Acta Anaesth. Bel., 2024, 75 (2): *99-106*

Original study

Evaluating the impact of skin perfusion on cerebral hemoglobin concentration measurement using modified Beer-Lambert and Spatially Resolved Spectroscopy: Preliminary findings

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Abstract

Background: **The impact of potential extracranial interference with the interpretation of cerebral Near-Infrared Spectroscopy (NIRS) values remains a matter of debate.**
Objective: **To examine the influence of skin perfusion variation on NIRS parameters in the NIROTM 200NX device (Hamamatsu), using an occlusive head band setup. We specifically investigated the alleged difference in sensitivity to extracranial blood flow of the parameters calculated using the Modified Beer-Lambert law [MBL: oxyhemoglobin (O2Hb), deoxyhemoglobin (HHb) and total hemoglobin (tHb)] versus those using Spatially Resolved Spectroscopy [SRS: Tissue Oxygenation Index (TOI and normalized Tissue Hemoglobin Index (nTHI)]. The manufacturer suggests that SRS values are less influenced by skin perfusion than MBL-based parameters. The NIRO device uses both methods (MBL and SRS) in its calculations of cerebral oximetry parameters.**
Design: **Prospective observational clinical study.**
Setting: **Single-centre, tertiary academic medical centre; inclusions February to December 2022.**
Methods: **Thirty-one patients undergoing elective cardiac surgery were planned to be included. After inclusion of the first two thirds of patients (n=21), we analyzed the data for this preliminary report. In a controlled setup, while recording cerebral NIRS and plethysmography, we obstructed extracranial blood flow for one minute under general anesthesia using an adjustable head band.**
Main outcome measures: **MBL-based (tHb) vs. SRS-based (nTHI) NIRS measurements of hemoglobin concentration, before and during application of an occlusive head band.**
Results: **Head band occlusion resulted in a wide and diverging range of SRS- as well as MBLbased parameter effects, but without a significant trend for either nTHI or tHB. Only nTHI rose significantly when the head band was released (p = 0,017). When comparing the differences of normalized data the Wilcoxon signed rank test showed no significant difference between changes in tHb and nTHI before and after attaching the head band (p-value = 0.06, confidence interval (CI): -0,05; 0.95). Intraclass correlation was poor at 0.055 (CI -0.37 – 0.46). These results were confirmed by Bland-Altman analysis pointing to a weak agreement between nTHI and tHb, with again no clear trend.**
Conclusions: **In this preliminary analysis, our data cannot confirm that NIRO parameters using SRS are less influenced by extracranial contamination than those measured using MBL when producing a diminishment of extracranial circulation using an occlusive head band.**

Keywords (MeSH): **Spectroscopy, Near-Infrared; Cardiac Surgical Procedures; Monitoring, Intraoperative.**

Trial registration: Ghent Ethical Committee, BC-08624, chairperson Prof. dr. P. Deron, approval 30th of June 2021.

Introduction

Near-infrared light spectroscopy (NIRS) is a form of oximetry, which measures oxy- and deoxygenated hemoglobin. This technique is based on the ability of light in the near-infrared (NIR) spectrum (700-1000 nm) to detect the oxygenation state of living tissue1. This measuring technique is mostly used to detect intraoperative cerebral desaturations in cardiac surgery[1,2]. During anesthesia NIRS can detect clinically silent episodes of cerebral desaturation, which could lead to adverse perioperative outcomes[3,4].

Since there is no real reference value for regional cerebral oxygen saturation (rSO2), it is not possible to state which monitor is the most valid one1. The cause of there being no consensus for the rSO2 value for diagnosing cerebral ischemia is that all devices use different algorithms, some not even disclosed by the manufacturer5. The current hypothesis is that cerebral rSO2 under 40-50%, or a change in baseline of more than 20%, is associated with hypoxic-ischemic injury[1].

NIRS is non-invasive, continuous and real-time1. However, its disadvantages include spatial limitations, sensitivity to artifacts, no standardization and wide interpatient variability. Most important is extracranial contamination: separation of NIRS signals originating from cerebral tissue from those coming from extracerebral tissue [scalp, temporal muscles, skull, frontal sinus, cerebrospinal fluid (CSF), dura][7,12].

