Clinical application of near-infrared spectroscopy in perioperative assessment of cerebral and peripheral tissue oxygenation

Anneliese Moerman
Ghent University
Faculty of Medicine and Health Sciences
Department of Anaesthesiology

Promotor

Prof. Dr. Patrick Wouters

Support committee

Prof. Dr. Stefan De Hert

Prof. Dr. Chris Verborgh

Members of the examination committee

Prof. Dr. Daniël De Wolf

Prof. Dr. Luc Herregods

Prof. Dr. Eric Mortier

Prof. Dr. Gunnar Naulaers

Prof. Dr. Yves Van Belleghem

Prof. Dr. Johan Vande Walle

Prof. Dr. Frank Vermassen

Thesis submitted in fulfillment of the requirements for the degree of Doctor in Medical Sciences.

Father and Daughter: A Father's Privilege

Child, why would you want to practice medicine?
Late hours, night calls, research projects, administration deadlines
Don't do medicine, look at my life
Do what makes you happy

Daughter, why are you stressing?
Don't do this. There are easier ways to make a living
It's not worth it, go ahead and live
Do what makes you happy

Doctor, don't you know there is a price for learning?
Nothing worth doing is done easily
The struggle cries there must be an easier way
Do what makes you happy

Dear Heart, you have chosen a difficult road and kept true
In medicine we meet as equals
An old man with eyes that leak now and again
Glad and proud that you do what makes you happy

Spencer S. Kee

This thesis is dedicated to the memory of my father

Contents

Chapter 1

General introduction

Adapted from: Moerman A, Wouters P. Near-infrared spectroscopy (NIRS) monitoring in contemporary anesthesia and critical care. Acta Anaesth Belg 2010; 61: 185-94

The primary goal in the hemodynamic management of patients undergoing surgery is to preserve oxygen delivery at a level sufficient to cover all metabolic needs. Nowadays, anesthesiologists can rely on a variety of monitoring tools to quantify cardiovascular performance and global oxygen delivery. Nonetheless, current standard anesthesia monitoring still has two major drawbacks. First, it provides a *global* assessment of the patient's status, and as such vital organ ischemia may go unnoticed until functional organ damage becomes evident. Case reports of dramatic neurologic outcome after minor surgery in healthy patients [1] point out the compelling need for organ-specific monitoring. A second drawback is that the majority of variables monitored in contemporary anesthesia focus on oxygen *supply* (cardiovascular performance, hemoglobin and arterial oxygen content) but do not assess imbalances between oxygen supply and demand. The use of central and mixed venous oxygen measurements

to assess oxygen consumption is gaining interest now in perioperative care [2]. However, current techniques for assessing venous oxygen saturation are invasive and therefore not routinely incorporated into clinical anesthesia.

Near-infrared spectroscopy (NIRS) is a non-invasive technology that continuously monitors regional tissue oxygenation. NIRS was originally introduced in clinical practice in 1985, for the assessment of cerebral oxygenation in preterm infants [3]. It was also welcomed with enthusiasm in cardiac and neuro-anesthesia, but its utility, particularly in the latter field of application, was seriously challenged by a series of reports on false positive as well as false negative readings. The technique was further discredited by anecdotal papers illustrating that NIRS oximeters generated near normal values when the probes were placed on an empty human skull filled with blood-soaked gauzes [4] or even on a pumpkin [5]. Even today, these papers are quoted to question the validity of NIRS monitoring. However, a fair understanding of the assumptions and limitations of NIRS technology suffice to understand that such observations are indeed possible, yet do not invalidate the use of NIRS to quantify changes in the oxygen status of human tissue. The interest in NIRS as a monitoring tool in anesthesia has revived over the past few years and several systems have now been approved for clinical use.

1.1 Near-infrared spectroscopy

The first attempt to monitor human tissue oxygenation non-invasively dates back to 1874 when the German physiologist Karl Von Vierordt showed that the amount of red light transmitted through a hand decreased after it was made ischemic [6]. His pioneering studies were essentially ignored for half a century until it was again reported that the variable transmission of red and infrared light through a human ear reflected changes in blood oxygenation [7]. The first small portable oximeter was developed in 1942 by Glen Milliken

[8], although the device was used only as an experimental tool in the aviation and the physiology laboratory. The concept of cerebral near-infrared spectroscopy originated with the observations of Jobsis [9] who irradiated a cat's head with near-infrared light and found that the intensity of the transmitted light varied with the oxygen metabolic state of the brain (Fig. 1.1).

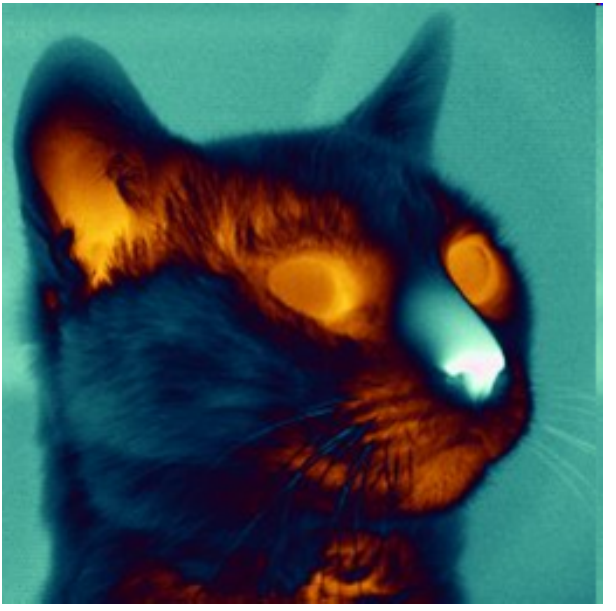

Figure 1.1

1.1.1 Principles of operation

The physical and mathematical basis for NIRS is provided by the Beer-Lambert law, which states that the quantity of light absorbed by a substance (A) is directly proportional to the specific absorption coefficient of the substance at a particular wavelength (ϵ), the concentration of the substance (c) and the pathlength of the light

through the solution (l) ($A = \epsilon \cdot c \cdot l$) [10].

The relative transparency of biological tissues to light in the near-infrared part of the spectrum (700-1000 nm) enables light photons to pass through the tissues, where they are attenuated due to a combination of absorption and scattering. Because of scattering by the tissue components, the light does not travel in a straight line. Therefore, the Modified Beer-Lambert law is applied: ($A = \epsilon \cdot c \cdot l \cdot B + k$), where B is the differential pathlength factor and k is an additive geometry-dependent term, reflecting scatter loss. The geometrical pathlength l has to be multiplied by B to find the true optical distance, because light that reaches the detector will have been scattered multiple times and therefore has travelled a much greater distance than the actual light emitter-detector distance. k corrects for the fact that not all emitted light reaches the detector, because some of it is scattered away from the detector, giving scattering losses. Scattering is a function of the tissue composition and the number of various tissue interfaces. Because B and k are unknown factors, no absolute values can be measured with the Modified Beer-Lambert law. NIRS technology is based on the assumption that the quantity of scattering remains constant and that changes in attenuation result solely from changes in absorption.

Several biological molecules, termed chromophores, absorb light in the near-infrared (NIR) spectrum. However, only hemoglobin and cytochrome oxidase are present in variable concentrations, reflecting blood and intracellular oxygenation, respectively. Other chromophores are assumed to be constant over the period of monitoring.

The wavelengths of NIR light used in commercial devices are selected to be sensitive to hemoglobin. Cytochroom oxidase has a crucial role in mitochondrial oxidative energy metabolism, and therefore provides a potential biomarker of the cellular oxygenation state, with substantial physiological and clinical importance. However, it is present in much lower concentrations in the tissue than oxygenated

and deoxygenated hemoglobin and its absorption spectrum overlaps that of these chromophores, and therefore, the validity of cytochroom oxidase measurements is debated, and the signal is not incorporated into any clinical monitors yet [11].

