Evaluation of a Novel Brain Tissue Oxygenation Probe in an Experimental Swine Model

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BACKGROUND: Cerebral microdialysis, cerebral blood flow, and cerebral oxygenation ($P_{br}O_2$) measurements using intraparenchymal probes are widely accepted as invasive diagnostic monitoring for early detection of secondary ischemia.

OBJECTIVE: To evaluate a novel $P_{br}O_2$ probe for continuous and quantitative oxygenation assessment compared with the existing gold standard $P_{br}O_2$ probe.

METHODS: In 9 pigs, 2 $P_{br}O_2$ probes (Neurovent-TO vs Licox) were implanted into the subcortical white matter. An intracranial pressure probe was inserted contralaterally. The $P_{br}O_2$ probes were tested during (1) baseline measurements followed by (2) hyperoxygenation (fraction of inspired oxygen [Fio_2] = 1.0), medically induced (3) hypo- and (4) hypertension, (5) hyperventilation, (6) tris-hydroxymethylaminomethane application, and (7) hypoxygenation ($Fio_2 < 0.05$). For statistical analyses, Bland-Altman plots were used.

RESULTS: The Neurovent-TO probe is easy to handle and does not need a specific storage or calibration. Bland-Altman analyses revealed good comparability of both technologies under baseline conditions ($mean_{diff}$ 2.09 mm Hg, standard deviation 0.04 mm Hg, range 1.98-2.20 mm Hg), but measurement dynamics during hyperoxygenation ($Fio_2 = 1.0$) revealed significantly different profiles, eg Neurovent-TO probe reached up to 1.53-fold higher $P_{br}O_2$ values than the Licox probe. During hypoxygenation ($Fio_2 < 0.05$), the Neurovent-TO probe detected the hypoxic level of 8.5 mm Hg 1.5 minutes earlier than did the Licox probe. All other maneuvers showed similar responses in both technologies.

CONCLUSION: The Neurovent-TO $P_{br}O_2$ device comparably measures $P_{br}O_2$ under most conditions tested compared with the Licox device. The Neurovent-TO is more sensitive to rapid Fio_2 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.

KEY WORDS: Cerebral oxygenation, Clark electrode, Intracerebral monitoring, Oxygen quenching

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The clinical benefit of multiparametric monitoring including cerebral microdialysis, cerebral oxygenation ($P_{br}O_2$), and cerebral blood flow has been largely documented since its introduction.[1-4] $P_{br}O_2$ monitoring has been suggested as a safe and reliable technique to assess the efficacy of treatments based on their power to maintain and restore adequate $P_{br}O_2$ levels.[5-8]

ABBREVIATIONS: **CPP**, cerebral perfusion pressure; **Fio_2**, fraction of inspired oxygen; **MAP**, mean arterial pressure; **$P_{br}O_2$**, cerebral oxygenation; **Pco_2**, partial pressure of carbon dioxide; **THAM**, tris-hydroxymethylaminomethane

Critically ill and comatose patients with severe traumatic brain injury, high-grade subarachnoid hemorrhage, and hemorrhagic/ischemic stroke may benefit from such monitoring.

Since its introduction in 1993, the Licox probe (Licox CC1.SB, Integra LifeSciences Corp, Plainsboro, New Jersey) has built up its reputation as the gold standard in clinical cerebral oxygenation monitoring.[4,9,10] However, in 1998, Dings et al[11] revealed a 13.6% technical complication rate for Licox probes, indicating

the need for improvement in sensor design and application. We tested a newly developed cerebral probe combining temperature and $P_{br}O_2$ measurement (Neurovent-TO; Raumedic AG, Helmbrechts, Germany; Figure 1) compared with the Licox probe in an experimental swine model that allows for standardized alterations of blood pressure and ventilation parameters as well as administration of tris-hydroxymethylaminomethane (THAM).

METHODS

Technical Development

Neurovent-TO $PbrO_2$ Technology and Probe Design.

Contrary to the Licox-Clark type electrode, the oxygen microsensor operates as an optode based on oxygen quenching. This measurement principle is described in detail in Figure 2. The Neurovent-TO does not need specific calibration nor does it require specific storage conditions before insertion. It can be inserted via a conventional multilumen bolt kit (Licox REF IP2.P; Integra LifeSciences Corp) because of its small diameter size (3 French). A thermocouple to measure brain temperature and to readjust the $P_{br}O_2$ automatically is an integral part of the probe. The Neurovent-TO is factory precalibrated within a fluid of 0 mm Hg partial pressure of oxygen. The measurement range of the probe is 0 to 200 mm Hg partial pressure of oxygen and its $P_{br}O_2$-sensitive area accounts for more than 13 mm^2 and is thus comparable to those of the Licox (14 mm^2). The response time (T90%/37°C) is 48 seconds on average for a change from 150.0 ± 15 mm Hg to 0.0 mm Hg and vice versa. A fiberoptic cable transfers the fluorescent light into a multiparameter recording logger (MPR; Raumedic AG) (Figure 1) and the actual $P_{br}O_2$ value is displayed.

