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Noninvasive measurement of cerebral hemoglobin oxygen saturation using two near infrared spectroscopy approaches

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Abstract. Spatially resolved spectroscopy (SRS) is a new near infrared spectroscopy (NIRS) method that, using the multi-distance approach, measures local cerebral cortex hemoglobin oxygen saturation [J. Matcher, P. Kirkpatrick, K. Nahid, M. Cope, and D. T. Delpy, *Proc. SPIE* **2389**, 486–495 (1995)]. Using a conventional continuous wave NIRS photometer, cerebral venous oxygen saturation (SvO_2) can be calculated from oxyhemoglobin and total hemoglobin rise induced by partial occlusion of jugular vein [C. E. Elwell, S. J. Matcher, L. Tyszczuk, J. H. Meek, and D. T. Delpy, *Adv. Exp. Med. Biol.* **411**, 453–460 (1997)]. The aim of this study was to compare direct measurements of forehead tissue oxygenation index (TOI) with the calculated SvO_2 during venous occlusion in 16 adult volunteers using a clinical two-channel SRS oximeter (NIRO-300). Measured TOI and calculated SvO_2 values of either right or left forehead did not significantly differ. A good agreement between the two NIRS methods was also demonstrated. On 16 other subjects, no significant differences were found between the right and left forehead TOI values measured simultaneously, and between the TOI values measured by channel 1 or 2 on the same side. The results confirm that cerebral cortex hemoglobin oxygen saturation, measured directly by the SRS method, reflects predominantly the saturation of the intracranial venous compartment of circulation.
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1 Introduction

A cerebral oximeter measures regional hemoglobin oxygen saturation by near infrared spectroscopy (NIRS).[1] This technique uses the light in the range 700–1100 nm for noninvasively monitoring brain and muscle oxygenation.[2] A number of clinical tissue oxygenation monitors are currently available worldwide. These instruments also provide either relative concentration changes in oxyhemoglobin $[O_2Hb]$, deoxyhemoglobin [HHb], the derived total hemoglobin volume $[tHb]([O_2Hb]+[HHb])$, or their absolute values. The latter parameter is strictly related to cerebral blood volume. Some instruments also claim to measure the intracellular oxygenation by the changes in the redox state of the copper band of cytochrome oxidase. Very recently, arterial cerebral oxygen saturation was derived from the NIRS signal measured by using fast sampling oximeters based either on continuous wave or frequency domain methods.

In 1988 Chance raised the need for testing cerebral oximeters *in vitro* on phantoms and *in vivo* correlating oxygen saturation values by NIRS with those ones obtained with other independent methods like pulse oximetry.[3] Since that year many investigators developed liquid and solid static/dynamic phantom brain models to be used for testing the NIRS instrumentation.[4–6] The most sophisticated one is represented by a solid plastic structure containing a vascular network perfused with blood and plastic shells of varying thickness, with a vascular network of their own.[6] For *in vivo* testing the best gold standard is represented by the oxygen saturation measured in the blood sampled from the superior sagittal sinus. This method can be applied only on laboratory animals.[7–9] Since the results obtained in animal models are not always transferable to humans, due to consistent anatomical differences, it is necessary to validate the NIRS devices directly in humans. In healthy volunteers and patients, NIRS regional oxygen saturation has been compared with global oxygen saturation measured by jugular bulb oximetry. However, in most of the studies the correlation was poor.[10–14] This can be attributable to dissimilar tissue sampling. Jugular bulb drains venous blood from intracranial and extracranial compartments of the homolateral hemisphere while NIRS oxygen saturation represents a regional mixed saturation of the venous (75%) and arterial/capillary (25%) compartments[1] mainly of the in-

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tracranial tissue, when an appropriate interoptode distance is used.

Spatially resolved spectroscopy (SRS) is a new NIRS method that, using the multi-distance approach, measures local cerebral cortex hemoglobin oxygen saturation. The theory behind this approach has been previously reported.[15] The reliability of the SRS to measure oxygen saturation has been recently evaluated. In particular, the NIRO-300 oximeter (Hamamatsu Photonics, Japan), that provides tissue oxygenation index (TOI), has been tested either *in vitro* on tissue-like phantoms, or *in vivo* during forearm ischemia.[16] TOI data showed an excellent correlation with the data from cooximetry *in vitro*, and with the data from time resolved spectroscopy measured in muscle forearm. A previous study, carried out using the prototype of the NIRO-300, demonstrated a good correlation between cerebral TOI and the oxygen saturation measured in the jugular bulb only in 12 out of the 24 patients undergoing routine cardiopulmonary bypass.[17]

An indirect NIRS method to measure neonatal cerebral venous oxygen saturation (SvO_2) using single distance continuous wave NIRS was described by Yoxall.[18] SvO_2 was calculated from O_2Hb and HHb rise induced by the partial occlusion of the jugular vein. The same method has been improved and also applied to measure SvO_2 on adults.[19]

The aim of this study was to compare direct measurements of forehead TOI with the calculated SvO_2 during venous occlusion in adult volunteers using a clinical SRS oximeter.