Two methods of measurement are used in the NIRO 200NX, based on either the modified Beer-Lambert law (MBL) or on spatially resolved spectroscopy (SRS). The modified Lambert-Beer law describes the relation between the amount of light absorption by certain molecules and the concentration of these molecules that absorb particular wavelengths, also known as chromophores: oxyHb (O2Hb), deoxyHb (HHb) and total Hb (tHb) in µmol/l[5,6,9].

Changes in cutaneous circulation potentially affect MBL measurements that aim at monitoring blood volume and oxygenation changes in deeper tissue layers e.g. muscle and brain[6]. The SRS methodology, on the other hand, is based on detecting the back-scattered light at multiple distances from the emitter and on assessing the slope of light attenuation with distance. This differential operation should virtually eliminate the common components in the detected signals that originate from superficial layers[6,10]. It measures tissue oxygenation by tissue oxygenation index (TOI), the ratio of oxyHb to total Hb in %, and total tissue Hb concentration by tissue hemoglobin index (nTHI) in arbitrary units (a.u)[9,11].

Sorensen et al. state that skin oxygenation contributes approximately 30% to the NIRS signal[8,9]. Hirasawa et al. indicated that the contribution of cerebral tissue varies widely in each subject[9].

Greenberg et al. observed a significant decrease in rSO2 values during pneumatic cuff inflation at two, three, and five minutes for two cerebral oximeters: INVOS 5100C and FORE-SIGHT ELITE3. Davie et al. noticed that EQUANOX, FORE-SIGHT and INVOS have increasing amounts of extracranial contamination in their rSO2 measurements. All previously mentioned devices use MBL and spatial resolution (SR)[4].

The purpose of this observational, quantitative, single center, diagnostic study was to explore the impact of extracranial contamination on cerebral NIRO 200NX measurements in adult patients undergoing elective cardiac surgery, using two key research questions:

1: To investigate the influence of extracranial blood flow on NIRO values: does head band application result in a difference in tHb (MBL-based) and / or nTHI (SRS-based) measurements?

2: Do both methods agree on the direction and extent of influence of head band application?

Methodology

In this study we used the NIRO 200NX: the newest NIRO device, which measures concentration changes in µmol/L for O2Hb (oxyHb), HHb (deoxyHb) and tHb (total Hb) using MBL, as well as tissue oxygenation index (TOI, %) and normalized tissue hemoglobin index (nTHI, arbitrary units) using SRS. It uses 3 wavelengths: 735, 810, 850 nm1.

In this preliminary report we examine the possible different influence of extracranial contamination on MBL and SRS parameters in NIRO 200NX device using a head band to exclude extracranial blood flow. Using this intermediate analysis we wanted to evaluate our current data set.

A power analysis was performed in G*power[15], allowing a power of 80% for a paired ttest, two-sided with a significance level of 0.05, for an expected clinically significant difference in tHb of 3µmol/l (SD 3µmol/l). Through this power analysis a required number of 21 patients was calculated. The power analysis was meant for the total of 31 patients, this intermediary analysis was performed on the first 21 included patients.

Exclusion criteria were as follows: no informed consent, emergency surgery, skin of the forehead not intact (e.g. wounds, skin disease), and carotid disease requiring surgery.

This study received approval by the ethics committee of Ghent university hospital (2021, ref: BC-08624). Inclusion of patients started in February 2022 and ended in December 2022. This study adheres to the STROBE statement[13]. After oral elucidation, patients signed the informed consent form during the preoperative anesthesia consultation.

Protocol

Monitoring was attached prior to induction of anesthesia according to standard practice

[electrocardiography, pulse oximetry, Bispectral Index™ (BIS™) Monitoring System (Medtronic)], as well as an arterial line in the right radial or brachial artery.

The Nellcor™ scalp reflectance pulse oximeter, placed on one side of the head, was used to control the exclusion of extracranial blood flow, signaled by loss of its signal when tightening the occlusion band. The NIRO monitor was attached contralaterally to the Nellcor (Figure 1).