Anesthesia and Operating Procedure

Animal protocols for the experiments were approved by the institutional animal care and use committee (protocol no. 35-9185.81/G-60/06).

Nine male swine with an average mean ± standard deviation (SD) weight of 30 ± 2.75 kg were anesthetized with ketamine (10 mg/kg), midazolam (5 mg/kg), and azaperone (40 mg/kg), administered by intramuscular injection. Animals were orally intubated and mechanically ventilated (fraction of inspired oxygen [Fio_2] = 0.3). Anesthesia was maintained using 1.5% isoflurane inhalation. Rectal and brain temperatures were continuously monitored. Rectal temperature was maintained at between 35.5°C and 37°C. After surgical exposure of the right femoral artery, a 4-French probe was placed for permanent monitoring of mean arterial blood pressure (MAP). A venous line was placed in the right ear vein and capillary oxygen saturation was monitored from the left ear.

Two burr holes (5-mm diameter) were placed over the right and left coronal sutures 1.2 cm apart from the midline. Afterward, the dura was coagulated and incised. Pial vessels at the probe entry points were coagulated to avoid parenchymal hemorrhage caused by probe insertion. All intraparenchymal devices were introduced and secured transcutaneously before insertion into the brain. In 9 male swine, 2 different $P_{br}O_2$ probes (Neurovent-TO and Licox) were implanted in the left hemisphere (subcortical area: 1.4 cm below the cortical surface, 3 mm apart from each other); thus, O_2-sensitive areas of both probes faced each other. On the contralateral side, an intraparenchymal ICP probe (Neurovent-P) was inserted for continuous monitoring of ICP and calculation of cerebral perfusion pressure (CPP). After probe placements, the 2 burr holes were sealed with bone wax. Postmortem cranial vaults were opened completely, brains were removed, and intraparenchymal probe locations were macroscopically inspected and interdevice distances and insertion depths were measured.

Experimental Protocol

After an equilibration phase of the $P_{br}O_2$ of 60 minutes, (1) baseline parameters were obtained over 15 minutes. Subsequently, the following procedures were performed: (2) hyperoxygenation (Fio_2 = 1.0 for 20 minutes), (3) hypotension (verapamil and/or amiodarone; MAP decrease >40 mm Hg for 25 minutes), (4) hypertension (norepinephrine; MAP increase >40 mm Hg for 20 minutes), (5) hyperventilation (partial

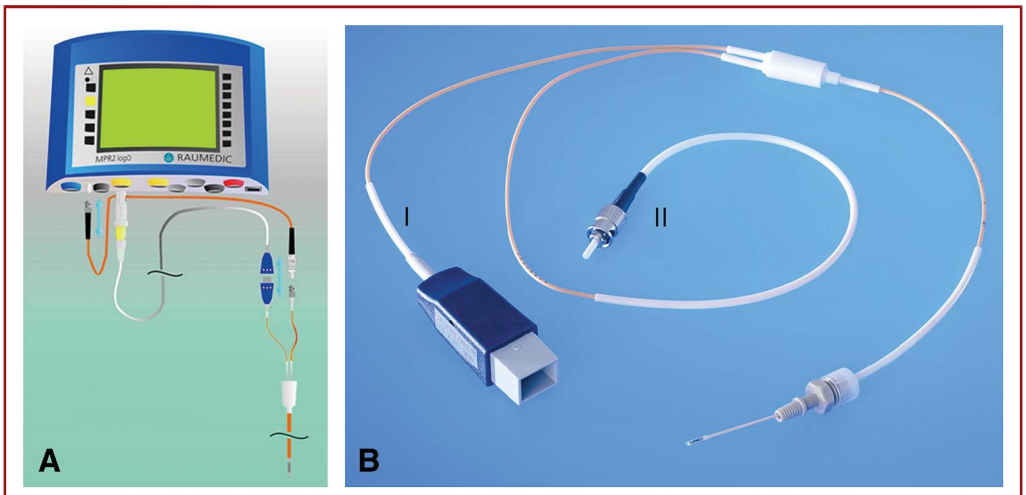

FIGURE 1. **A**, *the Neurovent-TO is demonstrated including the data logger and the cerebral oxygenation ($P_{br}O_2$) probe.* **B**, *probe design showing the temperature cable (I) and fiberoptic $P_{br}O_2$ cable (II) ending in a single wire.*

