blood flow and ICP [149, 245]. It is a prototype and has been used in animals [246]. The Foxy AL-300 has also been used in animals [247].

The "PO2-100DW" is a micro polarographic cell sensor (Clark type electrode) and has been used in an animal study [167].

Catheter Placement and Sampling Size

Catheters are generally placed in the right frontal lobe white matter in diffuse brain injury or for detecting global ischemia, 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 [197, 206, 229, 248-252]. During intraoperative aneurysm surgery and ICU treatment probe placement in the territory of the aneurysm harboring vessel has been advocated [44, 62, 63]. As expected pbtO₂ is lower in peri-contusional tissue than in normal appearing tissue on CT scanning in TBI patients [253]. Some groups, however, prefer measurements contralateral to the side of mass lesions [18, 39].

A run-in time of approximately 1 to 2 hours is required before valid measurements are available and a short oxygen challenge is useful to test proper performance [13, 67, 172, 197, 254]. In some cases the run-in time may be shorter or longer. We feel that a sensible approach is to wait until stable monitoring values show up on the monitor.

One paper has further investigated the effect of catheter location on the relationship between pbtO₂ and neurological outcome in severe TBI. They report that: "When the pbtO₂ probe was placed in abnormal brain, the average pbtO₂ was higher in those with a favorable outcome, 28.8 +/- 12.0 mm Hg, compared with those with an unfavorable outcome, 19.5 +/- 13.7 mm Hg (P = .01). PbtO₂ and outcome were not related when the probe was placed in normal-appearing brain". They conclude that "...the location of the pbtO₂ probe determines the pbtO₂ values and the relationship of pbtO₂ to neurological outcome" [252]. This may account for various pbtO₂ cutoffs and thresholds which have been reported, e.g. 16mmHg [314], or 29 mm Hg [255].

Although it is a local measurement, restricted to a small cerebral volume, its utility to reflect hemispheric conditions has been demonstrated in studies where pbtO₂ measurements were correlated with cerebral arteriovenous oxygen difference [AVDO₂] and cerebral blood flow (CBF) measurements. Not only did they show a strong correlation but they also showed that pbtO₂ measurements did pick up more ischemic events than the global measurement [120, 122, 256]. PbtO₂ monitoring is also a rather sensitive marker for cerebral ischemia, which "...allows for early recognition of low O₂ delivery, enabling appropriate therapeutic intervention" [24]. This finding is supported in a comparative study which confirmed a correlation between CBF and pbtO₂: "The level of pbtO₂ seems to be predominately determined by regional CBF, since changes in pbtO₂ were correlated in 90% of episodes to simultaneous changes of CBF" [47]. Further evidence to support the fact that CBF is a strong determinant of pbtO₂ is supplied in a study where O₂ reactivity was determined at various levels of rCBF. It showed a significant correlation between CBF and O₂ reactivity [240]. An observational study where pbtO₂ was recorded during surgery of incidental MCA aneurysms reports that: "pbtO₂ monitoring during aneurysm surgery shows brain tissue perfusion in real time and there is a correlation between any episode of reduced blood flow to the affected vascular territory during surgery and a decrease of pbtO₂ value [63]. A case report in a patient who developed seizures following CPR after a cardiac arrest showed dramatic pbtO₂ decreases along with large CBF

surges, which the authors interpret as: "...increased metabolic demand out of proportion to CBF increase" [76].

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 pbtO₂ within the cortex depend of the depth of probe placement [257]. This has also been shown in an early human study [13]. It was proposed that the differing base levels relate to the metabolism, microcirculation and overall microstructure of each environment. Furthermore, depending on the probes relationship to the arterial micro-vessels, 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 [121]. 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 pbtO₂ levels anywhere from 15 to 40 mmHg if the O₂ 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 30mmHg [121].

Impact on Clinical Situations and Treatment Strategies

There are numerous and, from a scientific/research as well as clinical/treatment point of view, most interesting findings which have derived from about 15 years of research using pbtO₂ technology. The following paragraphs summarize the important ones:

Definition of Normal and Pathological Values - A Complex Task

Normal pbtO₂ values based on Licox technology are around 25 to 30mmHg, based on animal research [119]. This was confirmed in patients with normal ICP and CPP [13, 256].

Functional stereotaxy operations for movement disorders with Licox based pbtO₂ measurements in normal white matter have confirmed these values. The authors report 22.6±7.2 mm Hg for frontal white matter intraoperative recordings during local anaesthesia. These measurements were confirmed during a 24-hour postoperative continued measurement with values of 23.1±6.6 mm Hg [67]. In addition, at optimal vascular reactivity in 27 TBI patients, pbtO₂ was 24.6 +/- 6.0 mmHg [258].

One group has investigated the relationship between markers of ischemia from cerebral microdialysis and an ischemic pbtO₂ threshold below 20 mmHg in SAH patients. They report that: "Mortality was associated with increased percentage of samples with elevated lactate and brain hypoxia 28% (interquartile range 9%-95%) in nonsurvivors". This study supports the current clinical practise that pbtO₂ below 20mmHg signals cerebral ischemia and may call for therapeutic interventions [217].

Normal pbtO₂ value in children may be higher than in adults. One paper suggests that 30mmHg may be normal in children based on their finding that a pbtO₂ of 30 mm Hg

was associated with the highest sensitivity/specificity for favorable neurological outcome at 6 months after TBI [39]. It must be noted, however, that they measured pbtO₂ in the uninjured frontal cortex. They emphasize that: "CPP was the only factor that was independently associated with favorable outcome. Surprisingly, instances of preserved pbtO₂ with altered ICP and CPP were observed in some children with unfavorable outcomes [39].

Normal pbtO₂ values based on Neurotrend technology are lower [259], a paper has suggested a threshold of 14mmHg [260].

A one-on-one direct intraparenchymal comparison between Licox and Neurovent in 33 patients showed no relevant differences between the Licox (19.5±7.1 mmHg) and Neurovent multiparameter probe derived values (21.7±9.5 mmHg) [71]. This was not confirmed in a preliminary report in 11 mixed TBI and SAH patients [261]. They increased MAP by 20 mmHg for 10 min and varied FiO₂ and they report that pbtO₂ differed significantly at all times. "The Licox probe reacted significantly faster to changes in FiO₂ and MAP. Limits of agreement ranged between -32.1 and 20.0 mmHg. Mean Licox values were 6.1 mmHg lower than Neurovent values". They conclude that: "These data therefore do not support the view that both probes can be used interchangeably" [261].

Based on analysis of ischemia markers from cerebral microdialysis a critical ischemic threshold below 10mmHg has been reported in an animal study, in which the Neurovent-PTO probe was used [262]. Some clinicians consider 7mmHg as the critical ischemic threshold [92]. One study reports on the significant association between serum levels of S100beta, neuron-specific enolase, and glial fibrillary acidic protein, which are considered serum biomarkers in severe TBI patients, and hypoxia measured by pbtO₂ prior to the onset of clinical symptoms [263].

The "Guidelines for the management of severe traumatic brain injury" issue a Level III recommendation for pbtO₂ monitoring and recommend maintaining pbtO₂ > 15mmHg [264].

A study published in 1998 demonstrated that the likelihood of death increased with increasing duration of time at or below a pbtO₂ of 15 torr (2.0 kPa) or with the occurrence of any pbtO₂ values of < or =6 torr (< or =0.8 kPa) [265]. This is supported by an analysis of 103 TBI patients in which the authors conclude that "...Brain hypoxia is associated with poor short-term outcome after severe traumatic brain injury independently of elevated ICP, low CPP, and injury severity. Other than ICP and CPP, pbtO₂ is an independent factor for outcome [266]. One paper has pointed out that initial radiographic and clinical scales, which are correlated with patient outcome after TBI, are not associated with subsequent ICP or pbtO₂ [267]. PbtO₂ may be an important therapeutic target after severe traumatic brain injury [268].