Randomization determined which probe was attached to which side of the head. The head strap was attached at least 1.5cm below the Nellcor plethysmography and NIRO, and above the eyebrows. The setup was completed after induction of anesthesia, and all measurements were recorded before the start of surgery and after placement of the central line, as to exclude interference from hemodynamic changes caused by surgery or changes in end-tidal CO2. The first recording of baseline NIRO values was made after completion of the set-up together with the Nellcor signal and other monitoring: event 1.

One minute later, the head strap (an adjustable tourniquet) was tightened until the Nellcor signal was lost, indicating extracranial ischemia: event 2. There was no way to measure headband pressure variations or absolute pressure values.

After one minute of occlusion the head strap was fully loosened and NIRO, Nellcor values and parameters were immediately measured again: event 3. The last measurement took place one minute later to serve as a second baseline: event 4 (Figure 2).

Statistics

All data processing, plotting and analyses were performed using custom-made code in R statistical software (R Foundation for Statistical Computing, Vienna, Austria. 2020, version 4.0.3)[14]. The criterion for rejection of the null hypothesis was a two-tailed $P < 0,05$. We presented data as an average (+/- standard deviation).

Averages were calculated over the 30 second interval after the event 1 (baseline, named 'event 1'), 30 seconds before event 3 (headband off, named 'event 2') and 30 seconds after event 4 (second baseline, named 'event 3'). These intervals were chosen to represent as much of a steady state as possible, to observe the dynamic nature of these

Fig. 1 — Set-up of NIRO, Nellcor plethysmography and occlusion head band.

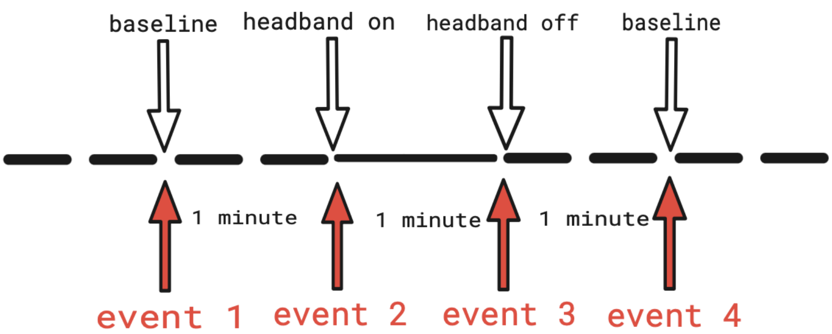

Fig. 2 — Time line of head band application and event naming.

measurements and to minimize the interference of head band manipulation on the NIRO measurements.

tHb and nTHI are hard to compare directly, as the former provides hemoglobin concentration changes with respect to an arbitrary initial level, while the latter indicates relative changes[12].

To account for this, we used of quadrant plots with Z-scores [(value minus average) / standard deviation], based on the averages calculated over 30 seconds, to compare the different parameters. We used the Wilcoxon signed rank test, intraclass correlation coefficient (ICC) test, and lastly Bland Altman analysis to look for the degree of agreement[16].

Results

Patient population

All patients undergoing elective cardiac surgery were assessed for eligibility between February 2022 and December 2022. In this preliminary report we describe 21 patients. Patient baseline characteristics were recorded: age, BMI (kg/m2), NYHA classification, type of cardiac surgery and baseline hematocrit (Table I).

Extracranial contamination

Initial visual analysis (using custom written code for extended replotting of raw data in R) showed that in most patients the attachment and release of the head strap produced a visually significant effect on NIRO parameters, more substantial than normal parameter variation. The direction and magnitude of the changes in MBL and SRS, however, were inconsistent, with some examples shown next. (Figure 3).