Oximetry relies on the fact that absorption of near-infrared light at specific wavelengths is different in deoxygenated hemoglobin (HHb) when compared with oxygenated hemoglobin (O_2Hb) (Fig. 1.2).

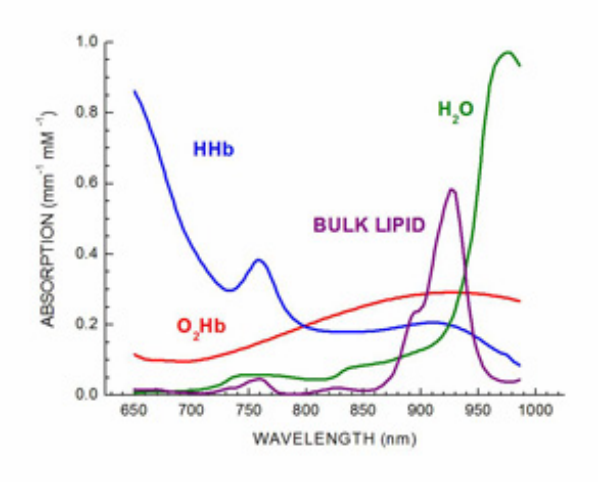

Figure 1.2: Distinct absorption spectra for water (H_2O), lipids, oxygenated (O_2Hb) and deoxygenated hemoglobin (HHb). Near-infrared spectroscopy measures light absorption at specific wavelengths to differentiate between O_2Hb and HHb. (https://Dosi.bli.uci.edu/userfiles/image/basis_spectra.jpg)

Commercial devices generally use wavelengths between 690 and 880 nm where the absorption spectra of O_2Hb and HHb are maximally separated and there is minimal overlap with that of water absorption (980 nm) (Fig. 1.2). Optical absorption at 1 wavelength

for each chromophore of interest must be known. NIRS devices use near-infrared light at two or more specific wavelengths to differentiate between O_2Hb and HHb. Similar to the principles used in pulse oximetry, the device measures the amount of light absorbed at these specific wavelengths and calculates the relative contribution of O_2Hb and HHb. The resulting ratio of O_2Hb to total Hb (THb) (expressed as a percentage) represents the oxygen saturation of tissue under the sensor: $O_2Hb.k/THb.k.100(\%)$, in which k, the constant reflecting the scattering, can be neglected. No attempt is made to measure optical scattering. The scale of measured changes is dependent on the application of assumptions of the scattering properties at different wavelengths, and is incorporated into the algorithm of the respective devices. Algorithmic formulae are complex, and their validity is contingent on the assumptions made. The variability in algorithms between NIRS devices implicates that there are differences in the chromofore concentrations derived, making comparisons between oximeters produced by different manufacturers problematic.

Jobsis [9] used *transmitted* light in his original experiments. Light was applied to one side of the body and received on the other side. However, attenuation of light due to absorption and scattering restricts usage of this method to very thin and transparent areas of the body such as the earlobe or finger. For that reason, *reflected* light rather than transmitted light is being used to study absorption of light in larger tissue samples. Reflectance probes locate the light emitter and detector adjacent to one another. The light takes a "banana-shaped" pathway through the tissues, with the depth of photon penetration proportional to the source-detector separation (principle of spatial resolution) (Fig. 1.3). In order to compensate for superficial tissue, which is not the tissue of interest, differentially spaced light detectors are used. Owing to the principle of spatial resolution, the closer receiver will measure more superficial tissue while the distal optode measures both superficial and deeper tissue. After subtraction of the interference from superficial tissues – the

mathematical details of which are not provided by the manufacturers – oxygenation in the deeper tissues is derived.

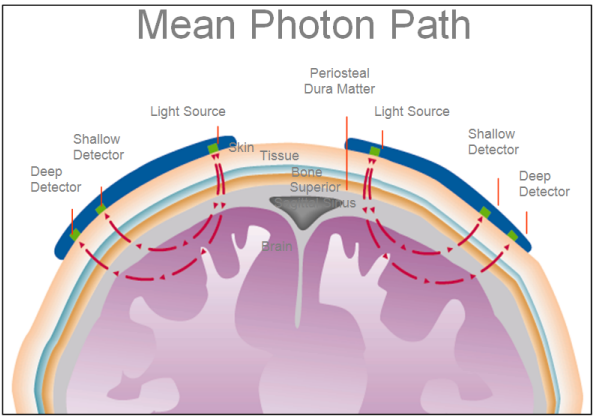

Figure 1.3: Principle of reflectance spectroscopy and spatial resolution (Permission for reproduction obtained from Somanetics Corporation, Troy, MI, USA).

1.1.2 Assumptions and limitations

As with any monitoring system it is essential for the clinician to understand its underlying technology, including the limitations and the assumptions made to translate a physical quantity into a clinically meaningful parameter.

First of all, NIRS does not quantify oxygen molecules, but calculates the ratio of light absorbencies at predefined wavelengths. External light sources may cause significant artefacts and careful shielding of the probes is therefore important. Theoretically any substance to which NIRS is applied can generate a value on the monitor. In fact, the technology is being used for more than 20 years now in the agricultural, chemical, and pharmaceutical industries, e.g. to determine the freshness of food.

Second, the algorithms used to calculate oxygen saturation assume a fixed distance for light to travel through the sampled area (the optical pathlength). However, different tissue components produce very different amounts of photon scattering and absorption. As a result, variations in probe positioning [12] as well as interindividual variations in the composition of tissue may result in 10 to 15% variability of the true optical pathlength measurement [13]. In fact, for cerebral NIRS, the influence of extracranial tissue and blood on the optical pathlength is not known [14]. It is therefore impossible to completely eliminate the potential interference of changes in extracranial flow on cerebral NIRS readings [15]. The significant inter-individual biological variability in tissue composition causes a wide variation in 'normal' baseline values of volunteers. Therefore, NIRS devices are best used as trend monitors. Rather than to base therapeutic decisions on absolute numbers, it is safer to rely on proportional changes of an individual's baseline value as a basis for clinical decision making. Although individual manufacturers claim that some monitors provide reliable absolute values which can be applied universally, this statement lacks any scientific basis. In fact, to subscribe such a statement, validation studies would be required to compare NIRS data to invasive measurements of oxygen saturation in tissue samples obtained directly from the brain. Such studies have not yet been performed.

Third, the physiological correlate to which tissue saturation measurements obtained with NIRS relate, remains a matter of debate. NIRS measurements are continuous, i.e. not time-gated with respect to the cardiac cycle. Furthermore, the interrogated tissue sample contains all the different vascular components and represents a mixture of arterial, capillary and venous oxygen saturations. In contrast, pulse oximetry incorporates the variation in optical density during the cardiac cycle which enables it to define the systolic fraction of the signal. It calculates the ratio between systolic and diastolic absorption values to determine arterial oxygen saturation (S_aO_2). In

contrast to NIRS, pulse oximeters have been subjected to a calibration procedure. During calibration, readings from pulse oximeters are being compared to simultaneously obtained arterial blood samples from volunteers who undergo a controlled desaturation (down to values of 70% S_aO_2). For NIRS measurement, the precise contribution from the various vascular beds is not known, but is assumed to represent a 30/70 ratio (or 20/80) of arterial to venous components [16]. However, relative changes in blood volume of the venous or arterial compartment can influence cerebral saturation independently, without a true change in saturation of either. A simple example of this is a change from the head-elevated Fowlers' position to the head-down Trendelenburg position [17].

Finally, one of the major criticisms against the use of NIRS as a neuromonitor is that marked decreases in cerebral oximetry may occur without apparent resultant neurological damage. It should be clear that low cerebral saturations reflect an oxygenation imbalance, indicating a potential risk of ischemia, but does not necessarily indicate tissue damage. The transition to irreversible injury depends on both the severity and duration of hypoxia. On the other hand, the measurements obtained with NIRS are regional, and strictly confined to the zone beneath the sensor. Clinically relevant focal cerebral ischemia in a brain area remote from the monitored area may easily go unnoticed. These limitations undoubtedly explain the relatively low sensitivity and specificity reported for carotid endarterectomy [18].

