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CONTINUOUS-WAVE NEAR-INFRARED SPECTROSCOPY IS NOT RELATED TO BRAIN TISSUE OXYGEN TENSION

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НЕПРЕРЫВНАЯ БЛИЖНЯЯ ИНФРАКРАСНАЯ СПЕКТРОСКОПИЯ НЕ СВЯЗАНА С НАПРЯЖЕНИЕМ КИСЛОРОДА В МОЗГОВОЙ ТКАНИ

Актуальность. Ближняя инфракрасная спектроскопия используется для церебрального мониторинга, особенно при кардиохирургических вмешательствах. Она получила признание в качестве церебрального мониторинга, хотя есть данные, показывающие ее неполную обоснованность.

Цель нашего исследования — определить корреляцию инвазивного определения кислорода в мозговой ткани ($PtiO_2$) с соответствующими значениями ближней инфракрасной спектроскопии (сатурация кислорода крови, rSO_2). Также исследовалась способность ближней инфракрасной спектроскопии определять ишемические процессы при $PtiO_2$<15 mmHg.

Материалы и методы. В исследовании приняли участие 11 пациентов с инвазивным мониторингом уровня кислорода в мозговой ткани, которым проводилась ближняя инфракрасная спектроскопия. Было определено отсутствие корреляции показателя инвазивного уровня кислорода в мозговой ткани с соответствующими значениями ближней инфракрасной спектроскопии. Измерение сатурации кислорода крови сопоставимо с «подбрасыванием монеты» в определении ишемии головного мозга, когда уже идентифицированы общепринятые признаки ишемии головного мозга: уровень кислорода в мозговой ткани, определенный инвазивным методом, был <15 mmHg.

Результаты. Ближняя инфракрасная спектроскопия является методом, непригодным для идентификации мозговой ишемии, определенной инвазивным измерением кислорода в мозговой ткани <15 mmHg. Исследование показало отсутствие корреляции между сатурацией кислорода крови и уровнем кислорода в мозговой ткани.

Выводы. Ближняя инфракрасная спектроскопия не может использоваться в качестве индикатора церебральной ишемии.

Ключевые слова: ближняя инфракрасная спектроскопия, уровень кислорода в мозговой ткани, церебральная травма, субарахноидальное кровоизлияние, смерть мозга.

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Actuality. Near-infrared spectroscopy (NIRS) has gained acceptance for cerebral monitoring, especially during cardiac surgery, though there are few data showing its validity.

Aim. We therefore aimed to correlate invasive brain tissue oxygenmeasurements ($PtiO_2$) with the corresponding NIRS-values (regional oxygen saturation, rSO_2). We also studied whether NIRS was able to detect ischemic events, defined as a $PtiO_2$-value of <15 mmHg.

Materials and methods. Eleven patients were studied with invasive brain tissue oxygen monitoring and continuous-wave NIRS. $PtiO_2$-correlation with corresponding NIRS-values was calculated. We found no correlation between $PtiO_2$ — and NIRS-readings. Measurement of rSO_2 was no better than flipping a coin in the detection of cerebral ischemia when a commonly agreed ischemic $PtiO_2$ cut-off value of <15 mmHg was chosen.

Results. Continuous-wave-NIRS (CW-NIRS) was unable to reliably detect ischemic cerebral episodes, defined as a $PtiO_2$ value <15 mmHg. Displayed NIRS-values did not correlate with invasively measured Pti_2-values.

Conclusion. CW-NIRS should not be used for the detection of cerebral ischemia.

Key words: near-infrared spectroscopy, brain oxygen tension, brain trauma, subarachnoid haemorrhage, brain death.

1. Purpose

Cerebral monitoring is commonly used in unconscious patients with brain pathology, to warn of otherwise undetectable adverse events. Even though intracranial pressure (ICP) monitoring in the patient with traumatic brain injury (TBI) is considered by many to be standard of care, the actual guidelines from the Brain Trauma Foundation only make a level 2 recommendation [1]. The same guidelines rate brain tissue oxygen monitoring ($PtiO_2$) as a level 3 recommendation. While there are no randomized studies on the effect of $PtiO_2$-targeted therapy in patients with TBI or subarachnoid haemorrhage (SAH), a recent Phase 2 study [2] and several retrospective studies have demonstrated that $PtiO_2$-monitoring can reduce mortality and improve 6-months outcome after TBI [3]. It would be ideal to be able to monitor brain oxygenation noninvasively, and some have recommended near-infrared spectroscopy (NIRS, or rSO_2, the regional oxygen saturation) for this purpose. There is considerable debate about the reliability of this technique, however, as some researchers have reported a positive correlation between the two methods [4; 5] whereas others have found NIRS useless in the detection of vasospasm [6] or generally uninterpretable because of significant extracerebral influences on the cerebral signal [7]. To complicate things further, different types of NIRS systems exist on the market and their data cannot be used interchangeably [8].