Using the NIRO 200NX Data Guide book we matched the plotted results to a clinical diagnosis[11]. Analyzing the MBL-based traces, we found that in 12/21 of patients only venous occlusion (rising HHb) was achieved, while the others were showing signs of additional arterial occlusion (lowering O2Hb). Both groups, however, represent changes in skin perfusion, of which we showed inconsistent results on MBL- and SRS-based parameters. In the group with only venous occlusion, tHb and nTHI concorded in only 58% of the cases (7/12). In the group with combined arteriovenous occlusion, concordance between tHb and nTHI rose to 67% (6/9). Overall concordance was 62%.

When dividing patients according to whether O2Hb increased or decreased, tHb values logically showed a similar trend, but no clear trend in nTHI emerged.

Using a boxplot as an overview of the entire population showed a few outliers, as well as a wider distribution for event 2 for both variables (Figure 4). Comparing the direction and magnitude of change after head band application for nTHI and tHb using quadrant plots, we note an inconsistent divergence between both parameters. After normalization it is confirmed that occlusion with the head band (events 1&2) leads to a dispersed quadrant plot without a clear trend for either nTHI or tHB. Both parameters return to baseline after head band release (events 1&3) (Figure 5).

The Wilcoxon signed rank test showed no significant difference between changes in tHb and nTHI before and after attaching the head band (p-value = 0.06, CI: -0,05; 0.95). Intraclass correlation was poor at 0.055 (CI -0.36 – 0.46). In Bland-Altman analysis the mean of difference of the normalized data points was close to the zero line, suggestion low bias, but the wide limits of agreement (z-scores of -2.6 to +1.7) point to a weak agreement between nTHI and tHb, with no clear trend (Figure 6).

Table I. — Baseline characteristics.

	Average	Standard deviation	Range
Age (years)	72	9,4	(49 - 91)
Body Mass Index (BMI) (kg/m^2)	27	5,1	(16 - 35)
Hematocrit (%)	40,5	4,6	(29 - 47)
Sex	Number	Percentage (%)	
Female	6	28,6	
Male	15	71,4	
New York Association class Heart (NYHA)	Number	Percentage (%)	
I	2	9,5	
II	2	9,5	
III	12	57,1	
IV	5	23,8	