These studies have also helped to establish a generally accepted treatment threshold, which has been confirmed by other papers although no clear cut-off value can be given for both TBI and SAH [56, 172]. Similar results have been reported for pediatric TBI and it has been stressed that: "...many patients experience episodes of compromised

pbtO₂ despite achieving acceptable treatment targets.” [28], and “...low brain oxygen levels during the first 24 h following head injury may not correlate necessarily with poor outcome [27]. Formal analysis of outcome prediction variables has shown that: “The combined use of microdialysis variables and pbtO₂, in addition to ICP, MAP, and CPP was found have the best predictive accuracy” [250].

Of interest is another paper that has reported that “The presence of anaerobic cerebral metabolism probably depends on duration and severity of the hypoxic episode” [232]. This conclusion is relevant for clinical practise because it shows that: *a.* pbtO₂ monitoring technology detects short episodes of cerebral hypoxia which are not picked up by other monitoring modalities *b.* magnitude and duration of cerebral hypoxia have prognostic relevance. One study also reports on the positive correlation and prognostic value of pbtO₂ measurements and longterm neuropsychological outcome after severe traumatic brain injury [269].

This section shows that various factors contribute for the different thresholds described above. Several others can be listed: age (paediatric, adult), co-morbidity, injury severity (GCS, ISS, etc), underlying pathology (see list of indications), timing of placement (pre-, intra-, post OP, secondary deterioration), catheter location (injured vs non-injured side, catheter location if monitored in the injured side, i.e. healthy tissue, penumbra zone, injury area), data acquisition frequency (minutely, hourly), therapeutic interventions [see below], time of outcome assessment [discharge, 3 months, 6 months], outcome measures (GOS, neuropsychological measures, etc.).

The Problem of the Randomized Controlled Trial [RCT]

Up to date there is no RCT (class one evidence) which has shown outcome improvement with pbtO₂ monitoring. Four controlled reports are available [226, 270-272]. All other papers are uncontrolled or case reports. Consequently the “Guidelines for the management of severe traumatic brain injury” issue a Level III recommendation for pbtO₂ monitoring [264]. The frequently proposed RCT is under way. It is called “Brain tissue oxygen monitoring in traumatic brain injury (TBI)” (BOOST 2), and can be found at: <http://clinicaltrials.gov/ct2/show/NCT00974259>. It started in October 2009 and it is scheduled to be finish in August 2014. No preliminary results are yet available.

In a series of 53 TBI patients 25 patients were treated using an ICP monitor alone while 28 patients had pbtO₂-directed care, with comparable ICP and CPP levels for each group [226]. The mortality rate was 44% for the first group, 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 pbtO₂ group, the outcome difference was significant [*p* < 0.05]. They conclude that “The use of both ICP and brain tissue PO₂ monitors and therapy directed at brain tissue PO₂ is associated with reduced patient death following severe TBI” [226]. This report on outcome was not confirmed in a larger, uncontrolled series [22]. The authors report that a pbtO₂ guided treatment supplementing ICP/ CPP therapy did not result in improved outcome at six months, despite a significant reduction in cerebral hypoxic episodes.

An outcome study of 145 TBI patients receiving either ICP or Licox-pbtO₂ monitoring reports that mortality, hospital length of stay, and ICU length of stay were equivalent. More patients in the Licox group achieved a moderate/recovered GOS at 3 months than in the Camino Group (79% vs 61%; *P* = .09). Six-month outcomes were also better although not at a statistically significant level [271].

One study confirms that an ICP/pbtO₂ directed protocol reduces the mortality rate after TBI in major trauma and resulted in improved 6-month clinical outcomes over the standard ICP/ CPP-directed therapy when compared to historical controls [270].

One paper, which was published in 2009 deserves special attention: This series has not confirmed the utility of pbtO₂ monitoring for TBI patients [272]. The authors report that: [1] The mortality rate in 123 patients with traumatic brain injury whose clinical management was guided by pbtO₂ monitoring was not reduced in comparison with that in patients who received ICP monitoring alone, and [2]. Brain tissue oxygen monitoring was associated with worse neurological outcome and increased hospital resource utilization [272]. In consideration of the possible implications of their findings the authors seek to find reasons for their findings. They report that the pbtO₂ monitored group was younger and more severely injured. They argue that their treatment threshold of 20mmHg may have been incorrect and that that treatment strategies, e.g. CPP augmentation using vasopressors may have caused more harmful side effects than beneficial effects. At last they argue that the potential for residual confounding is most likely due to the observational nature of their study with a lack of proper randomization. The authors conclude that a randomized trial is necessary to address the issue. This is in keeping with the arguments previously listed [200, 273].

PbtO₂ and Other Monitoring Parameters

An analysis of a large pediatric TBI series has suggested that pbtO₂ cannot be inferred from other clinical and physiological variables. The authors stress that: “Reduced pbtO₂ is shown to be an independent factor associated with poor outcome in pediatric severe TBI in the largest study to date. It appears to have a stronger association with outcome than conventionally evaluated measures [33]. They continue to conclude that: “Our data show that pbtO₂ is poorly predicted by clinical and physiological factors commonly measured in the pediatric ICU. Multimodality monitoring may be needed to detect all secondary cerebral insults in pediatric TBI after TBI” [32].

The same group also studied the frequency of an adverse event, defined as a pbtO₂ of less than 10mmHg, as a point prevalence at 24 and 72 h post-injury, compared with the cumulative burden measured as a frequency of the event over the full duration of monitoring They report that: “Reduced pbtO₂ was more common early than late after injury. The point prevalence of reduced pbtO₂ at the selected time points was relatively low [10 % of patients at 24 h and no patients at the 72-h mark post-injury]. The cumulative burden of these events over the full duration of monitoring was relatively high: 50 % of patients had episodes of pbtO₂ less than 10 mmHg and 88 % had PbtO₂ less than 20 mmHg”.

They conclude that: "Point-in-time monitoring in a dynamic condition like TBI may underestimate the overall frequency of adverse events, like reduced pbtO₂..." "It supports the utility of continuous rather than hourly monitoring and recording/charting [37].

Treatment Strategies

When it comes to treating reduced ptiO₂ "the nature and effectiveness of commonly used interventions in correcting compromised pbtO₂ in TBI remains unclear" [274]. In an attempt to evaluate the effectiveness and magnitude of interventions the authors report their retrospective review of a series of 92 TBI patients, in which they report that: "Five interventions: narcotics or sedation, pressors, repositioning, FIO₂/PEEP increases, and combined sedation or narcotics and pressors were the most commonly used strategies. Increasing the number of interventions resulted in worsening the time to pbtO₂ correction. Triple combinations resulted in the lowest DeltaICP and dual combinations in the highest DeltaCPP ($p < 0.05$) [274]. They conclude that: "Clinicians use a limited number of interventions when correcting compromised pbtO₂. Using strategies employing many interventions administered closely together may be less effective in correcting pbtO₂, ICP, and CPP deficits. Some pbtO₂ deficits may be self-limited" [274].

PbtO₂ monitoring has been used to study the effects of the neurological wake-up test with interruption of sedation and analgesics (IS) [229]. The authors report that: "In IS-trials that had to be aborted, a significant increase in ICP and decrease in pbtO₂ ($P < 0.05$), including 67% with critical values of pbtO₂ < 20 mmHg, a tendency to brain metabolic distress ($P < 0.07$) was observed" [229].

Hyperventilation

Several 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 will lead to ICP reduction, however in turn can cause reduced rCBF, hypoperfusion and ischemia and lead to exacerbation of brain swelling. PbtO₂ technology has the potential to guide the degree of hyperventilation because of its ability to indicate states of hypoperfusion and impending ischemia [70, 102, 112, 175, 241, 275, 276].

This utility has also been demonstrated intraoperatively in AVM surgery: "PbtO₂ monitoring has a high reliability in the detection of intraoperative tissue hypoxia" [65]. Similar recommendations have yet previously been reported [183]. One paper, however reports that in 3 of 17 TBI patients they noted an increase of pbtO₂ on hyperventilation, which they called a "paradox reaction" [277]. 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.