We therefore aimed to correlate invasive brain tissue oxygen measurements, which can be considered reasonably reliable, with the corresponding rSO_2-values, in a series of critically ill neurointensive care patients, to determine the clinical usefulness of the NIRS

technique in these patients. More specifically, we studied whether NIRS was able to reliably detect ischemic events, defined as a $PtiO_2$-value of <15 mmHg [1].

2. Methods

The primary endpoint of this prospective, unblinded study was the correlation of $PtiO_2$-values with rSO_2-readings. We studied 11 adult patients, aged (54.4±14.9) years (range 29–79), admitted to our neurosurgical intensive care unit between January 2010 to December 2012. There were 7 females and 4 male patients, of whom one patient suffered from TBI and 10 patients from subarachnoid haemorrhage (SAH). Further patient characteristics are presented in Table 1.

Patients were included if they were intubated and ventilated after a neurological injury, and invasive neuromonitoring had been inserted according to the clinical judgement of the neurointensivist. All patients had $PtiO_2$ measured by Licox probes through an Integra™Licox double lumen bolt (Integra LifeSciences, Ratingen, Germany) with simultaneous intracranial pressure (ICP) measurements by a Neurovent-P probe (Raumedic, Muenchberg, Germany). The catheter was connected to an electronic patient data management system (PDMS) using a Licox® PMO Box [9]. All probes were inserted frontally on either the right or left side (see Table 1). In patients with SAH, probes were inserted into the side mostly affected by vasospasm as seen in CT-angiography or in digital subtraction angiography. In the patient with TBI and brain swelling, the right side was chosen. In order to achieve reliable readings, a stability period of 2 h was allowed before $PtiO_2$-readings were recorded. Data were stored in the PDMS and later downloaded into an Excel data sheet for analysis.

rSO_2-values were recorded using a two-channel NONIN Equanox™ Model 7600 oximeter [10] and later downloaded into an Excel sheet through eVISION Data Management Software (NONIN Medical Inc). One EQUANOX™ Classic Plus Sensor was ap-

Table 1

Patient characteristics

CaseNo.	Age (years), sex	Intracranial pathology	$PtiO_2$ monitor side	Operative intervention	DIND	Brain death
1	55, F	SAH	Right	EVD,coiling	No	No
2	40, M	TBI	Right	None	—	Yes
3	50, F	SAH	Right	EVD, coiling	No	No
4	79, F	SAH	Right	EVD, clipping	Yes	No
5	43, F	SAH	Left	EVD, clipping	Yes	No
6	73, F	SAH	Right	EVD, clipping	Yes	No
7	67, M	SAH	Right	EVD, coiling	Yes	No
8	29, F	SAH	Right	EVD, clipping	Yes	No
9	55, M	SAH	Left	Coiling+clipping	Yes	No
10	53, M	SAH	Left	EVD, clipping	Yes	Yes
11	51, F	SAH	Right	EVD, coiling	Yes	Yes

Note. DIND delayed ischemic neurological deficit (as defined by [1]).

plied to each side of the forehead and data stored as rSO_2left or rSO_2right according to the side. The internal clocks of the PDMS and the oximeter were synchronized in order to allow analysis at identical time points. Correct time synchronization was checked every 24 h throughout the study period. rSO_2- and $PtiO_2$-values were recorded every minute.

2.1 Statistics

Normality of all data was evaluated using a Kolmogorov-Smirnov test with Lilliefors *p* values.

Cohen's kappa coefficient (κ) was calculated for $PtiO_2$ and rSO_2. Spearman's rank correlation coefficient (r) was calculated for every individual patient. Receiver-operator-curves (ROC) were calculated for all $PtiO_2$–rSO_2-data with a $PtiO_2$-cut-off of <15 mmHg. All calculations were performed using SPSS 22 (IBM Corp., Ehningen, Germany).