1.1.3 Validation

Several difficulties arise in the validation of cerebral oximetry, because there is no invasive direct measurement possible of the true oxygen saturation in the interrogated brain tissue. The accuracy of NIRS has been validated by comparison to internal jugular vein oxygen saturation ($S_{jv}O_2$) [19-22]. However, some factors need to be taken into account when validating the accuracy of any cerebral oximeter

with $S_{jv}O_2$: there is a considerable anatomical variation of cerebral venous drainage [23], NIRS measures regional oxygen saturation, whereas $S_{jv}O_2$ reflects global brain oxygenation, and $S_{jv}O_2$ measures venous oxygen saturation, whereas NIRS represents a mixture of arterial, capillary and venous oxygen saturation, of which the precise contribution of each compartment is not known [16]. Because of their fundamentally different sampling character, an expectation of close agreement between these measures is unjustified.

1.2 Clinical considerations in cerebral NIRS monitoring

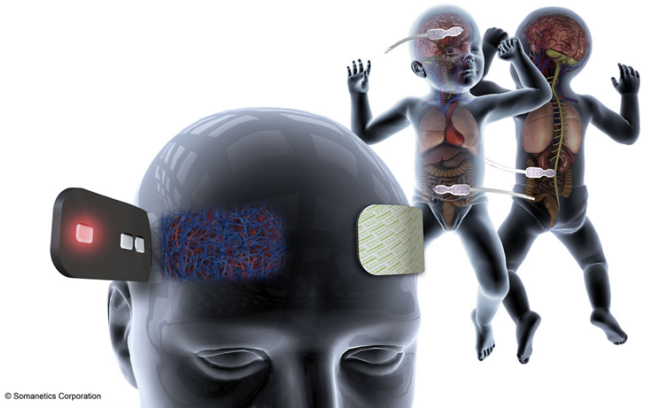

Figure 1.4: Illustration of placement of NIRS sensors (Permission for reproduction obtained from Somanetics Corporation, Troy, MI, USA).

To obtain an individual reference baseline value, NIRS monitoring is best initiated before preoxygenation and anesthesia induction. Self-adhesive sensors containing the infrared light source and light detectors are fixed on one or both sides of the forehead (Fig. 1.4). The values reported for regional cerebral oxygen saturation (rS_cO_2)

are 71 ± 6% in young healthy adults [20] compared with 67 ± 10% in cardiac surgery patients [24].

In most clinical studies cerebral desaturation is defined as a 20% reduction from baseline values or an absolute decrease below 50% [24]. However, the risk of irreversible tissue damage increases with the duration of cerebral desaturation. The degree and duration of reduction in rS_cO_2 associated with development of permanent neurologic injury was defined in experimental and clinical studies. In a piglet model, rS_cO_2 reductions to 30-45% produced immediate neurophysiologic impairment, manifested by increased lactate, decreased brain adenosine triphosphate (ATP), and altered synaptic activity [25], and by injury of mitochondria in the neurons [26]. If a rS_cO_2 of 35% lasted more than 2 hours, the incidence of structural brain damage increased linearly by about 15% per hour [27]. In neonates with hypoplastic left heart syndrome, prolonged low postoperative cerebral oximetry (<45% for >180 minutes) was associated with the development of new or worsened ischemia on postoperative magnetic resonance imaging [28]. Slater et al. identified a desaturation score of 3000 %.sec (calculated by the product of length of time and depth of rS_cO_2 <50%) to be an independent predictor of postoperative cognitive decline and extended hospital length of stay [29]. It is important to note that thresholds for the onset of cerebral impairment depend on the 'cerebral blood flow reserve', which is patient and disease specific, and which is also modified by factors, such as anesthesia, vasoactive drugs, and tissue temperature [30]. Therefore, there may be a much smaller margin for error with respect to cerebral ischemia than anticipated.

Figure 1.5 illustrates NIRS monitoring during anesthesia for defibrillator implantation. During anesthesia induction (Fig. 1.5(A)) an increase in rS_cO_2 is seen due to preoxygenation and suppression of cerebral metabolism. To test proper functioning of the defibrillator, ventricular fibrillation was induced, resulting in immediate and profound cerebral desaturation (Fig. 1.5(B)). After restoration of

circulation by defibrillation, rS_cO_2 instantly normalized.

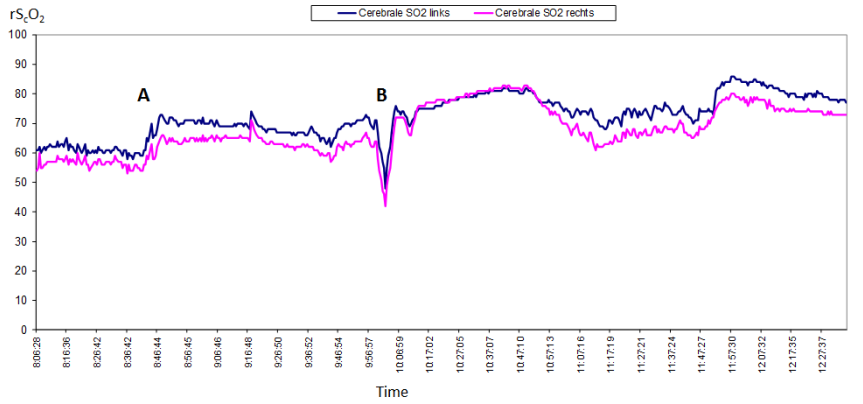

Figure 1.5: Time plot of cerebral oxygen saturation (rS_cO_2) from the left (blue line) and right (pink line) frontal cortex during implantation of a defibrillator. A: Anesthesia induction. B: Ventricular fibrillation.

A clinical algorithm to correct for decreases of rS_cO_2 values is depicted in table 1.1 on page 22. In case of decrease, first step is to rule out technical or mechanical causes. Verify that the sensors are well positioned, because an inappropriately applied sensor will capture ambient light and may display a wrong value [31]. Then rule out technical and mechanical causes of hypoperfusion. During extracorporeal circulation, a malpositioned arterial or venous cannula may compromize cerebral perfusion pressure, resulting in immediate cerebral desaturation. Proper repositioning of the cannula instantaneously leads to effective restoration of rS_cO_2 (Fig. 1.6). Since the introduction of NIRS in cardiac surgery, it turned out that NIRS is often the first and only indicator of cannula malpositioning [32], which strongly suggests that the incidence and impact of cannula misplacement have been underestimated in the past.

Once technical and mechanical problems have been excluded, the next step is to optimize those factors that influence NIRS

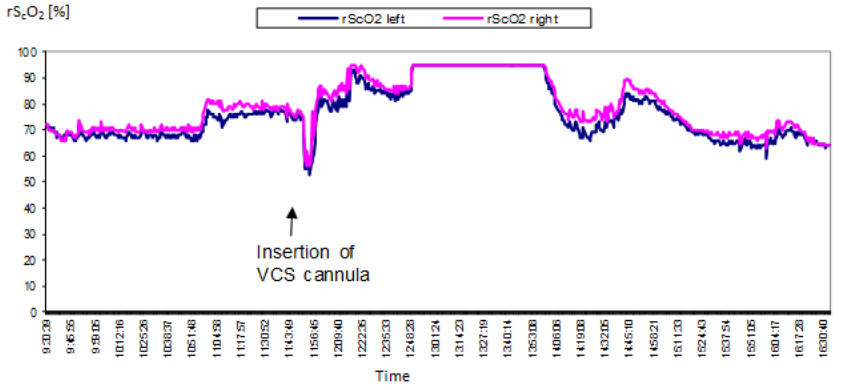

Figure 1.6: Time plot of cerebral oxygen saturation (rS_cO_2) from the left (blue line) and right (pink line) frontal cortex. Malpositioning of the venous cannula in the superior caval vein (VCS) induces immediate cerebral desaturation (arrow).

values. A change in NIRS values can be caused by a wide variety of pathophysiological conditions since every parameter that affects oxygen balance, both supply and demand, will change tissue oxygen saturation. Cerebral oxygen delivery can be increased by optimizing cardiac output and increasing arterial oxygen content (P_aO_2, hemoglobin (Hb)). Considering Hb is an important determinant of tissue oxygenation, low rS_cO_2 values may be related to low Hb levels. Some investigators have proposed using rS_cO_2 as a transfusion trigger [33,34]. However, transfusion will not invariably increase rS_cO_2 [35], considering Hb is only one determinant of tissue oxygenation and since blood processing may reduce Hb oxygen-carrying capacity by up to 90% [36].