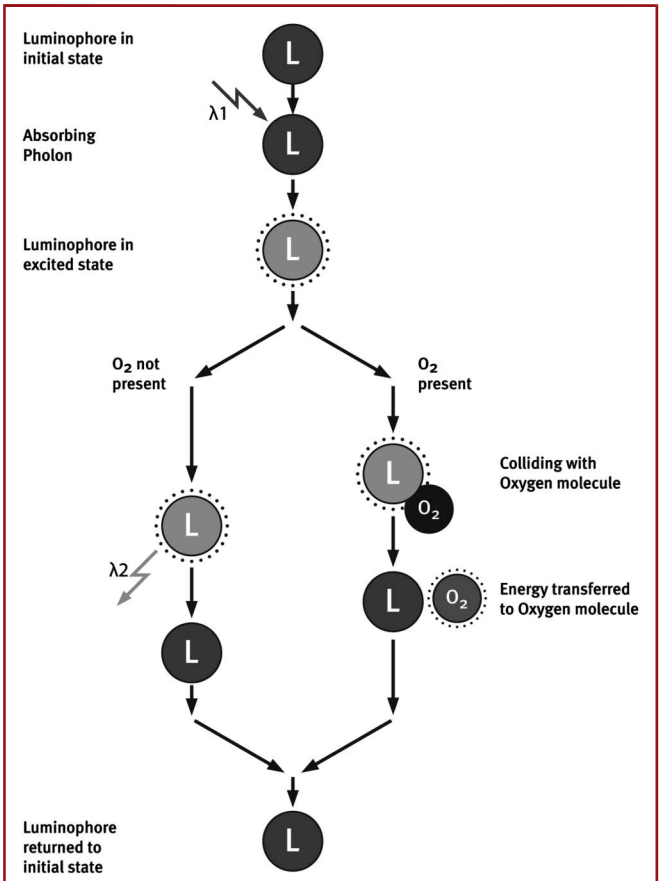

FIGURE 2. *Principle of oxygen quenching used in the Neurovent-TO probe. Fluorescent dye (luminophore: silicone-soluble ruthenium diamine complex) absorbs light (λ1) from a light source. Thus, dye molecules are transferred into an excited state. After a certain lifetime, the excited state drops down into its nonexcited state emitting light of a certain wavelength (λ2). In the presence of oxygen, the excited state can descend into its nonexcited state without emitting light because of collision processes with oxygen molecules. This process occurs highly specifically with oxygen and does not consume luminophore or oxygen. A correlation between the O_2 concentration of the probe, the luminescence intensity, and luminescence duration is known.*

pressure of carbon dioxide [Pco_2] <25 mm Hg for 25 minutes) followed by (6) application of THAM (60 mmol, fractionated over 10 minutes) administered intravenously. Thereafter, allowing another 20 minutes for $PbrO_2$ equilibration, protocol points 1 through 5 were repeated. Finally, (7) hypoxygenation (Fio_2 < 0.05 over 10 minutes) was induced until hypoxic cardiac arrest occurred. Between each maneuver, 10 to 20 minutes were allowed for parameter stabilization. Thus, the overall period of monitoring in a single swine lasted approximately 4.5 hours after the first $P_{br}O_2$ equilibration phase.

Monitoring

All relevant physiological parameters such as MAP, ICP, CPP, brain and rectal temperatures, heart rate, and oxygen saturation were continuously recorded, whereas blood-gas analyses were performed every 2 hours. ICP, CPP, MAP, and brain temperature were recorded by 1 data logger (MPR-1). Both $P_{br}O_2$ values and the brain temperature measured by the Neurovent-TO were simultaneously recorded on a second data logger (MPR-2). Continuous monitoring data were digitally sampled at 1 Hz. The Licox $P_{br}O_2$ probe was calibrated before insertion with the calibration card provided by the manufacturer. For correct $P_{br}O_2$ measurement with the Licox, the temperature was manually adjusted to the current brain temperature taken from the Neurovent-TO probe. Both data loggers were synchronized before each experiment.