3 Results

While there were no technical problems with $PtiO_2$ readings, only 73.7% of all rSO_2right readings were considered to be valid (any numerical value >0), and only 83.6% of all rSO_2left (Fig. 1).

Overall, there were 14,906 time points in the 10 patients where both $PtiO_2$ and either rSO_2right or rSO_2left were recorded. In patient No. 10, no paired data for $PtiO_2$ and rSO_2 were available. Correlation coefficients for $PtiO_2$ and rSO_2 are displayed in Table 2 where all $PtiO_2$ values are referred to ipsilateral rSO_2 values.

Correlations calculated for ipsilateral sides except in pat. 6 (calculated for contralateral side due to insufficient number of ipsilateral data)

In patient No. 6 the contralateral side only was analyzed, as there were insufficient data for the ipsilateral side. In patient No. 2 (who progressed to brain death) only $PtiO_2$

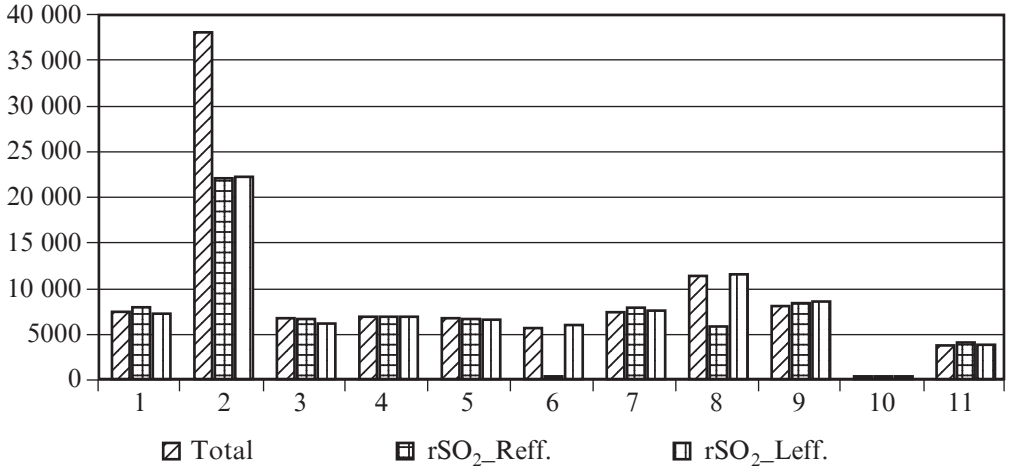


Fig. 1. Total rSO_2 time points and effective readings in 11 patients: Total — Total number of time points that were stored in the Oximetermemory; rSO_2_R eff./rSO_2_L eff. — rSO_2-readings with any numerical value >0. Pat. No. 6 did not show right frontal readings. Pat. No. 10 had no paired $PtiO_2$–rSO_2 readings and is not displayed

Table 2

Correlation coefficients of $PtiO_2$ and rSO_2

Pat	No. of measure-ments	Spear-man's r (*p* value)	Cohen's kappa (*p* value)
1	166	0.07 (.08)	0(.0)
2	85	0.60 (.06)	0 (.0)
3	5	0.95 (.04)	-0.9 (.08)
4	125	-0.26 (.07)	0 (.0)
5	120	0.86 (.02)	0 (.0)
6	87	-0.12 (.13)	0 (.0)
7	7275	0.22 (.01)	0 (.0)
8	5546	0.44 (.01)	0 (.0)
9	189	0.05 (.08)	0 (.0)
11	1131	0.33 (.03)	0 (.0)

Note. Correlations calculated for ipsilateral sides except in pat. 6 (calculated for contralateral side due to insufficient number of ipsilateral data).