Aneurysm Surgery - Intraoperative Utility

One paper addresses the utility of intraoperative pbtO₂ recording during MCA aneurysm surgery after SAH and the authors suggest that surgical action may be revised if pbtO₂ decreases. They report that: "Postoperative infarction in the

territory of MCA developed in cases with an abrupt decrease of pbtO₂ and a very low and persistent minimum value, during temporary clipping, and an incomplete recovery after definitive clipping. Verification of clip position should be considered when there is an incomplete recovery or a persistent fall in pbtO₂ after definitive clipping" [62]. The same group has also published on the same matter for surgery of unruptured MCA aneurysms. Here they report that: "PbtO₂ monitoring during aneurysm surgery shows brain tissue perfusion in real time and there is a correlation between any episode of reduced blood flow to the affected vascular territory during surgery and a decrease of pbtO₂ values. Unexpected low basal values were obtained in "uninjured" brain, with no influence from subarachnoid hemorrhage. The values of risk for brain infarction during temporary arterial occlusion still need further studies, but an incomplete recovery or a persistent fall in pbtO₂ values after definitive clipping should be considered as an indication for verification of the position of the clip [63].

Triple H Therapy

PbtO₂ technology has been used to investigate the utility of hypervolemia and hypertension therapy for prophylaxis and treatment of symptomatic cerebral vasospasm in SAH [278]. The authors, most interestingly, report that during 55 periods of moderate hypertension pbtO₂ increases were found in 50 cases (90%), with complications occurring in three patients (8%). During 25 periods of hypervolemia, pbtO₂ increases occurred during three intervals (12%), with complications occurring in nine patients (53%). During the 10 periods of aggressive hypervolemic hypertension, pbtO₂ increases were found during six of the intervals (60%), with complications in five patients (50%). They concluded that "in poor-grade patients, moderate hypertension (CPP 80-120 mm Hg) in a normovolemic, hemodiluted patient is an effective method of improving cerebral oxygenation and is associated with a lower complication rate compared with hypervolemia or aggressive hypertension therapy". A similar conclusion has been reported from another group [55]. Both reports support the utility of pbtO₂ for optimizing Triple-H-Therapy in SAH patients.

Vasospasm Detection After SAH

The utility of pbtO₂ monitoring in cerebral vasospasm after SAH is subject of three reports [279-281]. The first study reports that post-operative TCD vasospasm developed in 13 patients, all of which had intraoperative pre-clipping pbtO₂ < 10 mmHg and pbtO₂ was significantly lower in cases that developed TCD vasospasm. This association was independent of age, clinical status, or CT findings. The authors conclude that: "The finding of low intraoperative basal pbtO₂ values may be an indicator for a high risk of occurrence of post-operative TCD vasospasm in cases of aneurysmatic SAH" [279]. The second study reports a significant pbtO₂ increase in a series of vasospasm patients after endovascular treatment while CPP, ICP, SaO₂(_t), and FiO₂, did not. They conclude that: "pbtO₂ monitoring provides the interventionalist with an objective physiologic parameter to determine adequate spasmolysis" but point out that: "Further investigation is needed to establish target pbtO₂ rates indicative of adequate reperfusion, which can be used in the endovascular suite" [280]. The third study reports

that Erythropoietin increases pbtO₂ in severe SAH patients with severe cerebral vasospasm but they point out that the effect on outcome requires further investigation [281].

One interesting case report presents a patient suffering from delayed and profound post-traumatic vasospasm, which was recognized solely by pbtO₂ monitoring. The patient was successfully treated with intraarterial Verapamil and balloon angioplasty [57].

Head and Body Position

PbtO₂ 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 pbtO₂ 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" [10]. The effects of various other changes of head and body positions on pbtO₂ has been reported and the authors conclude that: "Positioning practices can positively or negatively affect pbtO₂ and ICP and fluctuate with considerable variability among patients. Nurses must consider potential effects of turning, evaluate changes with positioning on the basis of monitoring feedback from multimodality devices, and make independent clinical judgments about optimal positions to maintain or improve cerebral oxygenation" [282].

PbtO₂ technology has been used to assess the effects of prone position on CPP and pbtO₂ in SAH patients with acute respiratory distress syndrome (ARDS) [53]. The authors report a beneficial effect of prone positioning on pbtO₂ by increasing arterial oxygenation. This effect outweighs the adverse effect of prone positioning on cerebral tissue oxygenation by decreasing cerebral perfusion pressure in ARDS patients.

PbtO₂ during Patient Transport

Directions, magnitudes, and time courses of patient transport for CT scanning on pbtO₂ has been systematically assessed [283]. The authors conclude that: "... transport to and from the intensive care unit may adversely affect pbtO₂. This deleterious effect is greater when pbtO₂ is already compromised and may be associated with lung function." Fifty-seven CT scans in 34 TBI patients using a portable scanner without patient transport had no effects on pbtO₂ [284].

Decompressive Craniectomy and Ventricular Drainage

It has been shown in TBI and SAH patients that decompressive craniectomy improves pbtO₂ [212, 285]. Three papers have addressed the utility of pbtO₂ monitoring technology for timing of decompressive hemicraniectomy (DCH) in severe brain swelling [7, 42, 221]. One case report addresses its utility for DCH in a patient suffering from bacterial meningitis [83]. It has been shown that not only absolute pbtO₂ values should be considered for the indication of DCH but also magnitude and the time course of monitoring trends [7]. Another study has concluded that "...pbtO₂ monitoring could be an important tool for timing craniectomy in the future" [221]. This report is supported by

a case report [205]. 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" [6]. In another, however small, series of patients it was pointed out that despite a rapid pbtO₂ 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" [50]. This is in keeping with the long-standing and unresolved debate about the utility of DCH and its particular regard to outcome [286].

It has also been reported that ventriculostomy for control of intracranial hypertension in TBI leads to a significant pbtO₂ improvement, irrespective of the pre-procedural pbtO₂ level [287].

Nimodipine, Mannitol and Hypertonic Saline Solution

Other long and much debated issues in neurocritical care have been addressed under consideration of pbtO₂ measurements: 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" [51]. A pbtO₂ increase following intraarterial Nimodipine infusion was reported in 8 out of 9 SAH patients with refractory arterial vasospasm [288]. These reports will spark the academic discussion about whether Nimodipine should be used in patients suffering from aneurysmal subarachnoid hemorrhage. The most valuable conclusion for daily neurocritical care practice which can be extracted from this study is that using pbtO₂ monitoring technology will identify those patients in which Nimodipine has a negative effect [176].

In this context it can be noted that Nicardipine, when used to treat acute hypertensive emergencies in a combined aneurysmal SAH, ICH, AVM, and hypoxic brain injury series, had no effect on pbtO₂, despite significant CPP reduction [289].

With regard to Mannitol it has been shown that although Mannitol reduces ICP it has little effect on pbtO₂ [17, 176]. This is rather unexpected because it is expected that ICP reduction will improve pbtO₂. The important clinical conclusion from this finding - however is that pbtO₂ monitoring technology should be used in addition to ICP monitoring as the two monitoring parameters are not ultimately linked. Further evidence to support this finding is provided in a series of 12 patients after severe haemorrhagic stroke [78]. The authors report that: "...CPP increased 45 min [from 73 +/- 18 to 85 +/- 22 mm Hg, p=0.002] after the start of mannitol infusions, whereas mean arterial blood pressure and pbtO₂ did not change significantly [78]".

The effects of hypertonic saline solution [HSS] on pbtO₂ have been studied in 12 hypotensive patients after severe TBI [220]. The authors report a uniform and persistent pbtO₂ increase, along with a 45% ICP decrease, which lasted for six hours, a subsequent CPP increase, and less demand for inotrope use [220]. Similar results have been reported elsewhere [44, 219, 290], although the persistent pbtO₂ increase has not been confirmed in a combined TBI

and stroke series in which Mannitol and HSS were compared [77]. This may be due to different treatment thresholds and different time points for post infusion assessment of monitored variables in different series [290].