Because the cerebral circulation is very responsive to changes in carbon dioxide (CO_2), deliberate hypercapnia will increase rS_cO_2. In a patient with normal CO_2 reactivity, cerebral blood flow changes 1-2 ml/100g/min per mmHg CO_2 change [37].

Table 1.1: Algorithm to correct cerebral oxygen desaturation

Step 1:	
Check, check, check	- Check oximeter/sensors - Check equipment (ventilator/pump) - Check head/cannula position
Step 2:	
Optimize cerebral oxygen supply	- If reduced or maldistributed cardiac output: volume infusions, inotropics, vasodilators, etc... - If P_aO_2 too low : Raise F_iO_2/P_aO_2 - If Ht<25% : Blood transfusion - If P_aCO_2<45 mmHg : Raise P_aCO_2 - Raise perfusion pressure
Step 3:	
Decrease cerebral oxygen consumption	- Control hyperthermia - Increase anesthetic depth - Neuroprotective agent

P_aO_2: arterial oxygen partial pressure, F_iO_2: fractional inspired oxygen, Ht: hematocrit, P_aCO_2: arterial carbon dioxide partial pressure.

Theoretically, cerebral blood flow should be constant when cerebral perfusion pressures range between 50 and 150 mmHg. However, this concept of cerebral autoregulation is increasingly questioned, since there is an enormous individual variation in the autoregulation limits [30], and multiple causes during surgery might impair cerebral autoregulation such as hypothermia, vasoactive drugs, anesthetics, endothelial dysfunction and inflammatory responses [38,39]. It was shown that NIRS has the potential to identify impaired cerebral autoregulation and to detect otherwise unnoticed cerebral hypoperfusion [40-42].

If a reduction in rS_cO_2 values is observed despite optimization of cerebral oxygen delivery, steps to decrease cerebral oxygen consumption can be taken such as brain cooling and increasing anesthetic

depth.

In summary, decreasing NIRS values undeniably reflect a deterioration of the oxygen delivery-demand balance which should trigger a search for potential causes and provide an early opportunity for therapeutic correction.

1.3 Clinical studies

There is an exhaustive and still growing body of literature concerning the use of NIRS in clinical anesthesia. Whereas initial research focused on the use of NIRS as a mere brain monitor in neurosurgery and cardiovascular surgery, now interest extends to other surgical areas and to the evaluation of oxygenation of tissues other than the brain.

Neurosurgery/neurointensive care/interventional neuroradiology

The reliability of NIRS in the setting of neurosurgery and neurointensive care has been seriously questioned. In conditions where the brain is threatened, light absorption and scattering is highly variable, making accurate quantification impossible [43]. Also, NIRS values vary greatly after a neurological insult, depending on the secondary pathophysiological processes, defying interpretation [44]. Importantly, Maeda et al. [45] found cerebral oxygenation values ranging from 0.3% to 95% in 214 human cadavers. The variation was dependent on the total hemoglobin content, cause of death, and cadaver-storage conditions. Obviously, these data indicate that NIRS would not qualify to assess cerebral death.

NIRS monitoring may have a useful role in the detection and management of adverse events during neuroradiologic endovascular procedures. Bhatia et al. demonstrated that vasospasms as detected from angiography were strongly associated with reductions in ipsilateral NIRS values [46]. NIRS monitoring enabled prompt diagnosis and management of adverse intraoperative events in a study of 28

endovascular embolization procedures [47]. However, using NIRS in this specific setting requires accurate interpretation of measurements, with careful understanding of the ongoing step of the neuroradiologic procedure, and considering the influence of extrinsic factors that can affect results, such as patient systemic variables (blood pressure, hemoglobin concentration, arterial oxygen concentration, arterial carbon dioxide tension, cerebral metabolic rate). It is also important to note that while decreases in rS_cO_2 are sensitive indicators of potentially threathening changes, the converse does not apply, i.e. due to the regional measurement strictly confined to the zone beneath the sensor, largely stable rS_cO_2 values do not guarantee cerebral integrity.

Cardiac surgery

As the incidence of neurologic complications is particularly high in patients undergoing cardiac operations [48,49], the potential to monitor the brain in a simple, non-invasive way was appealing for anesthesiologists managing cardiac surgery patients.

In congenital heart surgery, most centres have adopted NIRS very quickly as standard of care. Because changes in cerebral hemodynamics and oxygenation are common during pediatric cardiac surgery, putting these children at risk for brain damage, real-time neurological monitoring is considered as an integral part of neuroprotective strategies for pediatric cardiac patients. A growing number of case reports describe the early detection of potentially catastrophic events by NIRS monitoring, which likely prevented brain injury [50-52]. In addition, the potential for instantaneous hemodynamic evaluation and timely intervention has been proven invaluable during high risk pediatric cardiac surgery [53,54].

The interest in NIRS extended soon from congenital to adult cardiac surgery. In several observational studies, routine use of perioperative cerebral oximetry monitoring in patients undergoing cardiac surgery has been demonstrated to reduce neurological complications

[55-57] and to shorten hospital stay [58]. However, to justify new technology it is important to prove that interventions based on this technology effectively improve clinical outcome. Currently, three interventional trials in the domain of cardiac surgery and anesthesia have addressed this question. The first one, from Goldman et al., compared 1245 patients who underwent cardiac surgery before cerebral oximetry was incorporated, with 1034 patients in whom rS_cO_2 was maintained near to each patient's pre-induction baseline [59]. The latter group had fewer permanent strokes (0.97% *vs* 2.5%), shorter ventilation times, and decreased hospital stay. The weakness of this study is its non-randomized and retrospective design. In the second interventional trial, Murkin examined perioperative major organ morbidity in a prospective, randomized, blinded study of 200 coronary artery bypass patients [60]. Hundred patients were randomized to intraoperative cerebral saturation monitoring with an active display and treatment intervention protocol, and 100 patients underwent blinded cerebral saturation monitoring. Significantly more major organ dysfunction (death, ventilation >48 h, stroke, myocardial infarction) was observed in the control group versus the intervention group. In the most recent interventional trial, Slater et al. found that patients with a higher desaturation score (a score accounting for both depth and duration of desaturation) had a significantly higher risk of early postoperative cognitive decline and prolonged hospital stay [29]. Due to poor compliance to the treatment protocol, Slater was not able to demonstrate that treatment of cerebral desaturation resulted in better outcome.

Carotid endarterectomy (CEA)

Perioperative stroke is a major risk of CEA. Stroke may be caused by hypoperfusion during cross-clamping of the internal carotid artery if collateral blood supply is insufficient, or by embolism during insertion of a shunt. Many studies investigated the usefulness of NIRS to detect patients developing cerebral ischemia during cross-

clamping, trying to define the indication for a shunt. Although several studies showed that rS_cO_2 during carotid cross-clamping decreased significantly more in patients who developed neurological symptoms [18,61], defining a meaningful cutoff for decline in rS_cO_2 associated with neurologic threat is very difficult [62]. A 20% reduction in rS_cO_2 from baseline is widely used as the threshold for shunt placement. With this cutoff value, sensitivity between 30% and 83% was reported, and specificity ranged between 25% and 98%, with a high negative predictive value (98%), but an unacceptable low positive predictive value (37%), hence cerebral oximetry cannot be relied on for decision making about placement of a shunt during CEA [61,63,64]. Despite the uncertainty as to the exact NIRS-derived threshold for the identification of critical ischemia, the body of evidence suggests broad equivalence with other modalities for identifying critical cerebral ischemia [61]. Although cerebral oximetry cannot be relied on for decision making about placement of a shunt during CEA, NIRS is currently used in many centres as the primary cerebral monitor during carotid surgery to guide systemic physiological management in order to optimize cerebral perfusion and oxygenation.