Statistics

All data presented are expressed as averages of individual means ± SDs. All data were normally distributed (Kolmogorov-Smirnov test). For descriptive and statistical analyses, SPSS 14.0 (SPSS Inc, Chicago, Illinois) was used. All plots were generated using Sigmaplot 10.0 (SYSTAT Software Inc, San Jose, California). Bland-Altman plots were used to statistically compare the Neurovent-TO and the Licox. For clinical measurements, comparison of a new measurement technique with an established one is often needed to see whether they agree sufficiently for the new one to replace the old. Such investigations are often analyzed inappropriately, notably by using correlation coefficients. The use of correlation is misleading. An alternative approach, based on graphical techniques and simple calculations, is the previously mentioned Bland-Altman plot, together with the relationship between this analysis and the assessment of repeatability.[12] To determine whether there was a significant difference in CPP values before and after hemodynamic maneuvers, a paired *t* test was used.

RESULTS

In 9 animals, a total of 108 episodes of (1) baseline, (2) hyperoxygenation (Fio_2 = 1.0), (3) hypotension, (4) hypertension, (5) hyperventilation, (6) THAM application, and (7) hypoxygenation (Fio_2 < 0.05) were recorded. No maneuvers led to unintended permanent changes in vital parameters, and the ICP remained within normal values. None of the animals herniated.

(1) Baseline measurements (18 episodes, total monitoring period of 270 minutes) revealed a mean difference between both technologies of 2.09 ± 0.04 mm Hg. The differences ranged from 1.98 to 2.20 mm Hg. The Bland-Altman plot (Figure 3) demonstrates small differences within the 2-SD limits (2 SD = ±0.09 mm Hg), thus the Neurovent-TO can be interpreted as equivalent to the Licox under baseline conditions.

(2) Significant differences occurred during normobaric hyperoxygenation. Oxygen challenges showed a maximum difference of all calculated $P_{br}O_2$ values of 16 mm Hg after 15 minutes of ventilation at an Fio_2 of 1.0. This equals a 1.53-fold maximum difference and a mean difference of 8.12 ± 5.93 mm Hg overall (Figure 4).

(3) Responses to significant ($P < .0001$) CPP reduction were equal with a mean difference of 0.59 ± 0.21 mm Hg. Figure 5A illustrates the relationship of both probes during hypotension. The Bland-Altman plot (Figure 5B) of this experimental sequence statistically proves this relationship.

(4) After significantly increased CPP, a mean difference of both probes of 1.39 ± 0.49 mm Hg was calculated, and

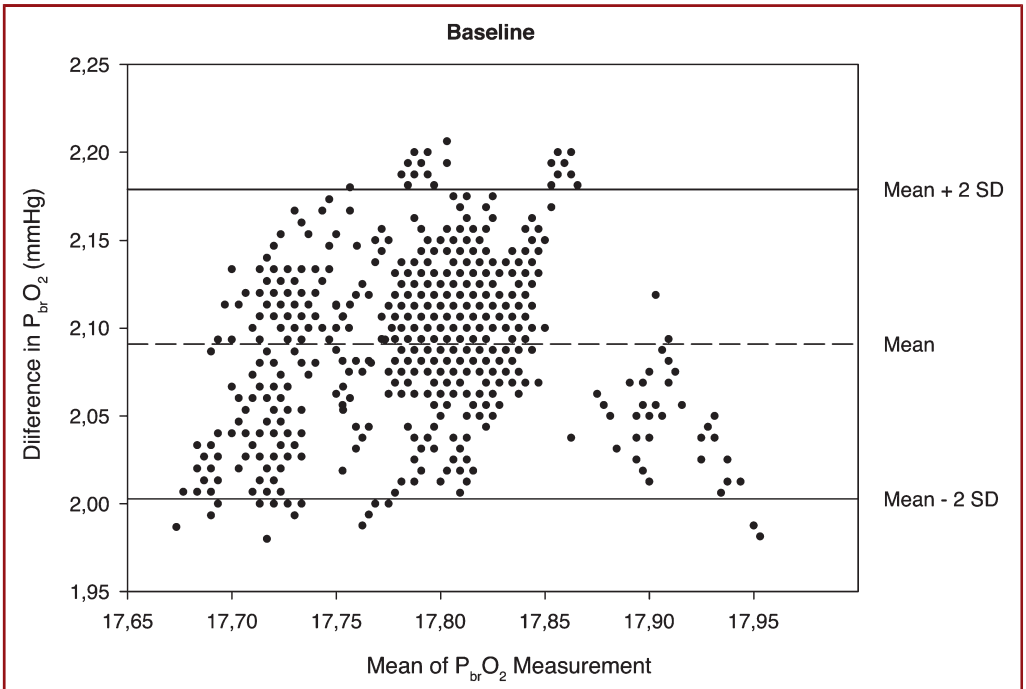

FIGURE 3. *Baseline cerebral oxygenation ($P_{br}O_2$) Bland-Altman plot displaying mean of $P_{br}O_2$ values (x coordinate) vs the corresponding difference of both probes (y coordinate). It presents an overall mean difference of 2.09 mm Hg ± 2 standard deviations of 0.09. However, this may allow the conclusion that Neurovent-TO will measure $P_{br}O_2$ comparable to the Licox.*