Vasopressors

Vasopressors are commonly used in neurocritical care. There is debate whether Dopamine or Noradrenaline should be preferred. PbtO₂ monitoring has been used to study the effects of both drugs in a 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" [225]. Phenylephrine doubled pbtO₂ in four of five TBI patients three hours after start of the infusion [228].

One animal study suggests adverse effects of Epinephrine on pbtO₂ during CPR [291]. It must be said, however, that measurements were not clearly intraparenchymally and they used an optical sensor which is used for arterial blood gas analysis.

Barbiturates and Sedatives

The effect of barbiturates on pbtO₂ has been studied in patients with refractory intracranial hypertension [2, 292]. One report concludes that "Of eight patients with prebarbiturate PtiO₂ levels above 10 mmHg, six had a further improvement in oxygenation" [2]. Obviously barbiturate therapy does not always lead to a pbtO₂ improvement. This finding has also been reported in a series of 10 patients. The authors report that two patients experienced a significant pbtO₂ decrease upon pentobarbital treatment [292].

The effects of a commonly used sedative in neurocritical care, propofol, have also been studied using pbtO₂ monitoring. Somewhat unexpectedly they found that burst suppression induced by propofol has no effect on cerebral oxygenation [96]. An intraoperative bolus of dexmedetomidine in patients undergoing neurovascular surgery also had no effect on pbtO₂ [60].

Blood Glucose Levels and Obesity

The issue of blood glucose levels and its relation to cerebral oxygenation in primary basal ganglia hemorrhage has been studied. The results show that a strict control of blood glucose levels (4-8 mmol/L) with continuous titrated insulin therapy is associated with improved cerebral oxygenation when compared to a conventional "sliding scale" (8.1 to 10 mmol/L) bolus subcutaneous insulin administration [74].

It has also been reported that obesity is an independent predictor of compromised pbtO₂. The authors speculate that this may be mediated through obesity-related pulmonary

dysfunction and inadequate compensatory mechanisms [293].

Fraction of Inspired Oxygen/Hyperoxia

The fraction of inspired oxygen (FiO₂) obviously affects cerebral pbtO₂ levels. One study has recently addressed this issue, which is important in the interpretation of measured pbtO₂ values [294]. The authors report a pbtO₂ increase from a baseline of 30±5 mmHg to 147±36 mmHg when the FiO₂ was increased from individual baseline values to 100%. When it was decreased to 0.6 FiO₂ pbtO₂ fell to 63±6 mmHg. Further evidence into the effects of FiO₂ levels on pbtO₂ is provided by a study which shows that the magnitude of pbtO₂ changes depends on rCBF [240]. It has also been shown that 2-hour periods of normobaric hyperoxia (NH) increases pbtO₂ values but do not produce oxidative stress and/or change antioxidant reserves in CSF (lipid peroxidation (F2-isoprostane (ELISA)), protein oxidation [protein sulfhydryl (fluorescence)] and antioxidant defenses (total antioxidant reserve (AOR) (chemiluminescence) and glutathione (fluorescence)) [239]. Another paper in 30 TBI patients reports that NH "...increased PaO₂ and PtiO₂ and significantly decreased the lactate pyruvate ratio in patients in whom baseline brain lactate levels were increased, suggesting that NH improved the brain redox state", and they conclude that NH "... may only be effective in a specific group of patients" [197].

The issue of O₂ reactivity in response to increased FiO₂ levels has been studied in 37 TBI patients [194]. The authors measured paO₂ and pbtO₂ after an increase in FiO₂ concentration from baseline to 1.0 for 20 minutes and created the "PF ratio". Patients with higher PF ratios achieved greater pbtO₂ during oxygen challenge than those with a low PF ratio because they achieved a higher PaO₂ after an oxygen challenge. They concluded that: "... lung function must be considered when interpreting brain tissue oxygenation" [194]. Using pbtO₂ monitoring and the O₂ reactivity in response to FiO₂ variations one group has reported that: "Acute lung injury is an independent risk factor for brain hypoxia after severe traumatic brain injury." [21]. They advocate: "the use of lung-protective strategies to prevent brain hypoxia in TBI patients."

The effects were also studied in a series of 28 children with severe TBI [34]. The authors conclude that: "Normobaric hyperoxia increases pbtO₂ in children with severe TBI, but the response is variable. The magnitude of this response is related to the change in PaO₂ and the baseline pbtO₂. A greater response appears to be associated with worse outcome."

A study of 52 TBI patients showed that normobaric hyperoxia treatment resulted in a significant improvement in biochemical cerebral markers [295]. 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"

[295]. Similar findings have been reported in a series of 8 TBI patients [193]. Another normobaric hyperoxia protocol was used in a study of 11 TBI patients, pbtO₂ measurements were supplemented by cerebral microdialysis and oxygen-15 positron emission tomography [230]. The authors conclude that: "...hyperoxia increases pbtO₂ with a variable effect on lactate and lactate/pyruvate ratio. Microdialysis does not, however, predict the universal increases in cerebral metabolic rate of oxygen in at-risk tissue, which imply preferential metabolic benefit with hyperoxia".

The effects of hyperbaric and normobaric hyperoxia [NBH] were assessed in a prospective, randomized clinical trial in a series of 69 severe TBI patients [296]. The authors conclude that: "Hyperbaric O₂ has a more robust posttreatment effect than NBH on oxidative cerebral metabolism related to its ability to produce a brain tissue PO₂ > or = 200 mm Hg. However, it appears that O₂ treatment for severe TBI is not an all or nothing phenomenon but represents a graduated effect. No signs of pulmonary or cerebral O₂ toxicity were present."

Hypo- and Hyperthermia

Four studies have addressed the relation between hypo- and hyperthermia and pbtO₂ [97-99, 202]. One study of 72 severe TBI patients reports that: "...hyperthermia does not seem to reduce pbtO₂ or increase the number of episodes of brain tissue hypoxia in patients with severe TBI. This provides evidence to support their conclusion: "These results suggest that hyperthermia may worsen outcome after TBI through mechanisms that may be separate from compromised brain oxygen" [99]. A study of 30 severe TBI patients reports that: "...brain tissue PO₂ decreased with hypothermia, with a significant reduction below 35 degrees C [97]". The effects of mild hypothermia [34 -36 degrees C] was studied in 33 severe TBI patients who had persistent increased ICP > 20 mmHg. In keeping with the previous study they report that: "Mild induced hypothermia decreased brain oxygen significantly from 33±24 mmHg to 30±22 mmHg (p < 0.05)" [98].

The effects of mild hypothermia on pbrO₂ in a large series of 148 TBI patients are not uniform [202]. PbtO₂ increased in patients with GCS 5 to 8 and decreased in patients with GCS 3 and 4.

It is possible that cerebral oxygenation may influence the effects of hypothermia, which has been reported in an animal study [143].

TBI and SAH Patients who developed shivering during induced normothermia were studied. The authors report that shivering was associated with an overall pbtO₂ reduction from 34.1±7.3 to 24.4±5.5 mmHg (P < 0.001), and they report a significant correlation between the magnitude of shivering-associated pbtO₂ decrease [Δ pbtO₂] and circulating water temperature (R = 0.82, P < 0.001). They, however, conclude that: "The clinical significance of shivering-induced decrease in brain tissue oxygenation remains to be determined" [290].

Anemia

"Anemia is frequently encountered in critically ill patients and adversely affects cerebral oxygen delivery and

pbtO₂" [58]. One group reports in a series of 80 TBI patients that: "a Hemoglobin level no greater than 9 g/dl (anaemia) was associated with compromised pbtO₂ (pbtO₂ <20 mmHg)" [297]. They also report that: "Anemia with simultaneous compromised pbtO₂, but not anemia alone, was a risk factor for unfavorable outcome, irrespective of injury severity" [297].