Noncardiac surgery

A large multicenter study (International Study of Post-Operative Cognitive Dysfunction (ISPOCD) [65] showed that after major noncardiac surgery, postoperative cognitive dysfunction was present in 26% and 10% of the patients respectively at 1 week and 3 months after surgery. Although the etiology is not completely clear, it is assumed that unrecognized cerebral hypoperfusion can be implicated in a significant number of perioperative brain damage. Casati prospectively monitored rS_cO_2 in 122 elderly patients undergoing major abdominal surgery [66]. Twenty % of the patients experienced a decrease in rS_cO_2 below 75% of baseline. Correcting low rS_cO_2 was associated with a lower incidence of immediate postoperative confusion and an earlier hospital discharge.

Other organ applications

The interest for using NIRS as a monitor of oxygen status in tissues other than the brain is growing. Regional saturation monitoring at somatic sites has been advocated as an early warning system for changes in the oxygen supply-demand balance. As cardiac output falls, the sympathetic stress response raises vascular resistance, redistributing blood flow to the brain and heart, leaving other tissues – typically kidneys, liver, and intestines - at increased risk for silent ischemia. Currently, rSO_2 monitoring of kidneys [67-71], liver tissue [72,73], splanchnic tissue [68,74] and muscles [68,75,76] are extensively being studied to evaluate their potential to detect perfusion deficits. Other promising applications of NIRS are prediction of splanchnic ischemia in neonates [77,78], diagnosis of compartment syndrome [79], assessment of peripheral vascular disease [80], monitoring of free flaps [81,82], and monitoring of spinal ischemia during thoracoabdominal aneurysm repair [83].

For all these applications it is important to realize that the mean depth of light penetration is proportional to the light source-detector distance, however the exact depth of penetration of near-infrared light is not known [84]. For a number of applications there is little evidence yet to guarantee that the device truly interrogates the organ of interest. One of the concerns with these new applications is that changes in the oxygen status of non-vital organs may be a too sensitive marker for hemodynamic compromise and result in a large number of unnecessary interventions. Future work is needed to identify which of these applications are of benefit in clinical practice.

1.4 Commercially available NIRS devices

Figure 1.7: Commercially available NIRS devices measuring cerebral oxygen saturation.

Several NIRS devices for measuring cerebral oxygen saturation are commercially available (Fig. 1.7), three of which are FDA-approved: INVOS 5100 (Somanetics Corporation, Troy, MI, USA), Foresight (CAS Medical Systems, Branford, CT, USA) and Equanox 7600 (Nonin Medical Inc., Minneapolis, MN, USA). NIRO-200NX (Hamamatsu Phototonics Corp, Tokyo, Japan) is not FDA approved. Despite the identical basic technology using near-infrared wavelengths

to detect changes in the concentration of O_2Hb and HHb, there are several technical differences, which are summarized in table 1.2. NIRO employs the technique of Spatially Resolved Spectroscopy (SRS, multiple closely spaced detectors to measure light attenuation as a function of source-detector separation) to measure tissue oxygen saturation and change in hemoglobin. Independently of the SRS method, NIRO measures changes in concentration of O_2Hb, HHb and THb using the Modified Beer-Lambert method. INVOS, Foresight and Equanox use the Modified Beer-Lambert law to measure tissue oxygen saturation, and eliminate the contribution of extracerebral tissue by using the principle of Spatial Resolution (depth of photon penetration proportional to the source-detector separation). The NIRS devices also differ significantly in applied computational algorithms to derive oxygen saturation values. Metz et al. evaluated the effect of basic assumptions in the algorithm on the generated NIRS values, and demonstrated that slight differences in the assumptions made, and the tissue investigated, have a relevant influence on the final NIRS value [85]. Penetration depth could differ depending on the wavelength and intensity of the emitted light, the sensitivity of the light detector, and the spacing between the light emitter and light detectors. The different devices also have a variable sensitivity to extracranial tissue contamination [15]. Therefore the comparability between the different NIRS devices is not clear. Since no real reference value exists for rS_cO_2, it is not possible to state if one monitor is more valid than another.

Table 1.2: Technical specifications of NIRS devices

	NIRO 200NX	**INVOS 5100**	**Foresight**	**Equanox 7600**
Measurement items	TOI (%) nTHI ΔO_2Hb ΔHHb ΔTHb	rSO_2 (%)	$SctO_2$ (%)	rSO_2 (%)
Measurement methods	MBL SRS	MBL SR	MBL SR*	MBL SR
Light source	LED	LED	Laser	LED
Wavelengths (nm)	735,810, 850	730,810	690,778, 800,850	730,760, 810,880
Detectors spacing	n.a.	3 and 4 cm	1.5 and 5 cm	2 and 4 cm
Sensors	Reusable	Single use	Single use	Single use

TOI: Tissue Oxygenation Index, nTHI: normalized Tissue Hemoglobin Index (arbitrary unit), ΔO_2Hb: change in oxygenated hemoglobin (μmol/l), ΔHHb: change in deoxygenated hemoglobin (μmol/l), ΔTHb: change in total hemoglobin (μmol/l), rSO_2: regional oxygen saturation, $SctO_2$: cerebral tissue oxygen saturation, MBL: Modified Beer-Lambert law, SRS: Spatially Resolved Spectroscopy, SR: Spatial Resolution, LED: Light-emitting diode, n.a.: not applicable, *applied in the adult sensors only.

1.5 References

1. Pohl A, Cullen DJ. Cerebral ischemia during shoulder surgery in the upright position: a case series. J Clin Anesth 2005; 17: 463-9
2. Shepherd SJ, Pearse RM. Role of central and mixed venous oxygen saturation measurement in perioperative care. Anesthesiology 2009; 111: 649-56
3. Brazy JE, Lewis DV, Mitnick MH, Jobsis vander Vliet FF. Noninvasive monitoring of cerebral oxygenation in preterm infants: preliminary observations. Pediatrics 1985; 75: 217-25
4. Schwarz G, Litscher G, Kleinert R, Jobstmann R. Cerebral oximetry in dead subjects. J Neurosurg Anesthesiol 1996; 8: 189-93
5. Litscher G, Schwarz G. Transcranial cerebral oximetry - is it clinically useless at this moment to interpret absolute values obtained by the INVOS 3100 cerebral oximeter? Biomed Tech 1997; 42: 74-7
6. von Vierordt K. Die quantative Spektranalyse in ihrer Anwendung auf Physiologie. Chemie und Technologie, H. Laupp, Tubingen, Germany, 1876.
7. Matthes K, Gross F. Fortlaufende Registrierung der Lichtabsorption des Blutes inzwer verschiedenen Spectralbezirken. Arch Exp Pathol Pharmacol 1939; 191: 381-90
8. Milliken GA. The oximeter: an instrument for measuring continuously oxygen-saturation of arterial blood in man. Rev Sci Instrum 1942; 13: 434-44
9. Jobsis FF. Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. Science 1977; 198: 1264-7
10. Wahr JA, Tremper KK, Samra S, Delpy DT. Near-infrared spectroscopy: theory and applications. J Cardiothorac Vasc Anesth 1996; 10: 406-18
11. Kakihana Y, Matsunaga A, Yasuda T, Imabayashi T. Brain oxymetry in the operating room: current status and future directions with particular regard to cytochrome oxidase. J Biomed Opt 2008; 13: 033001 1-14
12. Kishi K, Kawaguchi M, Yoshitani K, Nagahata T, Furuya H. Influence of patient variables and sensor location on regional cerebral oxygen saturation measured by INVOS 4100 near-infrared spectrophotometers. J Neurosurg Anesthesiol 2003; 15: 302-6
13. Duncan A, Meek JH, Clemence M, et al. Optical pathlength measurements on adult head, calf and forearm and the head of the newborn infant using phase resolved optical spectroscopy. Phys Med Biol 1995; 40: 295-304