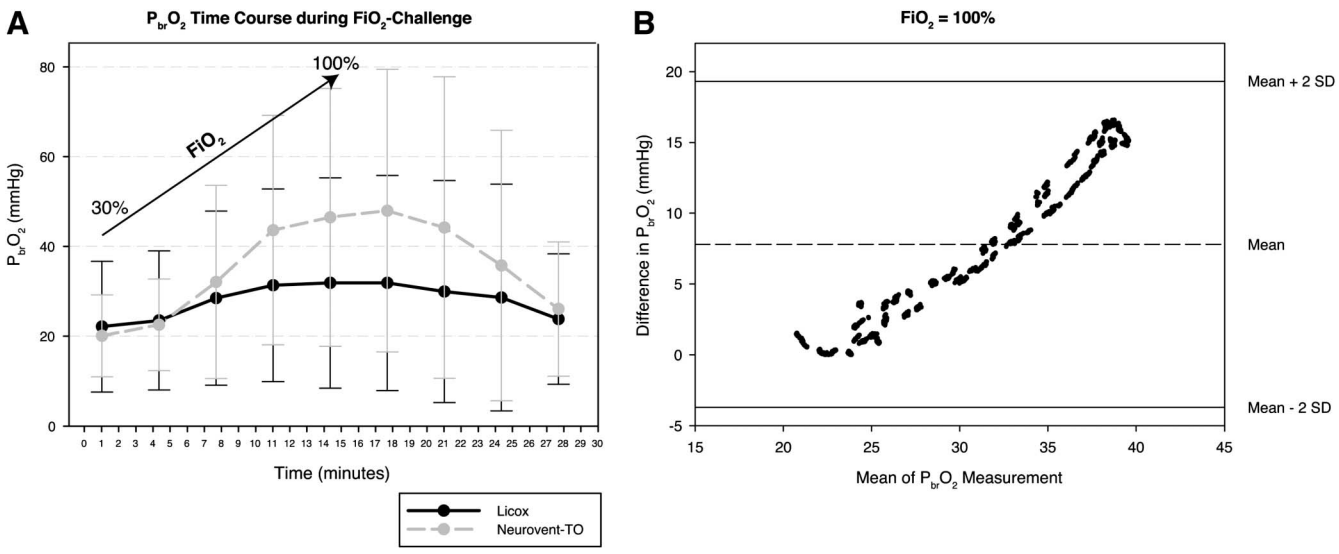

FIGURE 4. *Graph illustrating reaction to hyperoxygenation challenges (gradually increasing Fio_2 from 0.3 to 1.0) with significantly differing cerebral oxygenation ($P_{br}O_2$) profiles within 30 minutes ($P < .001$). **A**, 1.53-fold increase of $P_{br}O_2$ is seen using the Neurovent-TO probe after increasing Fio_2 to 100%. **B**, Bland-Altman plot illustrating that higher mean $P_{br}O_2$ values will result in greater differences in both $P_{br}O_2$ probes. Black line, Licox; gray dashed, Neurovent-TO.*