Anaemia which is treated prompts investigations on the effects of packed red blood cell transfusion (RBCT) on pbtO₂. One group reports a graded response of local cerebral oxygenation in a combined group of TBI and SAH patients. In 74% of patients they observed a pbtO₂ increase but did not provide a suitable explanation why it fell in 26% of patients. Cerebral perfusion pressure, CPP, SaO₂, and FiO₂ were similar before and after RBCT [298]. Another group reports in a series of sixty TBI Patients that "All of the patients with basal PtiO(2)<15mmHg showed an increment in pbtO₂ versus 74.5% of patients with basal pbtO₂ or=15mmHg (p<0.01, hour 3)." They conclude that Erythrocyte transfusion is associated with a variable and prolonged increment of cerebral tissue oxygenation in anemic patients with severe traumatic brain injury. Low baseline pbtO₂ levels (<15mmHg) could define those patients who benefit the most from erythrocyte transfusion [3]. Another severe TBI series demonstrated that 57% of patients had a pbtO₂ increase, whereas in 43% of patients, pbtO₂ either did not change or decreased. pbtO₂ improvement was not associated with baseline hemoglobin concentration or low pbtO₂ (<1 kPa) [299]. One paper reports that the effect of RBCT on pbtO₂ is greater in women than in men [300].

The effects of RCBT in 17 children after severe TBI have also been reported [35]. The pbtO₂ increase was transient and seen in 79% of RBCT. A transient decrease was seen in 21%. The authors also report that: "Brain tissue oxygen tension returned to baseline within 24 hrs. Reliable predictors of this brain tissue oxygen tension response to blood transfusion, however, remain elusive." [35].

The aspect of storage duration of RPBC on the effects of pbtO₂ has been studied in 66 anaemic male TBI patients [136]. The authors report that: "There was a significant short-lasting (3-4 hrs) increase in pbtO₂ values after transfusion of erythrocytes stored for <10 days, 10-14 days, or 15-19 days, compared with those at baseline. In contrast, no significant changes in pbtO₂ were observed after transfusion of erythrocytes stored >19 days" [136]. Similar findings have been confirmed elsewhere in an animal study [135].

Clazosentan

The effects of Clazosentan, a selective endothelin receptor subtype A antagonist, on pbtO₂ in SAH patients in a phase IIa study have been reported with so far little effects [46]. A non-peer reviewed paper reports on the effects of intraoperative intracisternal subarachnoid sodium nitroprusside (SNP) administration in patients with aneurysmal SAH [204]. High-dose intra-arterial verapamil for the treatment of cerebral vasospasm after subarachnoid hemorrhage Verapamil caused no significant pbtO₂ changes [301].

Cerebral Angiography

One study reports on the utility of pbtO₂ monitoring during cerebral angiography [68]. In their series of 14 patients four patients showed a linear pbtO₂ 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 pbtO₂ values, which was also reflected in an increased number of ischemic lesions on CT imaging [68].

CPP Management

Based on an analysis of 18 comatose intracerebral hemorrhage patients it has been suggested that: "...pbtO₂ monitoring can be used to identify CPP targets for optimal brain tissue oxygenation" [76]. A paper with 30 poor grade SAH patients reports that metabolic crisis and BTH are associated with mortality and poor functional recovery after SAH. CPP levels <70 mm Hg was associated with metabolic crisis and brain tissue hypoxia, and may increase the risk of secondary brain injury in poor-grade SAH patient [302]. The role of CPP management in severe TBI patients has been addressed in light of pbtO₂ measurements in order to restore "normal" cerebral oxygenation, i.e. ≥ 25 mmHg. A combination of sedation and CPP augmentation were effective in 73 and 66% of episodes of compromised brain oxygen, respectively [303]. A report in poor grade SAH patients which addresses the relationship between CPP, ICP and pbtO₂ confirms the observation that ICP and CPP monitoring "... may not always detect episodes of cerebral compromise in SAH patients" [304]. They suggest that: "...several complementary monitors may be needed to optimize the care of poor-grade SAH patients", i.e. cerebral microdialysis and pbtO₂ [304]. Similar reports have been presented for TBI patients [305]. Another group reports similar finding which represents an important clinical aspect: "CPP and ICP should not be used as surrogates for pbtO₂ since cerebral oxygenation varies independently of cerebral hemodynamics and pressures" [306]. This finding is again supported by a series of 16 TBI patients in which the authors conclude that: "No clear relationship was found between the temporal pattern of cytokines and the behavior of the intracranial pressure, brain tissue oxygenation, and the presence or absence of swelling in the computed tomography scan" [196]. This finding has been confirmed in children: "Although very high ICP is associated with reduced pbtO₂, in general, absolute ICP has a poor relationship with pbtO₂" [307].

Applied Physiology

More complex physiological matters, which have attracted much attention in neurocritical care have also been addressed using pbtO₂ technology: the role of cerebral autoregulation monitoring, i.e. the link between mechanisms of cerebral vascular regulation and cerebral oxygenation regulation [30, 141, 216, 242, 308, 309]. Studies have shown that the mechanisms are closely linked [4, 49, 54, 72, 178, 222, 223, 258, 310, 311]. Of note, it has been reported that "The severity of brain tissue oxygenation derangement correlates with increasing cerebrovascular dysautoregulation in patients succumbing to severe head injury,..." [4]. One study has concluded that "Assessment of pbtO₂-

autoregulation gives valuable information on which patient will benefit from an increase in CPP and which CPP should be achieved to do so" [49]. This finding is in keeping with the suggestion that CPP elevation may be beneficial for ICP control and pbtO₂ management in selected patients after TBI, those with intact cerebral autoregulation [199, 223].

Further support for this therapeutic concept is provided from a series of 38 TBI patients: "Driving cerebral perfusion pressure in excess of optimal cerebral perfusion pressure does not yield improvements in brain tissue oxygen after head injury and should be avoided, whereas cerebral perfusion pressure below optimal cerebral perfusion pressure may result in secondary cerebral ischemia" [258].

This view has recently been challenged with the authors' conclusions: "We show that pbtO₂ generally tracks the direction of CPP irrespective of the state of cerebral autoregulation" [309]. It must be noted, however, that their study examines spontaneous CPP changes while others have investigated pharmacologically induced CPP variations [178].

PbtO₂-based autoregulation monitoring using an index named "ORx" has also been investigated in SAH patients [54, 59, 312, 313]. The authors report that "ORx values from days 5 and 6 after SAH carried predictive value for the occurrence of delayed infarction but before this event ultimately occurred" [54]. They conclude that "ORx indicates impaired autoregulation in patients who develop delayed infarction after SAH [54]. Furthermore, this index may distinguish between patients who finally develop delayed infarction and those who do not [54]." Such identification would allow timely interventions during the so called "window of opportunity" [54]. A larger series has raised the issue that: "The status of cerebrovascular autoregulation (measured by the ORx) might be an important pathophysiological factor in the disease process after SAH because impaired autoregulation was independently associated with an unfavorable outcome" [59].

The utility of the ORx for TBI patients, however, has been questioned [308]. A preliminary study in SAH patients could not confirm the utility of the ORx Index [41], however, methodological issues makes comparison of study results difficult [310]. An observational pilot study showed that ORx is severely disturbed in the edematous perihemorrhagic tissue after spontaneous intracerebral hemorrhage [69].

One animal study in which pbtO₂ monitoring is compared with near infrared spectroscopy [NIRS] measurements (rSO₂) in pigs during cardiopulmonary resuscitation is noteworthy because transcutaneous NIRS monitoring is commonly used in cerebro- and cardiovascular surgery [123]. The authors report that in contrast to transcutaneous NIRS measurements, NIRS readings obtained from skull showed a significant correlation to brain tissue oxygen partial pressure values. This study questions the validity of commonly used transcutaneous NIRS measurements. Similar evidence is provided from a series of 22 TBI patients: "In patients with severe TBI, pbtO₂ and rSO₂ were directly and significantly related. Severe intracerebral hypoxia was better detected by rSO₂ than was moderate intracerebral hypoxia. However, the diagnostic

accuracy of rSO(2) was limited, and this measure should not be considered a substitute for routine pbtO₂ monitoring." [243].