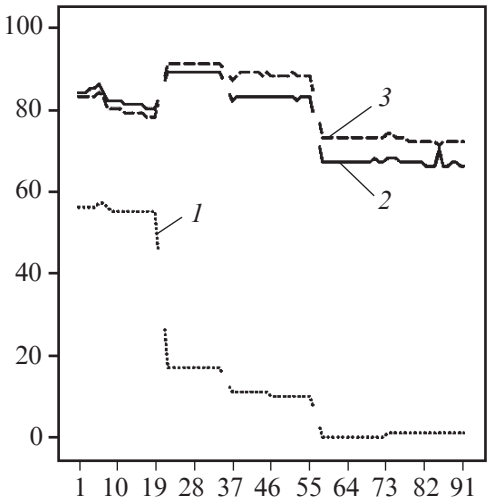


Fig. 2. $PtiO_2$, rSO_2_R and rSO_2_L in patient No. 2, evolving to braindeath. 85 common time points are displayed on the *X-axis*. *Y-axis*represents mmHg ($PtiO_2$) or percent of saturation (rSO_2right andrSO_2left). *Line interruptions* due to missing common time points.Overall time represented 59 h. Intracerebral circulatory arrest confirmed with CT-angiography (Fig. 3)

displayed values indicative of brain tissue ischemia (Fig. 2).

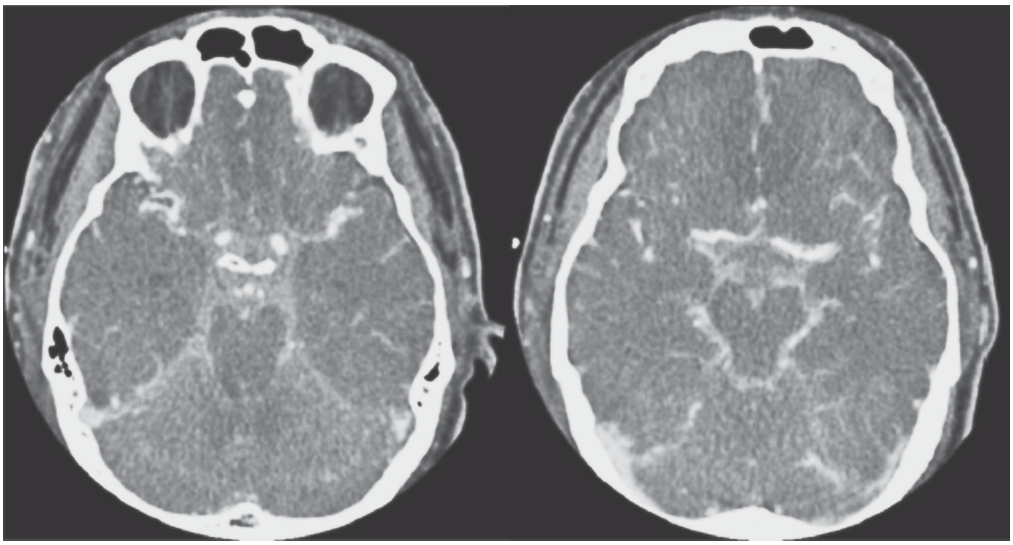
The absence of intracranial blood flow was con-firmed by CT-angiography in this patient (Fig. 3).

Patient No. 10 also progressed to brain death, but there were no paired time points for $PtiO_2$ and rSO_2. Patient No. 11 became brain dead only 5 days after removal of the $PtiO_2$ probe, so only the data obtained before this time point were analyzed. Figures 4 and 5 show $PtiO_2$–rSO_2 scatter plots for all data with $PtiO_2$ <21 mmHg versus rSO_2right or rSO_2-left, illustrating graphically the lack of correlation between ischemic values of $PtiO_2$ (<15 mmHg) and rSO_2-readings. Figure 6 shows the receiver-operating curves for rSO_2 detecting ischemia (a $PtiO_2$ <15 mmHg).

4. Discussion

$PtiO_2$ monitoring has been adopted widely, but has only recently been studied in a Phase 2-trial [11]. A treatment protocol guided by both ICP and $PtiO_2$ reduced the duration of brain tissue hypoxia, but there were no statistically significant differences in mortality or clinical outcomes. A phase 3 study has been planned by the same researchers [2]. Some clinicians consider $PtiO_2$ measurements to represent the product of CBF and the cerebral arteriovenous oxygen content difference, thereby being more indicative of brain tissue oxygen diffusion than of oxygen delivery [12].

Several studies have suggested that cerebral oxygenation could also be monitored with bifrontal NIRS which would avoid the need for an intracranial probe. NIRS measures the proportion of light that is returned over a wide range of optical wavelengths. The return signal is then plotted as a graph of absorbance at different wave-lengths called a spectrum. Manufacturers of NIRS machines claim cerebral tissue accuracy of 45–95% [13] without defining against what standard this accuracy has been tested.