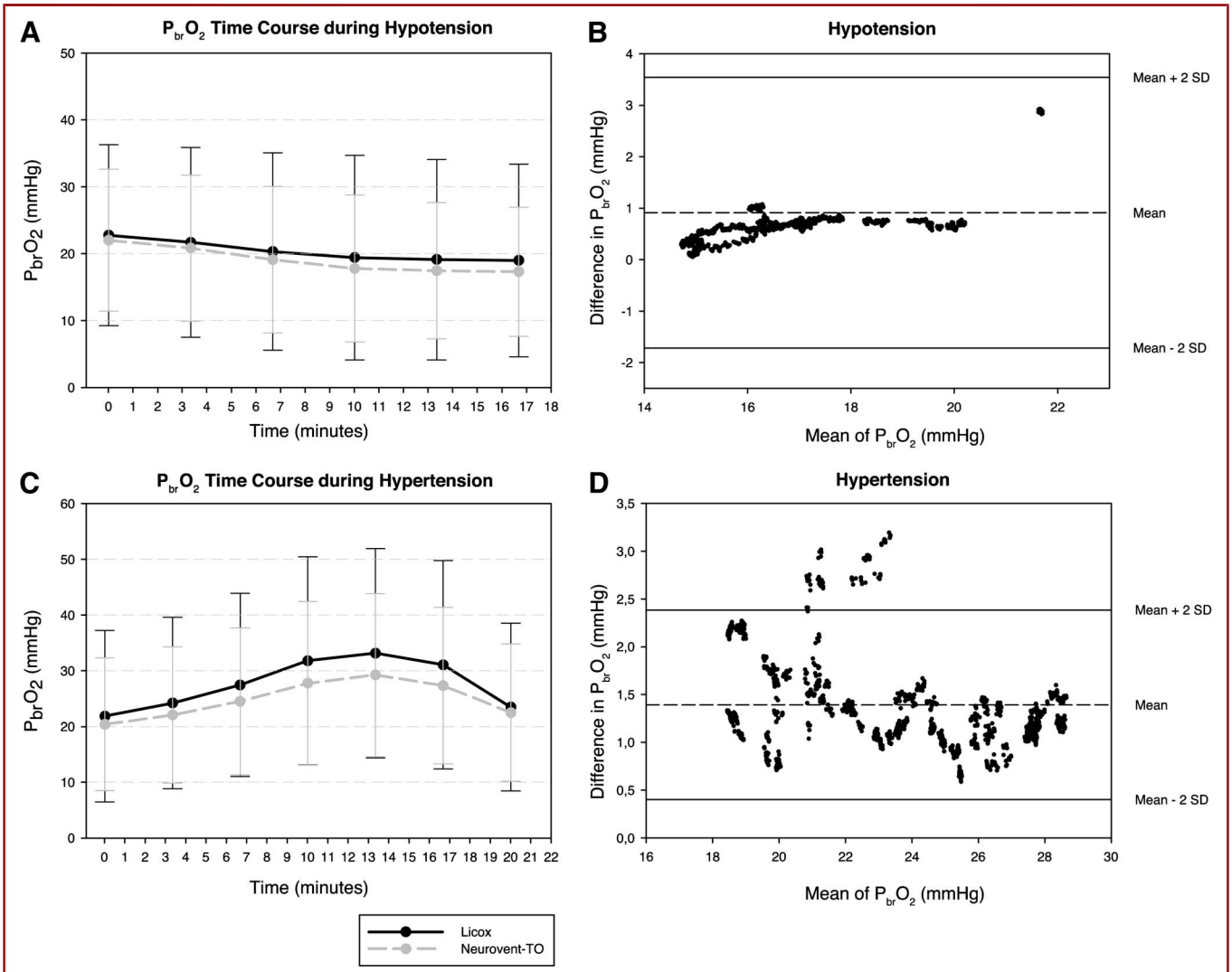

FIGURE 5. *Graphs illustrating the effects of medically induced hypotension and hypertension.* **A**, *after a significant (***P < .0001) cerebral perfusion pressure (CCP) decrease from a mean of 78 mm Hg to 54 mm Hg, a time-related similar reaction of both cerebral oxygenation ($P_{br}O_2$) probes without significant differences occurs.* **B**, *Bland-Altman plot of hypotension maneuver underscoring this finding displaying a constant mean difference of 0.59 mm Hg between both probes with minimal variance.* **C**, *after significant (***P < .0001)* CPP increase from a mean of 72 mm Hg to 115 mm Hg, a time-related comparable reaction of both $P_{br}O_2$ probes without significant differences occurs. **D**, *Bland-Altman plot of hypertension maneuver underscoring this finding displaying a mean difference of 1.4 mm Hg between both probes.*

no significant difference was detected between both probes (Figure 5C). The Bland-Altman plot confirms this finding (Figure 5D).

(5) During forced hyperventilation (Pco_2) of less than 25 mm Hg), the $P_{br}O_2$ decreased by 25% from 21.5 mm Hg to 15.93/16.61 mm Hg (Licox/Neurovent-TO).

(6) No discernible differences were seen for THAM buffer applications.

(7) Figure 6 shows that higher $P_{br}O_2$ differences occurred with continuous hypo-oxygenation during the time course of 10 minutes after onset of hypo-oxygenation. Hypoxic tissue $P_{br}O_2$ values (ie, $P_{br}O_2$ <8.5 mm Hg) were indicated approximately 1.5 minutes earlier by the Neurovent-TO compared with the Licox (Figure 6A). Figure 6B shows the Bland-Altman plot displaying higher mean $P_{br}O_2$ differences between both probes for lower mean $P_{br}O_2$ values.