2 Methods

After local research ethics committee approval and informed consent, 33 healthy volunteers (30 ± 9 y.o.; range: 22–58 yrs) were studied. In this study the four-wavelength NIRO-300 oximeter equipped with two channels was utilized. The design and the features of this device have been previously described.[16] A center-to-center 4 or 5 cm distance between the optodes of the emission and the detection (consisting of three separate sensors) probes was used. This instrument provides both TOI values and changes in $[O_2Hb]$, and [HHb]. These changes are calculated, independently from TOI, using the central sensor only as detector. The NIRO-300 optodes were positioned high in the forehead and sufficiently lateral from the midline to avoid the prominent temporalis muscle and the superior sagittal sinus, respectively. The optodes were kept at a constant distance and geometry by a rubber shell that in turn was firmly attached by a double sided adhesive sheet. All measurements were performed on subjects in a supine position. Sampling time was 0.5 s.

The reliability in the interchange of the two channels was tested on the adult forehead of 16 subjects. Probes of channel 1 and 2 were placed on the right and left forehead, respectively. After a 3 min recording, channel 1 and 2 were repositioned on the left and right forehead, respectively; then a 3 min recording was performed. The reported values of TOI are the average over 3 min.

The effect of the distance between emission and detection probes on TOI was studied on 13 subjects (12 subjects belonging to the first group). TOI values were recorded on both foreheads simultaneously using first a 4 cm distance, then 5 cm. The reported values of TOI are the average over a 3 min recording.

SvO_2 measurements were performed on another group of subjects ($n=16$). Between six and eight bilateral venous jugular occlusions, each of 10 s duration, were performed to calculate SvO_2 according to the method previously described.[19] Assuming that the increase in tHb is only venous blood and cerebral blood flow and oxygen consumption are unchanged, SvO_2 can be estimated from

$$SvO_2(\%) = (\Delta[O_2Hb] / \Delta[tHb]) * 100.$$

The data are presented as mean $\pm$ SD. Data were analyzed by a paired student's *t* test with the appropriate Bonferroni correction. Statistical significance was accepted at $P<0.05$. The Bland and Altman method was used to determine the agreement between the two NIRS methods.[20] The relationship between the variables was studied using a multiple linear regression analysis. The square of the regression coefficient (r^2) was determined. Occlusions producing r^2 less than 0.85 were excluded. The reported SvO_2 for each subject was the average of all the considered occlusions (6 ± 1).

3 Results

TOI values of right and left forehead, measured separately by channel 1 and 2, and using a 4 cm distance between the optodes are reported in Table 1 ($n=16$). No significant differences were found between the right and left forehead TOI values measured simultaneously using both channels ($P=0.16$ and 0.62). Also, no significant differences were found between right and left forehead TOI values using channel 1 or 2 ($P=0.12$ and 0.47).

TOI values of right and left forehead measured by the same channel, and using either a 4 or 5 cm distance between the optodes, are reported in Table 2 ($n=9$). At 5 cm, TOI was unreadable in four out of the 13 subjects because the linearity of the measured optical density at the three sensors was poor. No significant differences were found between the two distances in the right and left forehead ($P=0.40$ and 0.13).

The measured $[O_2Hb]$ and [tHb] changes, induced by partial venous occlusions, behaved similarly in all subjects. An example is given in Figure 1. O_2Hb and tHb promptly increased in response to the venous occlusion maneuver and returned to their corresponding base line values immediately after the pressure release. TOI did not change consistently during the short venous occlusion. Measured TOI (a 3 min average before venous occlusion maneuver) and calculated SvO_2 values of right and left forehead are reported in Table 3 ($n=16$). TOI and SvO_2 either of the right or the left forehead did not significantly differ ($P=0.03$ and 0.30). Also in this group TOI values of the right and the left forehead were not significantly different ($P=0.38$). The 32 TOI values of the 16 subjects were regressed against the calculated SvO_2 values. The linear regression, the intercept, the standard error of estimate (SEE), and 95% confidence intervals are shown in Figure 2. The r^2 value was 0.56 with $P<0.0001$. For the agreement test, the average of the oxygen saturation values obtained by the two methods was plotted against the difference between the two values (Figure 3). All data points, except two, lie well within the 95% confidence interval which represents the double standard deviation. The bias was 1.6%.