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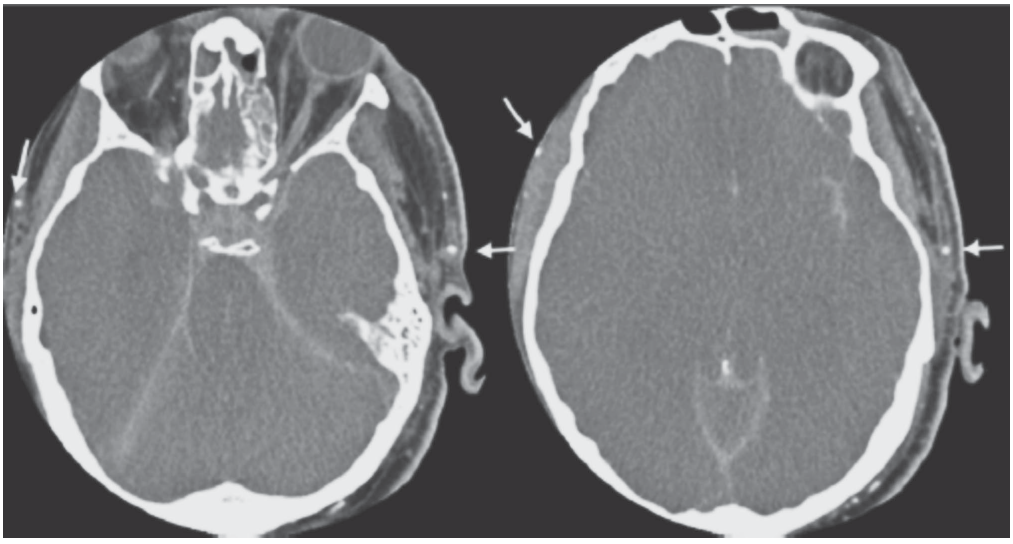

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Fig. 3. CT-Angiography in patient No. 2. CT-angiography a taken 20 h before start of time period as shown in Fig. 2, showing preserved cerebral circulation and b 40 min after last time point in Fig. 2, displaying intracerebral circulatory arrest. Arrows mark contrast media signal in the superficial temporal arteries, proofing correct injection of contrast media

NIRS is supposed to monitor hemoglobin oxygen saturation within the microvasculature [14].

In clinical practice, both modalities are used for monitoring of cerebral oxygenation. Although the vast majority of NIRS studies claim to measure cerebral oxygenation, a Pubmed database search including the keywords ‘‘near infrared spectroscopy’’, ‘‘brain

tissue oxygenation" and "adult" yielded 184 references with only 4 reporting of simultaneous measurements of $PtiO_2$ and NIRS values. One study concluded that there was no correlation between the parameters [15] while a second study found only a weak correlation and did not account for patients in the hypoxic-ischemic range [16]. Brawansky et al. [4] described a significant correlation between both $PtiO_2$ and NIRS, but patients in the hypoxic range of $PtiO_2$ were also excluded in their study. Leal-Noval et al. [5] found that rSO_2 could detect moderate intracerebral hypoxia ($PtiO_2$ <16 mmHg) with only low accuracy and severe hypoxemia ($PtiO_2$ <12 mmHg) with moderate accuracy, with a positive likelihood ratio of 5.3 and an area under curve of 0.82. There was a high rate of false-negative NIRS readings for severe hypoxemia (27%), and they concluded that NIRS should not be considered an acceptable substitute for $PtiO_2$ as it did not reflect invasive cerebral oxygenation.

All other 229 studies fail to report direct measurements of cerebral oxygenation and did not appear to account for possible extracranial influences. In a number of studies a surrogate endpoint was chosen (such as cardiovascular interventions), and better outcome in the group with NIRS-guided management was attributed to better cerebral oxygenation. Other studies compare indices of global oxygenation against rSO2-data [17–19]. Better outcomes could be related to better systemic oxygenation, however, and not to changes in cerebral oxygen supply.