14. Samra SK, Stanley JC, Zelenock GB, Dorje P. An assessment of contributions made by extracranial tissues during cerebral oximetry. J Neurosurg Anesthesiol 1999; 11: 1-5
15. Davie SN, Grocott HP. Impact of extracranial contamination on regional cerebral oxygen saturation: a comparison of three cerebral oximetry technologies. Anesthesiology 2012; 116: 834-40
16. Ito H, Kanno I, Fukuda H. Human cerebral circulation: positron emission tomography studies. Ann Nucl Med 2005; 19: 65-74
17. Kalmar AF, Foubert L, Hendrickx JF, et al. Influence of steep Trendelenburg position and CO2 pneumoperitoneum on cardiovascular, cerebrovascular, and respiratory homeostasis during robotic prostatectomy. Br J Anaesth 2010; 104: 433-9
18. Rigamonti A, Scandroglio M, Minicucci F, Magrin S, Carozzo A, Casati A. A clinical evaluation of near-infrared cerebral oximetry in the awake patient to monitor cerebral perfusion during carotid endarterectomy. J Clin Anesth 2005; 17: 426-30
19. Abdul-Khaliq H, Troitzsch D, Berger F, Lange PE. Comparison of regional transcranial oximetry with NIRS and jugular venous bulb oxygen saturation. Biomed Tech (Berl) 2000; 45: 328-32
20. Kim MB, Ward DS, Cartwright CR, Kolano J, Chlebowski S, Henson LC. Estimation of jugular venous O2 saturation from cerebral oximetry or arterial O2 saturation during isocapnic hypoxia. J Clin Monit Comput 2000; 16: 191-9
21. Nagdyman N, Ewert P, Peters B, Miera O, Fleck T, Berger F. Comparison of different near-infrared spectroscopic cerebral oxygenation indices with central venous and jugular venous oxygenation saturation in children. Paediatr Anaesth 2008; 18: 160-6
22. Daubeney PE, Pilkington SN, Janke E, Charlton GA, Smith DC, Webber SA. Cerebral oxygenation measured by near-infrared spectroscopy: comparison with jugular bulb oximetry. Ann Thorac Surg 1996; 61: 930-4
23. Beards SC, Yule S, Kassner A, Jackson A. Anatomical variation of cerebral venous drainage: The theoretical effect in jugular bulb blood samples. Anaesthesia 1998; 53: 627-33
24. Edmonds HL, Jr., Ganzel BL, Austin EH, 3rd. Cerebral oximetry for cardiac and vascular surgery. Semin Cardiothorac Vasc Anesth 2004; 8: 147-66

25. Kurth CD, Levy WJ, McCann J. Near-infrared spectroscopy cerebral oxygen saturation thresholds for hypoxia-ischemia in piglets. J Cereb Blood Flow Metab 2002; 22: 335-41
26. Hou X, Ding H, Teng Y, Zhou C, Tang X, Li S. Research on the relationship between brain anoxia at different regional oxygen saturations and brain damage using near-infrared spectroscopy. Physiol Meas 2007; 28: 1251-65
27. Kurth CD, McCann JC, Wu J, Miles L, Loepke AW. Cerebral oxygen saturation-time threshold for hypoxic-ischemic injury in piglets. Anesth Analg 2009; 108: 1268-77
28. Dent CL, Spaeth JP, Jones BV, Schwartz SM, Glauser TA, Hallinan B, Pearl JM, Khoury PR, Kurth CD. Brain magnetic resonance imaging abnormalities after the Norwood procedure using regional cerebral perfusion. J Thorac Cardiovasc Surg 2006; 131: 190-7
29. Slater JP, Guarino T, Stack J, et al. Cerebral oxygen desaturation predicts cognitive decline and longer hospital stay after cardiac surgery. Ann Thorac Surg 2009; 87: 36-44
30. Drummond JC. The lower limit of autoregulation: time to revise our thinking? Anesthesiology 1997; 86: 1431-3
31. Moerman A, De Hert S. Are cerebral oximeters designed to measure ambient light? Br J Anaesth 2011; 106: 753-5
32. Orihashi K, Sueda T, Okada K, Imai K. Malposition of selective cerebral perfusion catheter is not a rare event. Eur J Cardiothorac Surg 2005; 27: 644-8
33. Torella F, Haynes SL, McCollum CN. Cerebral and peripheral oxygen saturation during red cell transfusion. J Surg Res 2003; 110: 217-21
34. Torella F, McCollum CN. Regional haemoglobin oxygen saturation during surgical haemorrhage. Minerva Med 2004; 95: 461-7
35. Raj A, Bertolone SJ, Mangold S, Edmonds HL, Jr. Assessment of cerebral tissue oxygenation in patients with sickle cell disease: effect of transfusion therapy. J Pediatr Hematol Oncol 2004; 26: 279-83
36. Marik PE, Sibbald WJ. Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. JAMA 1993; 269: 3024-9
37. Brian JE, Jr. Carbon dioxide and the cerebral circulation. Anesthesiology 1998; 88: 1365-86
38. Dagal A, Lam AM. Cerebral autoregulation and anesthesia. Curr Opin Anaesthesiol 2009; 22: 547-52

39. Joshi B, Brady K, Lee J, et al. Impaired autoregulation of cerebral blood flow during rewarming from hypothermic cardiopulmonary bypass and its potential association with stroke. Anesth Analg 2010; 110: 321-8
40. Brady KM, Lee JK, Kibler KK, et al. Continuous time-domain analysis of cerebrovascular autoregulation using near-infrared spectroscopy. Stroke 2007; 38: 2818-25
41. Steiner LA, Pfister D, Strebel SP, Radolovich D, Smielewski P, Czosnyka M. Near-infrared spectroscopy can monitor dynamic cerebral autoregulation in adults. Neurocrit Care 2009; 10: 122-8
42. Brady K, Joshi B, Zweifel C, Smielewski P, Czosnyka M, Easley RB, Hogue CW Jr. Real-time continuous monitoring of cerebral blood flow autoregulation using near-infrared spectroscopy in patients undergoing cardiopulmonary bypass. Stroke 2010; 41: 1951-6
43. Buchner K, Meixensberger J, Dings J, Roosen K. Near-infrared spectroscopy - not useful to monitor cerebral oxygenation after severe brain injury. Zentralbl Neurochir 2000; 61: 69-73
44. Damian MS, Schlosser R. Bilateral near infrared spectroscopy in space-occupying middle cerebral artery stroke. Neurocrit Care 2007; 6: 165-73
45. Maeda H, Fukita K, Oritani S, Ishida K, Zhu B.L. Evaluation of post-mortem oxymetry with reference to the causes of death. Forensic Sci Int 1997; 87: 201-10
46. Bhatia R, Hampton T, Malde S, Kandala NB, Muammar M, Deasy N, Strong A. The application of near-infrared oximetry to cerebral monitoring during aneurysm embolization: a comparison with intraprocedural angiography. J Neurosurg Anesthesiol 2007; 19: 97-104
47. Mazzeo AT, Di Pasquale R, Settineri N, Bottari G, Granata F, Farago G, Pitrone A, Longo M, Santamaria LB. Usefulness and limits of near infrared spectroscopy monitoring during endovascular neuroradiologic procedures. Minerva Anestesiol 2012; 78: 34-45
48. Menache CC, du Plessis AJ, Wessel DL, Jonas RA, Newburger JW. Current incidence of acute neurologic complications after open-heart operations in children. Ann Thorac Surg 2002; 73: 1752-8
49. Newman MF, Kirchner JL, Phillips-Bute B, et al. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. N Engl J Med 2001; 344: 395-402
50. Sakamoto T, Duebener LF, Laussen PC, Jonas RA. Cerebral ischemia caused by obstructed superior vena cava cannula is detected by near-infrared spectroscopy. J Cardiothorac Vasc Anesth 2004; 18: 293-303