Table 1 TOI values (%) of right and left forehead measured separately by channel 1 and 2 (CH1, CH2) using a 4 cm distance between the two optodes (emitter/detector). TOI value is a 3 min recording average; the value in parentheses represents its SD.

	Right		Left	
No.	**CH1**	**CH2**	**CH1**	**CH2**
1	80.0(0.7)	66.0(1.5)	85.6(0.9)	86.9(1.0)
2	79.2(1.0)	70.0(1.2)	72.5(0.8)	70.0(1.1)
3	81.4(1.1)	80.5(0.9)	72.1(0.8)	75.6(1.3)
4	74.4(0.6)	73.7(1.1)	74.0(0.8)	70.7(1.1)
5	77.3(0.7)	79.3(2.3)	77.4(0.9)	74.4(1.1)
6	73.9(0.8)	75.9(1.3)	70.7(1.0)	76.9(1.3)
7	74.6(0.8)	74.4(0.7)	74.0(0.7)	74.0(0.8)
8	78.2(0.7)	75.9(0.7)	75.2(0.8)	75.7(0.8)
9	75.9(1.0)	73.0(1.2)	73.4(0.8)	70.4(0.9)
10	76.5(1.0)	75.9(1.4)	77.1(1.4)	73.0(1.0)
11	82.3(0.9)	84.5(0.8)	85.0(0.7)	79.9(0.9)
12	74.7(0.8)	72.1(1.6)	75.2(1.2)	77.7(1.1)
13	72.5(1.1)	70.7(1.1)	75.9(1.0)	72.4(0.8)
14	81.2(0.8)	79.4(0.9)	82.2(0.9)	83.0(0.6)
15	71.4(0.9)	73.8(1.0)	72.4(1.1)	71.4(0.7)
16	70.9(0.9)	71.1(0.8)	67.6(0.9)	68.9(0.9)
Mean	**76.5**	**74.8**	**75.6**	**75.1**
SD	**3.6**	**4.6**	**5.0**	**5.0**

Table 2 TOI values (%) of right and left forehead ($n=9$) measured with the same channel and using a 4 or 5 cm distance between the two optodes (emitter/detector). TOI value is a 3 min recording average; the value in parentheses represents its SD.

	Right CH2		Left CH1	
Subject	**4 cm**	**5 cm**	**4 cm**	**5 cm**
1	66.0(1.5)	78.5(3.4)	85.6(0.9)	88.5(1.5)
2	70.0(1.2)	69.3(3.0)	72.5(0.8)	75.6(0.9)
3	80.5(0.9)	68.6(2.4)	72.1(0.8)	71.3(1.1)
4	73.7(1.1)	69.7(1.2)	74.0(0.8)	70.1(0.9)
5	79.3(2.3)	77.9(3.0)	77.4(0.9)	77.8(0.9)
7	74.4(0.7)	71.0(0.9)	74.0(0.7)	71.4(2.0)
10	75.9(1.4)	73.4(0.5)	77.1(1.4)	70.4(1.1)
11	84.5(0.8)	79.6(0.8)	85.0(0.7)	72.2(0.9)
17	74.0(0.8)	73.0(0.7)	78.1(0.9)	73.0(0.9)
Mean	**75.4**	**73.5**	**77.3**	**74.5**
SD	**5.6**	**4.2**	**5.0**	**5.8**

4 Discussion

The recent introduction of frequency domain and SRS multichannel oximeters has filled the lack to measure directly tissue hemoglobin oxygen saturation that is an important parameter to be monitored in different clinical fields. Until now no data were available on the reliability of the simultaneous use of channels in two head regions. We found that, the distance between the optodes being equal, the two NIRO-300 channels provide no significantly different TOI values measured on the same forehead side. This result is extremely important in clinics because it makes it possible to use SRS instruments for cerebral mapping (i.e., to evaluate the cerebrovascular reactivity and to follow the recovery after stroke). The dynamic of TOI during carotid compressions has recently been evaluated in cerebrovascular patients.[21] In addition we found no significant differences between right and left forehead TOI values in healthy subjects (Table 1). These results agree with those obtained by using other NIRS instruments.[22–25] The contamination of the extracranial compartment on the measurements of the NIRS parameters has been previously discussed.[26] For an interoptode distance greater than 4.5 cm the extracranial contribution is negligible. Since any significant difference between TOI values measured at 4 and 5 cm was found (Table 2), the extracranial contribution can be considered negligible also using an interoptode distance of 4 cm.