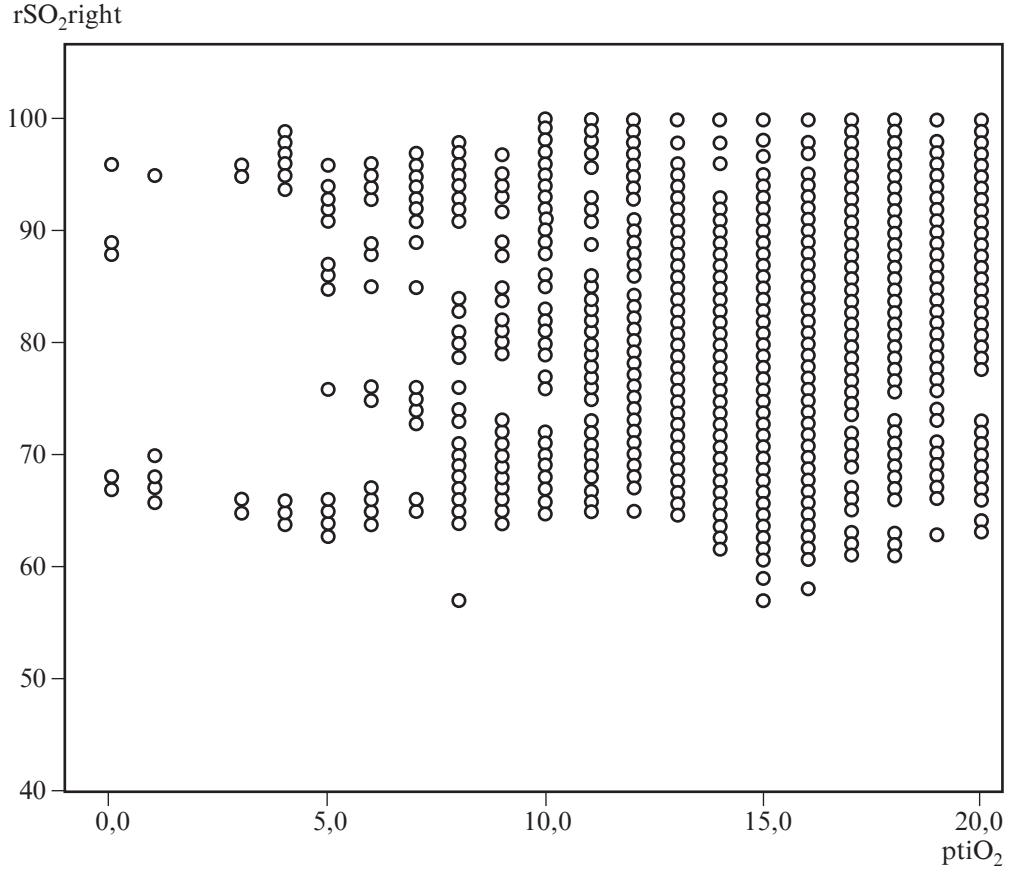

Fig. 4. Scatterplot for all data $PtiO_2$<21 mmHg–rSO_2 right

Our study was performed to clarify these issues. Our data demonstrate that there is no correlation between intracerebral oxygen tension measured invasively and a NIRS-derived assessment of oxygenation. Although we found acceptable values for Spearman's correlation in patients 2, 3, and 5, this was only significant in patient 3 where only 5 shared time points could be analyzed. Cohen's kappa coefficient, which is a more conservative measure of inter-rater variability, was zero or even negative in our patients, demonstrating no agreement between the two measurement modalities. Our data also demonstrate that rSO_2 was no better than flipping a coin for the detection of cerebral ischemia when a commonly agreed ischemic $PtiO_2$-cut-off value of <15 mmHg was applied, as the ROC area under the curve was 0.539 for rSO_2right and 0.584 for rSO_2left (Fig. 5).

There are few other studies describing correlations between cerebral oxygenation measured by NIRS and other methods, and these do not provide evidence that NIRS reflects intracerebral oxygenation. Rosenthal et al. [20] used ultrasound-tagged NIRS and found a correlation between NIRS-measurements and jugular bulb venous oxygen saturation, but not between $PtiO_2$ and NIRS. As it is known that extracranial contamination accounts for up to 6.6% of blood in jugular bulb measurements [21], we would argue that there was significant extracranial contamination in their study, all the more so as con-