DISCUSSION

Within the setting of multiparametric neuromonitoring for critically ill patients, measurement of $P_{br}O_2$ has evolved to be a valuable parameter. Its clinical usefulness was confirmed in several studies.[1,3,11,13-18] Especially after ischemic stroke, traumatic brain injury, subarachnoid hemorrhage, and intracranial

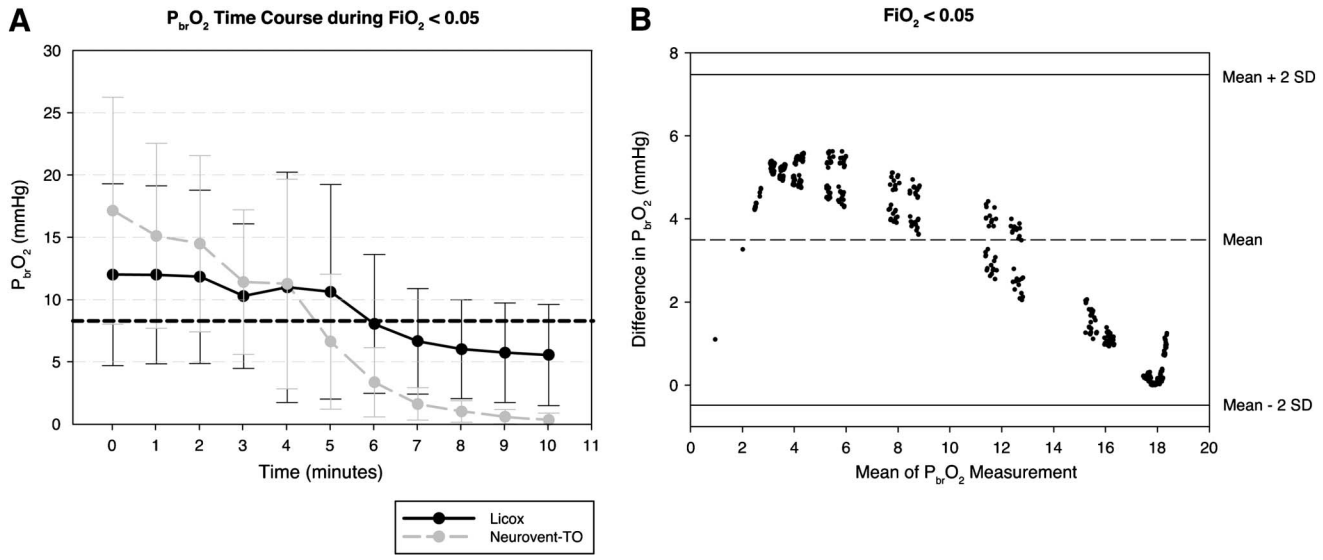

FIGURE 6. **A**, *graph illustrating cerebral oxygenation ($P_{br}O_2$) profiles within 10 minutes after induction of hypoxia ($Fio_2 < 0.05$). Black dashed line indicates the hypoxic level of 8.5 mm Hg. The hypoxic $P_{br}O_2$ level is indicated approximately 1.5 minutes earlier by the Neurovent-TO probe compared with Licox.* **B**, *Bland-Altman plot illustrating that lower mean $P_{br}O_2$ values will result in greater differences in both $P_{br}O_2$ probes.*

hemorrhage when ICP and/or CPP is suspected as no longer sufficient, $P_{br}O_2$ provides additional information on whether and how aggressive intensive care therapies such as surgical decompression, hypothermia, and barbiturate coma should be applied. Additional $P_{br}O_2$-based valuable information may be added by calculating the optimum CPP based on the oxygen pressure reactivity index as a measure of cerebral autoregulation.[14,15] However, clinical benefit of $P_{br}O_2$ monitoring in terms of outcome has been reported only once, highlighting the urgent need for more such studies.[19]

From a technical standpoint, after other competitors withdrew their products from the market, the Clark-type electrode (Licox) remained as the only well-validated $P_{br}O_2$ monitoring system. In contrast to the Licox, the new Neurovent-TO probe works on the principle of oxygen quenching, which is at least theoretically superior because of the absence of sensitivity to scattering light because of phase shift measurement, lack of an "O_2 consumptive" effect, and high signal-to-noise ratio.