Another animal study is noteworthy [126]. The authors describe the effects of volatile anesthetics on pbtO₂ and other physiological parameters at various FiO₂ levels. They conclude that "cerebral PO₂ cannot be inferred directly from measurements of other parameters, indicating that methodology incorporating continuous direct measurement of brain oxygen will lead to a better understanding of cerebral oxygenation under anesthesia and hypoxia."

One animal study has aimed to define the optimal chest compression/ventilation ratio for basic life support [BLS] using pbtO₂ recordings. They conclude that: "During BLS, a compression/ventilation-ratio of 100:5 seems to be equivalent to 30:2, while ratios of 100:2 or compressions-only deteriorate peripheral arterial oxygenation and reduce the chance for return of spontaneous circulation" [108].

Cerebral Circulatory Arrest and Brain Death

PbtO₂ monitoring in 6 patients with cerebral circulatory arrest has been investigated. The authors point out that pbtO₂ "...decreased toward 0 mmHg as ICP increased and CPP decreased. PbtO₂ reached 0 only when there was clinical evidence for brain death (BD). During the subsequent 12 hours until the second (BD) examination, pbtO₂ remained 0 mmHg and did not respond to oxygen challenge". They contrast these patients to five other patients in whom pbtO₂ was 0 mmHg but who were not brain-dead. They report that: "These episodes were transient (<30 minutes) and responded to an oxygen challenge, directed treatment or catheter replacement". They conclude that "A sustained (>30 minutes) brain pbtO₂ of 0 is consistent with BD" and they suggest that "...pbtO₂ may be used to determine when a BD examination is appropriate in the pharmacologically suppressed patient" [88].

Further investigation into the reliability of clinical variables and neuromonitoring data as predictors of brain death shows that patients at risk of progressing to BD were those with low pbtO₂ (<16mmHg) on admission and during the first 24 hours of neuromonitoring [314]. Multivariate logistic regression showed that a low pbtO₂ level on admission was the best independent predictor for BD [314]. Similar evidence is provided in a study which reports that: "The first 72 hours of pbtO₂ neurologic monitoring predicts mortality. When the pbtO₂ monitor remains below 29 mm Hg in the first 72 hours of monitoring, mortality is increased" [255].

Brain tissue oxygenation in brain death has been published twice as in case series studies. The reports are quite uniform: "A sustained [>30 minutes] brain pbtO₂ of 0 is consistent with brain death [88] and " pbtO₂ fell to 0 in all patients who experienced brain death, and all patients with pbtO₂ of 0 experienced brain death. None of the 61 patients who did not experience brain death had confirmed pbtO₂ readings of 0" [73]. The authors, however, do point out that larger series are needed to assess sensitivity and specificity. Similar experiences have been reported in a series of 5 children diagnosed with brain death [315].

Safety Issues and Technical Considerations

PbtO₂ monitoring is considered safe in both children and adults [13, 23-25, 30, 316]. There are no published reports that persons involved in direct care of the patients have been harmed or injured while using pbtO₂ monitoring technology. Several papers have by now systematically addressed technical issues related to using pbtO₂ monitoring technology [13, 71, 130, 177, 317-319].

One paper reports two "clinically relevant" cerebral hemorrhages in 23 catheter insertions. Few further details are presented except for the fact that one of the two patients had an AVM which was considered the source of bleeding while the other remained "unexplained". Obviously this latter case was not large enough to require surgical evacuation [91]. Although no other adverse effects using pbtO₂ monitoring have been published 3 cases of acute subdural hematoma related to pbtO₂ monitoring probe insertion are known to the first author! The outcomes of these cases are unknown. The second author has not encountered problems other than very few minor haemorrhages along the catheter trajectory in > 150 probe insertions.

Catheters - Pros and Cons

If one assumes that the insertions techniques and all monitoring algorithms for all catheters are very alike the question becomes which one to use for one's own unit and clinical practise? There are no relevant technical pros or cons for any catheter which a priori precludes using any of them. The differences of the measurement principles are stated above in the paper.

Based on the authors and their colleagues' experiences it is not only important to understand the basics and principles of each technology but also to become familiar with one's own technology and know its potential clinical shortcomings. This section is designed to show all comparative papers, both peer-reviewed and non-peer-reviewed, in order to achieve this goal.

LICOX

Some authors consider the Licox probe the "gold standard" [71]. It does not represent the authors' opinion and it is likely that it is the "non-gold standard". It must be noted that the Licox technology uses a Clark-type electrode which is the most widely established partial pressure of oxygen monitoring device – it is used in the great majority of all original publications.

In 1998 a comprehensive study has addressed technical considerations and safety issues. 118 Licox catheters, which were used in 101 patients were assessed [13]. This paper includes finding of a previous publication based on an assessment of 73 catheters [317]. The results are as follows:

1. Small iatrogenic hematomas were observed for two patients (1.7%). This number compares favorably to what has been published for similar monitoring devices, e.g. intraparenchymal intracranial pressure monitoring. This number is much smaller to 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 to 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 PO₂ display errors were measured during the first 4 days of continuous monitoring. There is 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 degrees C and 37 degrees C and tested at oxygen pressures of 0, 44, and 150 mm Hg. This number is low and is irrelevant for daily clinical practise.
7. The zero display error was -0.21 ± 0.25 mm Hg. This number is low and is irrelevant for daily clinical practise.
8. Excluding the first 1 hour after insertion, data are reliable, with almost 100% good data quality.

Similar features have been reported from other groups: No infections or hematomas, one catheter failure, and 2 transport-related dislodgements in 30 TBI patients monitored with Licox [18]. This paper notes a six-hour hyperoxia treatment due to misinterpretation of treatment algorithms [18].

One paper reports that recordings in 5 out of 186 patient recordings obtained with Licox probes were excluded from an analysis because the drift exceeded preset limits without further details provided [276].

An extensive institutional practise review of 61 cases of multimodality monitoring, including 59 cases in which pbtO₂ was monitored reports an unusually high percentage of device malfunction or dislodgement of 43%; n = 26. Their hematoma- and infection rates were 3 and 5%, respectively, which includes a wide range of invasive cerebral monitors. Wit regard to the Licox probe they report a 17% hardware malfunction rate and discuss the possible reasons for that high number. They did, however, not return the devices to the manufacturer for further assessment of "hardware malfunction". They also report one large right frontal hematoma upon monitor insertion in a patient who was taking two antiplatelet function medications They conclude that: "...collaboration among institutions is necessary to establish practice guidelines for the choice and placement of multimodal monitors. Further advancement in device technology is needed to improve insertion techniques, inter-device compatibility, and device durability, ..." [320]. Some authors advocate a post-probe-insertion CT to ensure correct placement [237, 267, 304].

LICOX AND NEUROTREND

In vitro accuracy, long-term drift and response-time were addressed in a paper published in 2005 [177]. This paper also compares the Neurotrend and Licox system. The authors conclude:

1. Both systems measure oxygen tension sufficiently.
2. Licox technology measures more accurately than Neurotrend.
3. Neurotrend sensors read significantly lower pO₂ in 1% O₂.
4. Neurotrend sensors show an increasing deviation with higher oxygen concentrations which was due to two of twelve probes.
5. A slight drift towards lower oxygen tension readings for both sensors, but more pronounced for the Neurotrend, does not impair long-term use.

A comparison is presented in a non-peer reviewed paper [130]. Using 49 Licox catheters in 42 patients the authors report that 37 patients [88%] has artifact-free data collected. Using 50 Neurotrend catheters in 35 patients they had 14 patients [40%] with artifact-free data collected. They report a 20% catheter/bolt breakage and 8% catheter/sensor malfunction for Neurotrend compared with 0% and 2% for Licox. In their series of 99 catheters total they report 2 hematomas, no further details on size or other details, however, are provided [130]. It is also noteworthy that monitoring-related infections did not occur.