51. Han SH, Kim CS, Lim C, Kim WH. Obstruction of the superior vena cava cannula detected by desaturation of the cerebral oximeter. J Cardiothorac Vasc Anesth 2005; 19: 420-1
52. Gottlieb EA, Fraser CD Jr., Andropoulos DB, Diaz LK. Bilateral monitoring of cerebral oxygen saturation results in recognition of aortic cannula malposition during pediatric congenital heart surgery. Paediatr Anaesth 2006; 16: 787-9
53. Hoffman GM. Neurologic monitoring on cardiopulmonary bypass: what are we obligated to do? Ann Thorac Surg 2006; 81: S2373-80
54. Kussman BD, Wypij D, DiNardo JA, et al. Cerebral oximetry during infant cardiac surgery: evaluation and relationship to early postoperative outcome. Anesth Analg 2009; 108: 1122–31
55. Yao FS, Tseng CC, Ho CY, Levin SK, Illner P. Cerebral oxygen desaturation is associated with early postoperative neuropsychological dysfunction in patients undergoing cardiac surgery. J Cardiothorac Vasc Anesth 2004; 18: 552-8
56. Olsson C, Thelin S. Regional cerebral saturation monitoring with near-infrared spectroscopy during selective antegrade cerebral perfusion: diagnostic performance and relationship to postoperative stroke. J Thorac Cardiovasc Surg 2006; 131: 371-9
57. Orihashi K, Sueda T, Okada K, Imai K. Near-infrared spectroscopy for monitoring cerebral ischemia during selective cerebral perfusion. Eur J Cardiothorac Surg 2004; 26: 907-11
58. Hong SW, Shim JK, Choi YS, Kim DH, Chang BC, Kwak YL. Prediction of cognitive dysfunction and patients' outcome following valvular heart surgery and the role of cerebral oximetry. Eur J Cardiothorac Surg 2008; 33: 560-5
59. Goldman S, Sutter F, Ferdinand F, Trace C. Optimizing intraoperative cerebral oxygen delivery using noninvasive cerebral oximetry decreases the incidence of stroke for cardiac surgical patients. Heart Surg Forum 2004; 7: E376-81
60. Murkin JM, Adams SJ, Novick RJ, et al. Monitoring brain oxygen saturation during coronary bypass surgery: a randomized, prospective study. Anesth Analg 2007; 104: 51-8

61. Moritz S, Kasprzak P, Arlt M, Taeger K, Metz C. Accuracy of cerebral monitoring in detecting cerebral ischemia during carotid endarterectomy: a comparison of transcranial Doppler sonography, near-infrared spectroscopy, stump pressure, and somatosensory evoked potentials. Anesthesiology 2007; 107: 563-9
62. Pennekamp CW, Bots ML, Kappelle LJ, Moll FL, de Borst GJ. The Value of Near-Infrared Spectroscopy Measured Cerebral Oximetry During Carotid Endarterectomy in Perioperative Stroke Prevention. A Review. Eur J Vasc Endovasc Surg 2009; 38: 539-45
63. Samra SK, Dy EA, Welch K, Dorje P, Zelenock GB, Stanley JC. Evaluation of a cerebral oximeter as a monitor of cerebral ischemia during carotid endarterectomy. Anesthesiology 2000; 93: 964-70
64. Stilo F, Spinelli F, Martelli E, et al. The sensibility and specificity of Cerebral Oximetry, measured by INVOS-4100, in patients undergoing carotid endarterectomy compared with awake testing. Minerva Anestesiol 2012; 78: 1126-35
65. Moller JT, Cluitmans P, Rasmussen LS, et al. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. Lancet 1998; 351: 857-61
66. Casati A, Fanelli G, Pietropaoli P, et al. Continuous monitoring of cerebral oxygen saturation in elderly patients undergoing major abdominal surgery minimizes brain exposure to potential hypoxia. Anesth Analg 2005; 101: 740-7
67. Hoffman GM, Ghanayem NS, Tweddell JS. Noninvasive assessment of cardiac output. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 2005; 8: 12-21
68. Chakravarti SB, Mittnacht AJ, Katz JC, Nguyen K, Joashi U, Srivastava S. Multisite near-infrared spectroscopy predicts elevated blood lactate level in children after cardiac surgery. J Cardiothorac Vasc Anesth 2009; 23: 663-7
69. Rao RP, Danduran MJ, Loomba RS, Dixon JE, Hoffman GM. Near-infrared spectroscopic monitoring during cardiopulmonary exercise testing detects anaerobic threshold. Pediatr Cardiol 2012; 33: 791-6
70. Ortmann LA, Fontenot EE, Seib PM, Eble BK, Brown R, Bhutta AT. Use of near-infrared spectroscopy for estimation of renal oxygenation in children with heart disease. Pediatr Cardiol 2011; 32: 748-53

71. Owens GE, King K, Gurney JG, Charpie JR. Low renal oximetry correlates with acute kidney injury after infant cardiac surgery. Pediatr Cardiol 2011; 32: 183-8
72. Weiss M, Schulz G, Fasnacht M, et al. Transcutaneously measured near-infrared spectroscopic liver tissue oxygenation does not correlate with hepatic venous oxygenation in children. Can J Anaesth 2002; 49: 824-9
73. Mitsuta H, Ohdan H, Fudaba Y, et al. Near-infrared spectroscopic analysis of hemodynamics and mitochondrial redox in right lobe grafts in living-donor liver transplantation. Am J Transplant 2006; 6: 797-805
74. Kaufman J, Almodovar MC, Zuk J, Friesen RH. Correlation of abdominal site near-infrared spectroscopy with gastric tonometry in infants following surgery for congenital heart disease. Pediatr Crit Care Med 2008; 9: 62-8
75. Cohn SM. Near-Infrared Spectroscopy: Potential Clinical Benefits in Surgery. J Am Coll Surg 2007; 205: 322-32
76. Creteur J. Muscle StO2 in critically ill patients. Curr Opin Crit Care 2008; 14: 361-6
77. Fortune PM, Wagstaff M, Petros AJ. Cerebro-splanchnic oxygenation ratio (CSOR) using near infrared spectroscopy may be able to predict splanchnic ischaemia in neonates. Intensive Care Med 2001; 27: 1401-7
78. Stapleton GE, Eble BK, Dickerson HA, Andropoulos DB, Chang AC. Mesenteric oxygen desaturation in an infant with congenital heart disease and necrotizing enterocolitis. Tex Heart Inst J 2007; 34: 442-4
79. Tobias JD, Hoernschemeyer DG. Near-infrared spectroscopy identifies compartment syndrome in an infant. J Pediatr Orthop 2007; 27: 311-3
80. Vardi M, Nini A. Near-infrared spectroscopy for evaluation of peripheral vascular disease. A systematic review of literature. Eur J Vasc Endovasc Surg 2008; 35: 68-74
81. Repez A, Oroszy D, Arnez ZM. Continuous postoperative monitoring of cutaneous free flaps using near infrared spectroscopy. J Plast Reconstr Aesthet Surg 2008; 61: 71-7
82. Whitaker IS, Pratt GF, Rozen WM, et al. Near infrared spectroscopy for monitoring flap viability following breast reconstruction. J Reconstr Microsurg 2012; 28: 149-54
83. Moerman A, Van Herzeele I, Vanpeteghem C, Vermassen F, François K, Wouters P. Near-Infrared Spectroscopy for Monitoring Spinal Cord Ischemia during Hybrid Thoracoabdominal Aortic Aneurysm Repair. J Endovasc Ther 2011; 18: 91-5

84. Mansouri C, L'Huillier JP, Kashou NH, Humeau A. Depth sensitivity analysis of functional near-infrared spectroscopy measurement using three-dimensional Monte Carlo modelling-based magnetic resonance imaging. Lasers Med Sci 2010; 25: 431-8
85. Metz AJ, Biallas M, Jenny C, Muehlemann T, Wolf M. The effect of basic assumptions on the tissue oxygen saturation value of near infrared spectroscopy. Adv Exp Med Biol 2013; 765: 169-75

Chapter 2

Objectives of the research

The present work aims to address the applicability of NIRS for the detection of perioperative compromized tissue perfusion, and explores its potential to assess the physiological determinants of tissue oxygen saturation in different patients groups. The ultimate goal is the optimization of patient care in daily anesthesia practice.