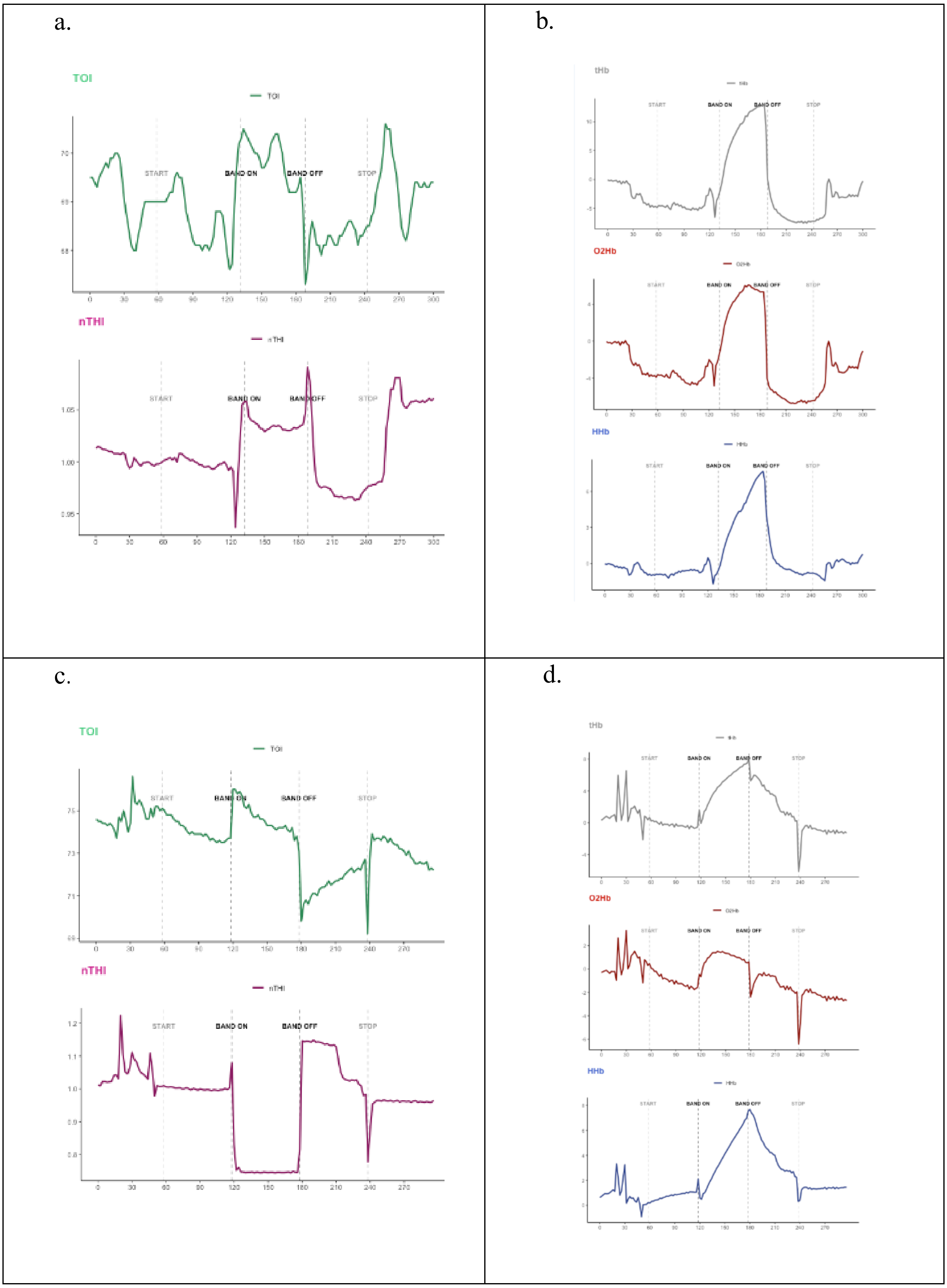

Fig. 3 — Representative examples of divergent trends in normalized Tissue Hemoglobin Index (nTHI) – total Hemoglobin (tHb).
Venous occlusion and concordance between nTHI (a) and tHb (b), as opposite to venous occlusion and discordance between nTHI (c) and tHb (d).

Discussion

In this study we looked at the possible different influence of extracranial contamination on MBL and SRS parameters in NIRO 200NX device using a head band to exclude extracranial blood flow in patients under general anesthesia for elective cardiac surgery. We established that our head band occlusion set-up resulted in diverging patterns in MBL- and SRS-based parameters.

The use of an occlusive head band is similar to the one described in various other studies. Different

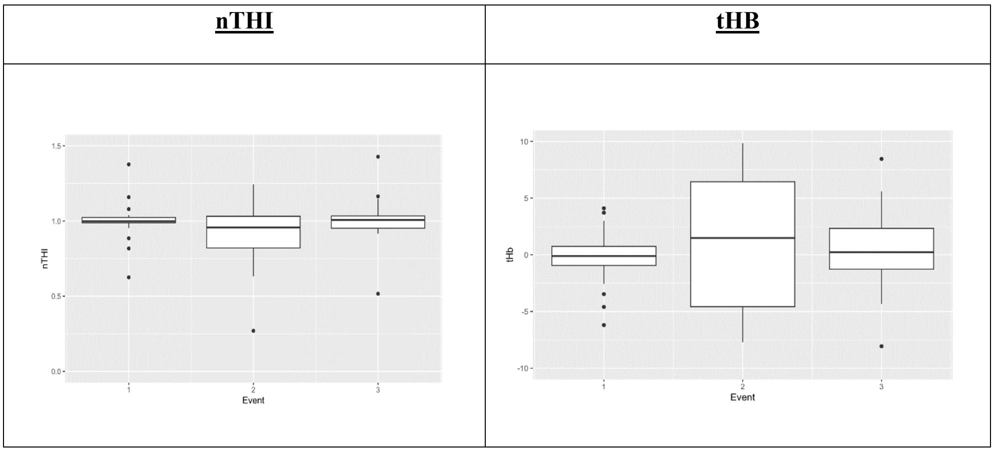

Fig. 4 — Boxplot for normalized Tissue Hemoglobin Index (nTHI) and total Hemoglobin (tHb).