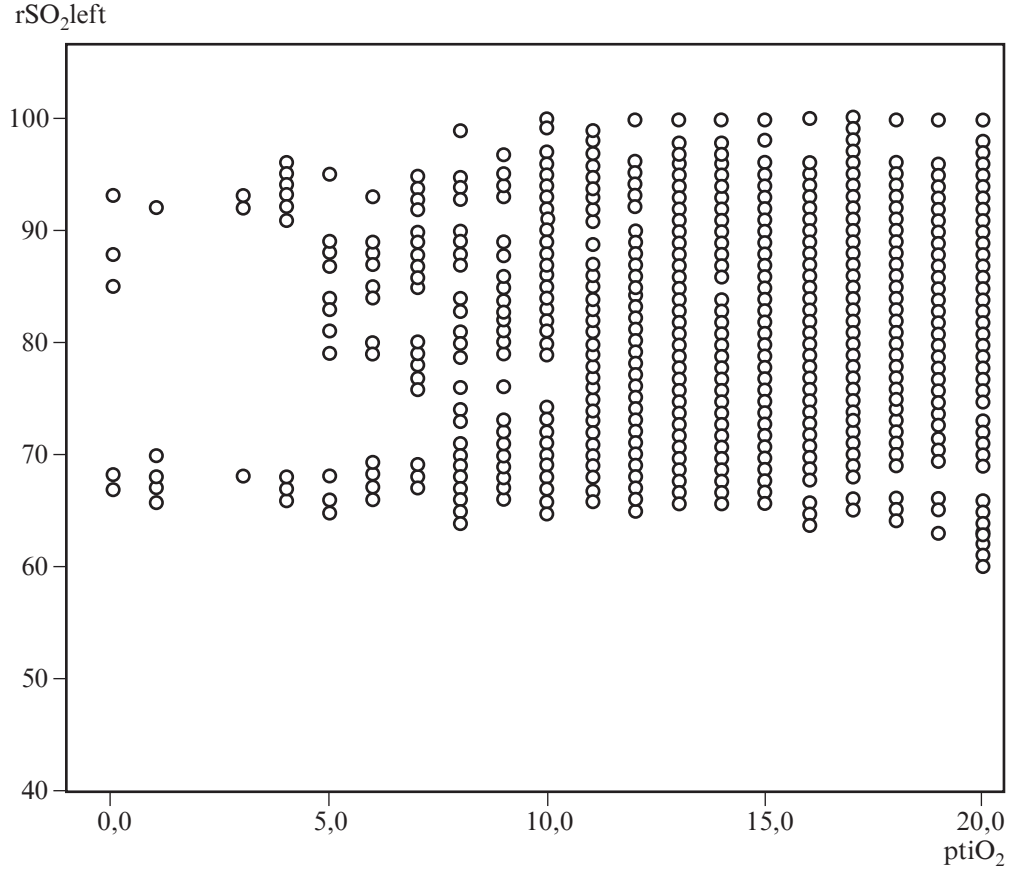

Fig. 5. Scatterplot for all data $PtiO_2$<21 mmHg–rSO_2left

tamination can only be avoided by catheter placement less than 2 cm out of the jugular bulb as well as by withdrawal rates of less than 2 ml/min [22]. Both of these factors were not reported in their paper but could contribute to invalid measurements. Furthermore, a prior study has shown that jugular bulb saturations ($SvjO_2$) do not correlate with $PtiO_2$ readings and are therefore not adequate for cerebral monitoring [23]. Other researchers have also reported NIRS and $SvjO_2$ to be only weakly correlated [24]. The study by Taussky et al. [25] reported a significant correlation between NIRS readings and CT-perfusion based cerebral blood flow (CBF), but does not provide a correlation coefficient and included only single-time measurements in a small number of patients with normal CBF. No further conclusions can therefore be drawn regarding the value of NIRS monitoring in critically ill patients.

Several studies have however already shown that NIRS readings do not reflect intracerebral oxygen status. Ogoh et al. [26] found that a decrease in rSO_2 after phenylephrine infusion was due to vasoconstriction in the extracranial vasculature rather than a decrease in cerebral oxygenation. Davie et al. [27] found that induction of extracranial hypoxia-ischemia by inflating a circumferential pneumatic head cuff resulted in a significant reduction in regional cerebral oxygen saturation measurements in all three NIRS devices studied.