Results of our study comparing methods in a swine model demonstrated the differences between the 2 systems. Whereas under physiological conditions and in all maneuvers aiming to provoke changes in ICP/CPP $P_{br}O_2$, Neurovent-TO results were within expectations and thus comparable to those of the Licox; normobaric changes in Fio_2 (hyper-/hypo-oxygenation) led to significant differences (Figures 4 and 6), giving the impression that the Neurovent-TO has a faster and better dynamic response to such Fio_2 challenges. These differences raise speculation as to whether such inconsistent results may be predicated on marked technical differences in both probes such as the O_2 consumptive effect of the Clark-type electrode or the moving average calculation (most recent 300 measurements before an absolute value is given) in the Licox system. In their recent publication, Purins et al[20] contributed data on sensor response times of the Neurovent-PTO compared with the Licox that likewise concluded that the Licox response to oxygen changes was slower than that of the Neurovent-PTO. Furthermore, accuracy tests in this particular study also demonstrated that in vitro oxygen concentrations were lower in the Licox than in the Neurovent-PTO. The higher the oxygen concentration is, the lower the reading by the Licox is compared with the Neurovent-PTO. However, the Licox $P_{br}O_2$ values differed less from the calculated concentrations in the in vitro buffer solution. Considering this finding, Neurovent-PTO may overestimate the amount of available $P_{br}O_2$, which may not have any clinical impact.

When testing $P_{br}O_2$ probes in vitro, oxygen is continuously supplied, and the previously mentioned O_2 consumption phenomenon is unlikely to occur. This may pose another explanation for why we found an up to a 1.5-fold difference in $P_{br}O_2$ during hyperoxygenation in vivo. In contrast, in vitro conditions with endless oxygen-supplying conditions will not allow oxygen consumption.

Critically low $P_{br}O_2$ values are of special interest during neurointensive care therapy because they have an impact on outcome.[7,19,21-24] $P_{br}O_2$ profiles after hypoxia ($Fio_2 < 5\%$) were significantly different between the 2 sensors (Figure 6). If one assumes that the hypoxic lower $P_{br}O_2$ cutoff is 8.5 mm Hg for both probes,[25-27] this cutoff would be indicated by the new probe by at least 1.5 minutes in advance. This might be interpreted as an advantage of the Neurovent-TO probe being able to detect critical $P_{br}O_2$ earlier than the Licox. Alternatively, differences of $P_{br}O_2$

responses during hypo-oxygenation may suggest that there is no ultimate hypoxic $P_{br}O_2$ value, but rather a probe/technology-specific cutoff. This cutoff for each technology needs to be established separately, eg, by surrogate parameters of cerebral blood flow, metabolism (cerebral microdialysis), or histological analysis.

A limitation of this experimental study is that we do not present monitoring data beyond 6 hours after insertion of the probes. Only long-term patient use will prove feasibility and usefulness in the clinical setting. Furthermore, we did not induce any distinct cerebral pathology and therefore cannot provide specific monitoring data, ie, for ischemic stroke, intracranial hemorrhage, or traumatic brain injury.

CONCLUSION

We provide data that the new $P_{br}O_2$ technology (Neurovent-TO) will measure $P_{br}O_2$ in vivo. However, there were significant differences between both probes in response to normobaric hyper-/hypo-oxygenation. Thus, Neurovent-TO–specific thresholds for critically low $PbrO_2$ values need to be established. Neither technical nor handling concerns exist for the routine clinical application of this new $P_{br}O_2$ tool.

Disclosure

This research project was sponsored by Raumedic AG, Helmbrechts, Germany. Raumedic was not involved in the experimental design, data collection/analysis, or the preparation of this manuscript. The authors have no personal or institutional financial interest in any of the drugs, materials, or devices described in this article.

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COMMENT

Orakcioglu et al provide experimental data on a new brain tissue Po_2 monitor, the Neurovent-PTO. This device measures the partial pressure of brain tissue oxygen using an optode that senses oxygen quenching rather than the Clark electrode technology used with the Licox. The authors compared the performance of the Neurovent-PTO

with that of the Licox in a porcine model under a variety of physiologic conditions as well as after the administration of tris-hydroxymethylaminomethane. The advantages of the new monitor are that it is factory precalibrated and does not need the calibration card that comes with the Licox. In this study at least, Neurovent-PTO appears to respond to Fio_2 changes faster than does the Licox. On the other hand, the Neurovent-PTO may overestimate the amount of available tissue oxygen. Future studies need to address the effect of brain temperature on the Neurovent-PTO, but it will be good for clinical neurophysiology to have an alternative to the Clark electrode for brain tissue oxygen monitoring.

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