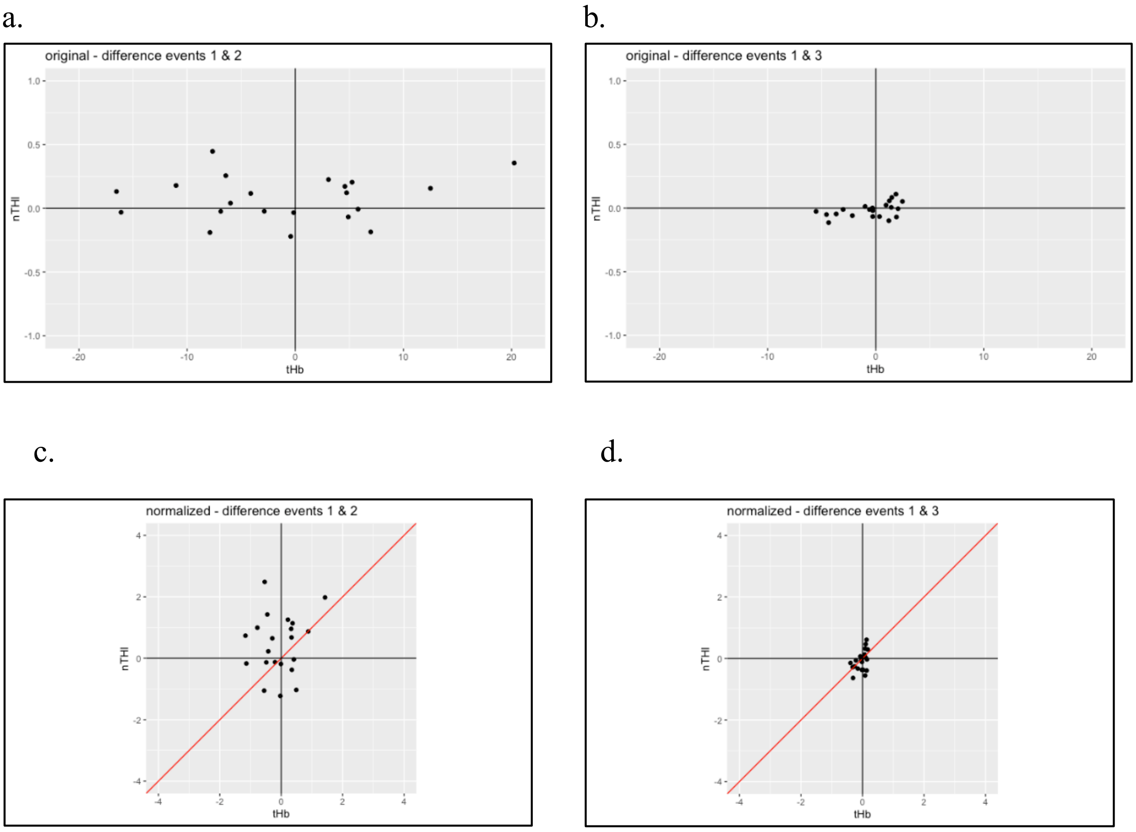

Fig. 5 — Four-quadrant plots of original (subplots a and b) and normalized data (subplots c and d). Left sided panels (a and c) compare the effect of head band application on both total hemoglobin (tHb) and normalized Tissue Hemoglobin Index (nTHI), while the right sided panels (b and d) compare the baselines before and after headband release.

studies do have variable protocols: use of different NIRS devices, a head band or pneumatic head cuff with differing periods of inflation, and patients are often young, healthy volunteers who are awake[3-5,9].

It is therefore important to note that only a minority of studies on extracranial contamination include patients with cerebrovascular disease, in whom cerebral perfusion varies from the healthy population10. A major strength of our study is that it is the first, to our knowledge, to examine extracranial contamination in the adult patient population for elective cardiac surgery under general anesthesia. This model results in a setting closer to everyday NIRO use in cardiac surgery than studies using subjects from the healthy and/or awake population.