Another non-peer reviewed Licox/ Para-Neurotrend *in vitro* comparative study [319] reports:

1. 95% response times were 102 ± 13 seconds for first generation Licox probes and 135 ± 24 s for Paratrend.
2. Second generation probes were 134 ± 4 and 116 ± 16 s respectively.
3. At pO₂ 150 mmHg Licox and Paratrend probes were accurate with 2.2% and 2.1% error, respectively and 2.6% and 4.1% for later generation.
4. At pO₂ 18 mmHg, Paratrend overestimated by 16.5% (absolute error range 2.18 to 4.18 mmHg), 7.4% for Neurotrend, Licox underestimated by 1.8% (absolute error range 0.08 to 0.52 mmHg) with 3.6% for the second generation probe.

The authors draw a sensible conclusion: "Although there were statistically significant differences between the first generation probe types, this difference may not be clinically relevant. Overestimation of pO₂ by Neurotrend and small underestimation by Licox partially explain differences in published thresholds for cerebral ischemia. The Neurotrend was slightly more accurate and faster than the Paratrend system." [319].

Additional aspects of a direct Licox-Neurotrend comparison were reported in a non-peer reviewed study in 7 TBI/SAH patients [259]:

1. Mean PtIO₂ was generally lower when assessed by the Neurotrend, as compared with the Licox [Licox 27.7 mmHg vs Neurotrend 20.9 mmHg.

2. The amplitude of PtiO₂ elevations during ventilation with 100% oxygen was higher with the Licox, but this did not reach statistical significance (Licox 55.2 mmHg vs Neurotrend 50.2 mmHg).
3. Regarding clinical stability of the sensors, only one Neurotrend sensor provided valid function over the desired monitoring period. Five Neurotrend sensors dislocated or broke and one sensor did not show any function after insertion.
4. No malfunction occurred with the Licox sensors.

LICOX PMO

Formal testing results of the combined pbtO₂-temperature probe called "PMO" was published in 2008 [318]. Accuracy and response times of the PMO probe was assessed over a range of PO₂ values and temperatures under controlled laboratory conditions. In addition they tested the automated card calibration system and describe their clinical experience. The authors report:

1. The new Licox PMO probe accurately measures oxygen tension over a wide range of oxygen concentrations and physiological temperatures, but it does have a small tendency to underestimate oxygen tension (mean error, $-3.8 \pm 3.5\%$) that is more pronounced between the temperatures of 33 and 39 degrees C.
2. The thermistor of the PMO probe also has a tendency to underestimate temperature when compared with a resistance thermometer (mean error: -0.67 ± 0.22 C).
3. The card calibration system was also found to introduce some variability in measurements of oxygen tension when compared with a manually calibrated system.
4. Clinical experience with the new probe indicates good placement within the white matter using the improved bolt system and low rates of hematoma (2.9%), infection (0%), and dislodgement (5.9%).

LICOX AND NEUROVENT

A formal comparison between Raumedic - Neurovent (NV) and Licox (LX) [215] yields the following:

1. In all gas concentrations, NV and LX sensors measured pO₂ with high accuracy and stability *in vitro* (mean differences from calculated values were for NV 0.76-1.6 mmHg and for LX -0.46-0.26 mmHg).
2. Both sensors showed a shorter response time to pO₂ increase (for NV 56 ± 22 s and for LX 78 ± 21 s) compared to pO₂ decrease (for NV 131 ± 42 s and for LX 215 ± 63 s).
3. NV pO₂ values were more stable for changes in temperature, while LX sensors showed larger standard deviations with increasing temperature (the difference from the calculated values in 19.7 mmHg O₂) at 40 degrees C were for NV probes between 0.5 and 1.7 mmHg and LX between -2.3 and 1.9 mmHg).

4. Both sensors gave stable results with low standard deviations during long-term (10 days) use, but with a slight elevation of measured pO₂ levels by time.

The conclusions are: "Both NV and LX were accurate in detecting different oxygen tensions, and they did not deviate over longer recording times. However, LX needed a significantly longer time to detect changes in pO₂ levels compared to NV. Furthermore, LX probes showed an increased standard deviation with higher temperatures." Similar to the data presented above [319] these differences are unlikely to be clinically significant.

Another formal comparison between Raumedic - Neurovent (NV) and Licox (LX) is available [71]. This group reports:

1. The average of individual mean pbtO₂ measurements showed no relevant differences between the Licox (19.5 ± 7.1) and Neurovent multiparameter probe (21.7 ± 9.5).
2. Twenty-eight Licox probes out of 30 showed proper functioning over the desired monitoring period. Raumedic multiparameter probes displayed a higher malfunction/handling error frequency (2 device errors, 11 handling errors).
3. A comparison of the pbtO₂ data between the Licox and Raumedic systems according to Bland and Altman was possible in 18 out of 30 patients and showed acceptable results (mean difference -1.24 mm Hg; limits of agreement: -25.1 to +22.6 mm Hg). A total of 95.2% of 96,083 recordings was within the calculated limits of agreement.
4. *Ex vivo* tests of the probes after explantation revealed stable ICP and TBr function of the Raumedic probe. Precision of Zero pbtO₂ did not differ between the probes, whereas precision of the 150 mm Hg pbtO₂ was greater in the Raumedic probes.

Their conclusions are: "Interpretation of our data is limited by several factors: [1] monocentric study; [2] reduced mechanical probe stability, handling difficulties with the double lumen bolt; [3] design changes to improve mechanical stability will require further study; [4] conflict of interest with Raumedic because of its support for the study. The conclusion drawn from our study is that the new multiparameter probe evaluated does measure ICP, TBr, and pbtO₂. But all the initial data given in this paper have to be interpreted cautiously. A new study will be necessary when the mechanical stability of the new probe has been improved".

A peer reviewed, yet preliminary formal comparison in eleven SAH and TBI patients with simultaneously recorded Licox and Neurovent pbtO₂ for ORx calculation reports a mean ORx difference of 0,1 with Licox producing higher values [313]. ORx agreement was between -0.6 to +0.7. For the calculation of the optimal CPP (CPP(opt)), based on cerebral autoregulation assessment, they report a mean difference of 0 mmHg, however the limits of agreement ranged between -16.5 and +16.4 mmHg. They conclude that: "The main result is that Licox and Raumedic showed consistent differences in ORx and CPP(opt). Therefore, ORx values of both probes cannot be interchanged and should not

be viewed as equivalent. This should be taken into consideration when discussing ORx data generated by different pbtO₂ probe types” [313].

Another formal comparison between the Neurovent PTO and the Licox probe was carried out in an animal model [321]. Probes were compared on seven manoeuvres (a) baseline measurements followed by (b) hyperoxygenation (fraction of inspired oxygen (Fio₂)=1.0), medically induced (c) hypo- and (d) hypertension, (e) hyperventilation, (f) tris-hydroxymethylaminomethane application, and (g) hypoxigenation (Fio₂<0.05). The authors report that:

1. Both probes show good comparability under baseline conditions (meandiff 2.09 mm Hg, standard deviation 0.04 mm Hg, range 1.98-2.20 mm Hg).
2. Measurement dynamics during hyperoxygenation (Fio₂=1.0) revealed significantly different profiles, eg Neurovent-TO probe reached up to 1.53-fold higher pbtO₂ values than the Licox probe.
3. During hypoxigenation (Fio₂<0.05), the Neurovent-TO probe detected the hypoxic level of 8.5 mm Hg 1.5 minutes earlier than did the Licox probe.
4. All other maneuvers showed similar responses in both technologies. The authors conclude that: “The Neurovent-TO PbrO₂ device comparably measures PbrO₂ under most conditions tested compared with the Licox device. The Neurovent-TO is more sensitive to rapid Fio₂ changes. Further studies are necessary to clarify these differences. It is questionable whether existing knowledge of Licox tissue oxygenation, ie, hypoxic threshold, can be directly transferred to the Neurovent-TO [321].