The oxygen dissociation curve relates hemoglobin percentage saturation to the partial pressure of oxygen. The partial pressure of oxygen at which hemoglobin is 50% saturated, the p50, is 26.6 mmHg, and the cerebral ischemic oxygen partial pressure threshold is commonly agreed to be <15 mmHg [1]. The absolute value of $PtiO_2$ is lower than local venous oxygen tension, reflecting oxygen consumption by the tissues as oxygen diffuses. NIRS devices do not generate absolute oxygenation values, but reductions of more than 20 % from baseline have been hypothesized to represent ischemia. A correlation between both monitoring modalities can not be found, however.

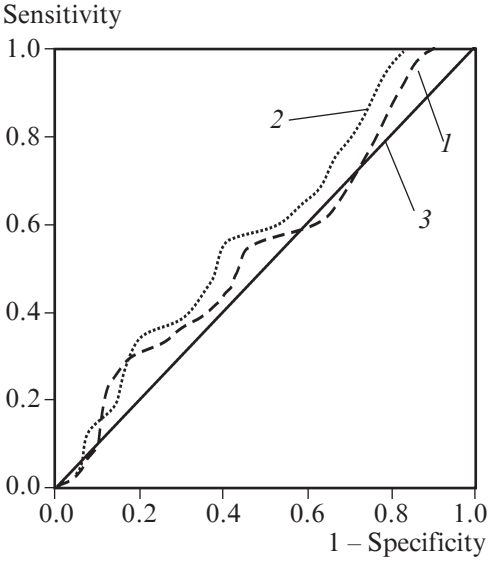

Fig. 6. Receiver-operating curve for $PtiO_2$ cut-off<15 mmHg. Area under the curve 0.539 (rSO_2right) and 0.584 (rSO_2left). p<0.000: *1* — rSO_2right; *2* — rSO_2left; *3* — reference line

Furthermore, in our study NIRS failed to identify an absence of intracranial blood flow in a brain-dead patient, which is extremely concerning given the marketing of these devices and the therapeutic decisions clinicians might infer from NIRS readings. In our patient, $PtiO_2$ oscillated between 0 and 1 mmHg, indicating an absence of perfusion which was confirmed by absent perfusion in the CT-angiography study. Other studies have also found $PtiO_2$ to indicate brain death reliably with a reading of 0 mmHg [28] while NIRS could not detect absent cerebral perfusion [29].

In our study, we deliberately did not use a standardized challenge (such as hyperventilation, hyperoxia, or modifying cerebral blood pressure) to test for a potential agreement between $PtiO_2$ and NIRS. Our hypothesis was that, if there was a true correlation between the 2 modalities, it should

be apparent in the clinical data without any provocation test, and especially so when the ischemic threshold has been passed. Physiological conditions were similar as both modalities were applied simultaneously, so we did not report on these data. The NIRS method used in our study was based on a continuous-wave NIRS-method (CW-NIRS) which is the simplest method of NIRS, based only on intensity alterations of the emitted light. How other, more sophisticated methods of NIRS such as frequency — (FD) or time-domain based measurements would perform, is open to speculation. A study comparing FD-NIRS in healthy volunteers and cadavers found a significant decrease of oxyhemoglobin in the cadaver group [30]. No data on the use of FD-NIRS have been reported in adult critical care, whereas the FD-NIRS technique may hold promise in the pediatric population [31]. NIRS may also be more reliable in the pediatric population for anatomical reasons, and circulatory arrest can be detected with a high sensitivity albeit low specificity in this age group [32]. Recent developments, such as diffuse correlation spectroscopy have been shown to be related to cerebral blood flow and may hold future promise [33]. Our study was conducted using the Equanox™ Model 7600 oximeter and it is possible that our results would have been different using another manufacturer's device, but since the underlying principles behind all CW-NIRS devices are the same, we consider this to be unlikely.

5. Conclusion

There was no correlation between rSO_2 measured by CW-NIRS, and invasively measured $PtiO_2$ values, in our cohort of 11 critically ill neurological patients. CW-NIRS was unable to detect ischemic cerebral episodes, defined as a $PtiO_2$ value <15 mmHg. CW-NIRS should not be used for the detection of cerebral ischemia.

Compliance with ethical standards

Ethical standard. The protocol for this study has been approved by the local ethics committee (Ethikkommission der LandesaerztekammerRheinland-Pfalz). Upon hospitalization, all patients or their proxies agree to the use of their anonymized data for scientific purposes by signing the admission contract. Individual patient consent was not required for this study. The study was performed in compliance with the Helsinki Declaration.

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