To control the exclusion of extracranial blood flow we used the loss of signal from the Nellcor scalp reflectance pulse oximeter as a reference. An important limitation and possible interference with measurement accuracy remains that we had no means of assessing the absolute pressure imposed on the cutaneous vessels with our head band setup.

This pressure as such could theoretically be higher or lower than MAP or systolic blood pressure and could result in venous or arteriovenous occlusion. Another important limitation involves that our study

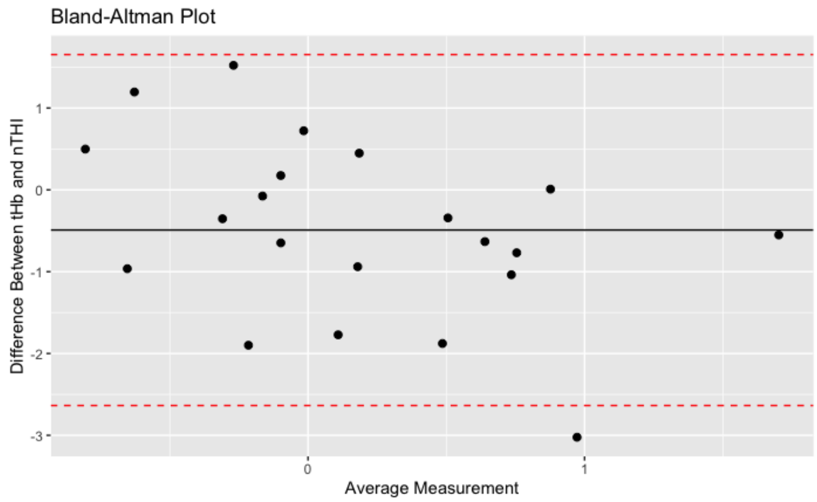

Fig. 6 — Bland-Altman plot performed with normalized values as a way to compare Modified Beer-Lambert (MBL) and Spatially Resolved Spectroscopy (SRS) parameters. This showed low bias but wide limits of agreement.

is a preliminary subset analysis and has a small sample size of 21 patients.

At present we do not have one conclusive explanation for our varying findings in MBL and SRS parameters when occluding extracranial flow using a head band: different trends could be the result of variable pressure exerted by the head band, resulting in solely venous or veno-arterial extracranial occlusion. Other possible explanations could be a confounder or interpatient variability of extracranial vascular distribution.

An additional challenge remains as to how we can compare the MBL and SRS parameters: how does for example a decline in nTHI from 1.0 to 0.95 compare to a decline of tHb from 0 to -5 micromol/L? Our methodology of normalization has the advantage of being able to compare both parameters in a relative way as there is no direct way to compare these relative and absolute measurements and little information on this topic is provided by the manufacturer.

It remains unclear to what degree extracranial contamination is clinically relevant and affects our decision-making when using NIRS. NIRS is used as a trend monitor, so it is possible to argue that if extracranial contamination would be constant, this would have little influence on our use of NIRS parameters. However, if factors like an in- of decrease in extracranial blood volume could influence the amount of contamination, the actual NIRS parameters could suffer from a variable amount of distortion.

The result of diverging patterns in MBL- and SRS-based parameters as a reaction on extracranial vascular occlusion, as well as the clinical relevance of extracranial contamination would both require elucidation in follow-up studies.

In the preliminary analysis we found inconsistent and diverging trends in MBL and SRS parameters on exclusion of extracranial blood flow by use of an occlusive head band. Furthermore, our preliminary data cannot confirm that NIRO parameters using SRS are less influenced by extracranial contamination than those measured using MBL when excluding extracranial circulation using an occlusive head band.

Acknowledgements, funding and Conflicts of Interest (COI) : We thank Dr. Ineke Van Gremberghe (Faculty of Medicine and Health Sciences, UZ Ghent) for providing assistance in statistics.
The authors received no funding for this study nor do they hold any potential conflict of interest.

Data sharing policy: Upon request, data and programming code are available from the authors.

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doi.org/10.56126/7.2.43