Four other, yet non peer reviewed, Licox-Neurovent comparisons are available [166, 322-324].

The first paper with a series of seven SAH patients reports clinically acceptable, i.e. stable monitoring parameters [322]. They report:

1. Mean pbtO₂ from Licox and Neurovent PTO was 16.1 +/- 9.0 mmHg and 17.5 +/- 11.9 mmHg respectively.
2. Mean ORx was 0.35 +/- 0.44 and 0.31 +/- 0.43 respectively.
3. The pbtO₂ difference was -2.73 +/- 10.1 mmHg (Licox – Raumedic).
4. The difference for the calculated ORx was far smaller (0.03 +/- 0.31; Licox – Raumedic) and the correlation coefficient higher than for both pbtO₂ values (0.76 for ORx vs 0.56 for pbtO₂) [322].

The second paper reports on the testing of eight Licox and eight Neurovent-PTO sensors for 10 min at 37 °C, atmospheric pressure, at an oxygen content of 0% and 100% before and after the *in vivo* test. The same probes were implanted in pigs, which underwent hepatectomy. A 100% FiO₂ challenge for 10 min was performed 2h post-abdominal surgery [323].

They report:

1. At 0% O₂ content values varied from 0.2 to 7 mmHg, at 100% O₂ content from 130 to 165 mmHg. No difference between probes was found.
2. *In vivo* tests: Raumedic showed statistically significant higher pbtO₂ (mean +6.3 mmHg) compared with Licox.
3. During O₂ challenge, both probes responded similarly; however, Raumedic had a 10% higher, statistically significant response amplitude.
4. After explantation there was again no difference between the two sensors.

They conclude that Neurovent sensors measured higher pbtO₂ values. There was no significant difference regarding overall measurement of *in vitro* accuracy between the two probes, which proved to be robust when used consecutively for longer periods and in different environments [323].

The third paper reports on 18 TBI and SAH with simultaneous Licox and Neurovent pbtO₂ measurements [324].

They report:

1. Both types of probes were able to display spontaneous pbtO₂ fluctuations and reactions to therapy.
2. Mean measurement difference between the probes was -2.3 mmHg, with corresponding 95% limits of agreement of -32.3 to 27.5 mmHg.
3. Regarding an ischemia threshold of 15 mmHg, both probes were in agreement in 78% and showed disparate results in 22%.

They conclude that: “Our data suggest that the pbtO₂ measurements of the two systems cannot be interchanged. Although we were unable to determine which system delivers more valid data, we do think that more rigorous testing is necessary before implementing the new probe in clinical routine” [324].

The fourth and final paper, which is an animal study with simultaneous Licox and Neurovent recordings after hepatectomy in swine reports that:

1. Despite a statistically significant mean pbtO₂ difference of 6.2 mmHg, the mean ORx (Licox) was 0.139, the mean ORx(Neurovent) was 0.146 (p = 0.2098).
2. Correlation coefficient of ORx values assessed every minute and every hour was 0.52 and 0.58 respectively.
3. They conclude that: “Despite this significant difference in absolute pbtO₂ values the derived mean ORx values were not different. Similar to the established Licox system, the Raumedic system seems to enable a valid ORx recording [166].

LICOX AND FOXY AL-300

Performance of the Licox and the Foxy AL-300 system was compared in an animal study [247]. They took measurements at (a) baseline with 100% FiO₂, (b) during episodes of apnea, and (c) during recovery at 100% FiO₂.

They report

for (a): Foxy-ptiO(2) 62+/-24 mm Hg, and Licox-ptiO(2) 55+/-29 mm Hg,

for (b): Foxy-ptiO(2) 37+/-12 mm Hg, and Licox-ptiO(2) 31+/-16 mm Hg,

for (c): Foxy-ptiO(2) 78+/-26 mm Hg, and Licox-ptiO(2) 62+/-32 mm Hg,

with no further statistical analysis. The authors conclude that: "The present study demonstrates the feasibility of pO₂ measurements in ... cerebral microcirculation using a novel uncoated fluorescence quenching probe. The technology (Foxy AL-300) allows for real-time investigation of pO₂ changes at a temporal resolution of 0.05 to 10 Hz" [247].

PbtO₂ Monitoring Reviews & Critical Appraisal

After pbtO₂ monitoring technology has been introduced into clinical practise in the mid 1990's it has been subjected to several formal reviews with an increasing number since 2003 [1, 130, 171-173, 175, 185, 186, 188, 190, 192, 195, 198, 200, 206, 208-210, 214, 231, 233, 273, 325-346]. This increasing number reflects the fact that pbtO₂ monitoring has established itself as an additional monitoring tool for neurointensive care [347]. It has even been said to be "... as close to a gold standard of cerebral oxygenation as we have at the bedside" [233]. The Licox Clark type electrode is considered a reference or "gold standard" electrode in experimental setups [247, 261]. All but one review indicate that this technology is useful for routine clinical practise [206]. This paper recommends that both AVDO₂ monitoring and pbtO₂ monitoring should only be used for scientific research based on the conclusion that these technologies have at present not been demonstrated to be associated with a clinical benefit [206]. A similar yet less conclusive statement is presented in another review [188]. The authors point out that "...pbtO₂ monitoring may allow one to find individual trends and to react therapeutically to counter local tissue ischemia but must not be mistaken for a 'crystal ball' that can predict the ultimate outcome" [188]. It has also been emphasized that the surgeon/physician in charge of pbtO₂ monitoring must have experience in data interpretation: "It is equally important that the clinician understands relevant aspects of brain oxygen physiology and head trauma pathophysiology to enable correct interpretation of the monitored data and therefore to direct an appropriate therapeutic response that is likely to benefit, not harm, the patient" [348].

Three reviews have underlined the known fact of a lack of a randomized trial to prove the utility of pbtO₂ monitoring which, speaking from a strictly scientific point of view, is needed to recommend its unrestricted routine use [200, 273, 325]. In keeping with this view a recent comprehensive pbtO₂ review concludes that the current scientific literature implies that: "... These results imply that treating patients to increase pbtO₂ may improve outcome after severe TBI. This question will require further study" [316]. This group has previously suggested that: "...pbtO₂ monitoring might even have the potential to improve outcome [226].

If clinicians, however, were to restrict all monitoring modalities unless proven by such trials were available, little if any routine neuromonitoring would be established.

A 2010 paper including 41 severe TBI reports that: "The use of pbtO₂ monitors to guide therapy was associated with higher cumulative fluid balance, more vasopressor use, and the development of both pulmonary edema and refractory intracranial hypertension" [20]. They also report that patients who had a pbtO₂ monitor had a worse neurological outcome. Although the authors present various approaches to account for this association a conclusive explanation is not presented.

CONCLUSIONS

Based on this review it is concluded that pbtO₂ monitoring 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 to established cerebral monitoring devices. Pathologic values have been established in peer-reviewed research, which are not only relevant to outcome but are treatable.

The effects of virtually all ICU treatment modalities on cerebral oxygenation have been investigated, and pbtO₂ monitoring technology offers new insights into cerebral physiology and pathophysiology. The benefits clearly outweigh the risks, which remains unchallenged in almost all publications retrieved except for two. It is particularly attractive because it offers continuous, real-time data and it is available at the bedside.

This technology represents an invasive cerebral monitoring modality which requires cranial access and harbors a small risk of causing subdural or intraparenchymal hematoma. 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 practise [218, 332, 349].

Only a randomized trail, which is currently under way, will eventually prove that pbtO₂ monitoring will lead to improved outcome in any of the conditions for which this technology is currently used.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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DISCLOSURES

Erhard Lang is a member of the Integra Speakers Bureau and consults Integra for complaints received with the use of Licox probes. Matthias Jaeger has nothing to disclose.

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