Due to the lack of gold standards for tissue saturation measured by NIRS, it is still not clear if the provided values from each instrument are really representative, therefore if they might be considered clinically relevant for medical decision. In the last five years several NIRS instruments had become commercially available, and several articles reported the com-

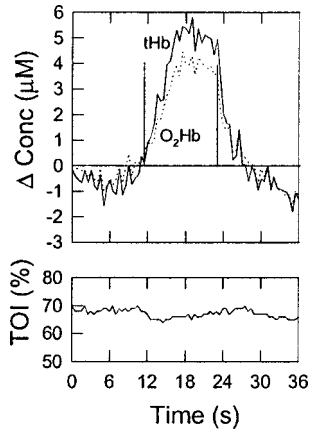

Fig. 1 Time course of [O_2Hb] and [tHb] changes (upper panel), and TOI in the right forehead during a 10 s jugular occlusion. Concentration changes are expressed in μM using the age-dependent differential pathlength factor (see Ref. 33). The vertical bars indicate the duration of the venous occlusion maneuver.

Table 3 Forehead hemoglobin oxygen saturation expressed as TOI and SvO_2. TOI value is a 3 min recording average. SvO_2 is the mean value calculated from 6 ± 1 venous occlusions (range: 3–8).

	Right		Left	
No.	TOI (%)	SvO_2 (%)	TOI (%)	SvO_2 (%)
1	74	67	75	72
2	79	76	76	71
3	79	79	72	75
4	75	74	69	71
5	77	65	73	69
6	83	81	80	80
7	80	78	83	79
8	72	77	72	74
9	80	78	83	82
10	72	72	72	75
11	67	66	66	65
12	74	73	72	73
13	74	73	77	78
14	72	68	66	61
15	78	75	85	76
16	71	71	72	75
Mean	**75**	**73**	**75**	**74**
SD	**4**	**5**	**6**	**5**

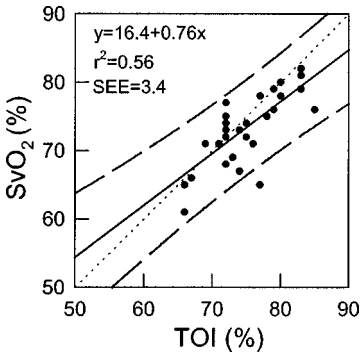

Fig. 2 Comparison between the cerebral oxygen saturation data (TOI and SvO_2) obtained using two NIRS methods. Solid line, first order regression that fits all data points ($n=32$); dashed line, 95% confidence intervals; dotted line: identity line. SEE: standard error of estimate.

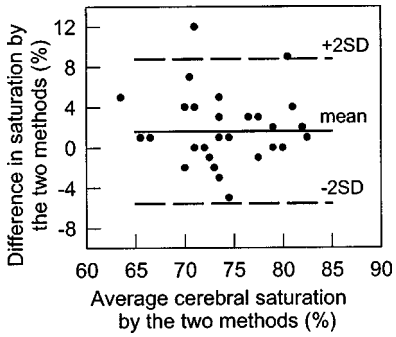

Fig. 3 Bland and Altman test (see Ref. 20) for cerebral oxygen saturation data (TOI and SvO_2) obtained using two NIRS methods. Middle line represents the bias.

parison of their performances in detecting changes in cerebral oxygen saturation in adult volunteers and patients.[27–31] Some limitations of these devices in clinical use were also identified.

A first attempt to compare TOI values with SvO_2 was made in one subject in normoxia and hypoxia by Elwell et al.[19] In our study, performed on 16 subjects breathing room air, we found that TOI values do not differ significantly from the calculated SvO_2 values (Table 3 and Figure 3). A good agreement was also found between the two NIRS methods and the bias (1.6%) reflects the tendency of mixed tissue saturation (TOI) to be higher than SvO_2. The same agreement should also be investigated during conditions that alter the arteriovenous partition of cerebral blood such as hypo- and hypercapnia and hypo- and hypertension.[14]

Concerning the SvO_2 method, the series of occlusions did not provoke any discomfort to the subjects, but some subjects (about 10%) could not be included in the study because it was difficult to localize the jugular veins. Pathlength could change up to 10% during venous occlusion,[32] however, since SvO_2 is calculated from a ratio of O_2Hb and tHb changes optical pathlength does not affect this calculation. It is possible to perform a series of compressions in most clinical conditions because the estimation of SvO_2 only requires a partial occlusion.

In conclusion, these results confirm that cerebral cortex hemoglobin oxygen saturation, measured directly by the SRS method, predominantly reflects the saturation of the intracranial venous compartment of circulation. In addition, the reliability of using both channels to monitor hemoglobin oxygen saturation on two head areas simultaneously was reported.

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