Chapter 1 briefly reviews the basic principles of operation, the inherent limitations of the technology and the clinical data that have been acquired with NIRS monitoring in the broad field of acute clinical medicine.

Chapter 2 describes the objectives of the research project.

Chapter 3 discusses the use of NIRS monitoring for detection of *global* cerebral perfusion deficit in patients at high risk for cerebrovascular incidents, and also in patients at low risk for cerebrovascular incidents, but undergoing surgery with a relatively high risk for adverse neurological outcome. Physiological changes that were associated with cerebral oxygen desaturation were identified.

Chapter 4 reports the applicability of NIRS to monitor *regional* organ perfusion. The use of NIRS is examined during aortic cross-clamping, where the perfusion of the left brain, the peripheral tissues, and the spinal cord has been temporarily interrupted. Determinants of oxygenation debt are described.

Chapter 5 evaluates the feasibility of NIRS to provide a non-invasive estimate of systemic venous oxygen saturation.

Chapter 6 explores the impact of different physiological determinants of tissue oxygen saturation on cerebral and whole body oxygen saturation.

Chapter 7 discusses the main findings and conclusions reported in this thesis.

Chapter 8 summarizes future perspectives and proposals for further research.

Chapter 3

NIRS for monitoring global cerebral perfusion

3.1 Background

Despite its vital importance, the human brain remains a poorly monitored organ in clinical anesthesia. Several clinical conditions routinely encountered in our daily practice have the potential to disrupt the balance between the cerebral oxygen supply and demand, exposing to the risk of adverse postoperative neurological outcome. These alterations in oxygen balance might remain unnoticed if we do not specifically monitor it.

Central nervous system monitoring is technically difficult and demanding, and therefore its use is not commonly incorporated into routine anesthesia monitoring. Direct monitoring of brain oxygenation can be obtained by direct measurement of brain tissue oxygen tension (P_tO_2), or by monitoring the jugular venous oxygen saturation ($S_{jv}O_2$). Limitations of these techniques are that P_tO_2 is a focal measurement and therefore identification of ischemia is crucially dependent on the position of the probe, whereas $S_{jv}O_2$ is a global measurement which may miss regional ischemia. Furthermore, these

techniques are invasive, may be associated with severe complications, and are not usually available outside specialist centres. Transcranial doppler ultrasonography (TCD) allows a non-invasive assessment of the adequacy of cerebral blood flow by measuring blood flow velocity in the proximal portions of large intracranial arteries. However, its use is technically demanding and operator dependent, and unless the diameter of the vessel is established by some other means it is not possible to determine the actual blood flow. Electrical activity in the brain can be measured non-invasively with electroencephalography (EEG), allowing detection of brain ischemia. However, EEG is difficult to interpret by non-specialists. Moreover, neither TCD nor EEG provide direct information on the adequacy of brain tissue oxygenation.

There is therefore the need for a non-invasive, easy to use, bedside monitor that provides a reliable and real-time assessment of alterations in the cerebral oxygen balance. NIRS provides a non-invasive, continuous method to measure cerebral oxygen saturation. This technique has been demonstrated repeatedly to provide an early warning sign of cerebral hypoperfusion during procedures with high risk for adverse neurological outcomes.

3.2 Objective

The aim of the present studies was to evaluate NIRS monitoring in patients where global cerebral perfusion might be compromized and to identify the physiological changes that were associated with cerebral oxygen desaturation. Our study population comprised patients undergoing shoulder surgery in the beach chair position, because cases of dramatic neurological outcome in relatively healthy patients undergoing this surgery, questioned the adequacy of brain perfusion during beach chair position. We also evaluated NIRS monitoring in a patient with moyamoya disease, in whom this underlying pathology severely compromizes blood supply to the brain.

3.3 NIRS monitoring in beach chair position

Cerebral oxygen desaturation during shoulder surgery in beach chair position. A. Moerman, S. De Hert, T. Jacobs, L. De Wilde, P. Wouters. Eur J Anaesthesiol 2012; 29: 82-87

Abstract

Context. Cases of ischemic brain damage have been reported in relatively healthy patients undergoing shoulder surgery in the beach chair position. Unrecognized cerebral hypoperfusion may have contributed to these catastrophic events, indicating that routine anesthesia monitoring may not suffice. Near-infrared spectroscopy (NIRS) provides a non-invasive, continuous method to measure regional cerebral oxygen saturation (rS_cO_2).

Objectives. The aim of this clinical investigation was to evaluate the prevalence of regional cerebral oxygen desaturation in patients undergoing shoulder surgery in the upright position during routine anesthesia management. We also aimed to identify some causal factors for cerebral desaturation.

Design. Prospective, observational, blinded study.

Setting. University hospital. Observation period from 19 05 2008 to 26 08 2008.

Patients. Twenty consecutive adult patients presenting for elective shoulder surgery under general anesthesia in the beach chair position were enrolled. Patients with clinically apparent neurological or cognitive dysfunction were excluded.

Interventions. Routine anesthesia management and standard monitoring were used. The responsible anesthesiologist was blinded to the rS_cO_2 data and was not informed about the purpose of the study.

Main outcome measures. The prevalence of cerebral oxygen desaturation was measured.

Results. With beach chair positioning, rS_cO_2 decreased significantly

from 79 ± 9 to 57 ± 9% on the left side and from 77 ± 10 to 59 ± 10% on the right side (P<0.001). A relative decrease in rS_cO_2 of more than 20% occurred in 80% of patients when the beach chair position was adopted. Postural decreases in cerebral oxygenation were related to blood pressure (r=0.60, P=0.007) and end-tidal carbon dioxide concentration (r=0.47, P=0.035).
Conclusion. The high prevalence of significant cerebral oxygen desaturation during shoulder surgery in the upright position underlines the need for close monitoring. NIRS might constitute a valuable technique to detect cerebral hypoperfusion in this high-risk group of patients.

3.3.1 Introduction

A series of case reports reporting dramatic adverse neurological outcomes in patients after shoulder surgery in the upright position have recently alarmed the surgical and anesthesic communities. The complications ranged from cranial nerve injury [1] to visual loss [2] and cerebral infarction [3,4], occurring in relatively healthy middle-aged patients considered to be at low risk for cerebrovascular incidents. Although the exact pathogenesis of these events remains largely unexplained, it has been assumed that the specific positioning of the patient for shoulder surgery, that is, the beach chair position, may be responsible for these complications. The beach chair position may be associated with malrotation of the head and result in mechanical obstruction of the cerebral vessels. It has also been suggested that such positioning may induce unfavourable hemodynamic alterations with cerebral tissue hypoperfusion related to the gravitational effect of upright tilting. Finally, management of shoulder surgery often includes general anesthesia with controlled hypotension, which may further compromize cerebral blood flow. These reports mandate that more attention should be paid to the effects of patient positioning on cerebral perfusion and that in these circumstances, routine anesthesia monitoring may not suffice.

Near-infrared spectroscopy (NIRS) provides a non-invasive, continuous method of measuring cerebral tissue oxygen saturation. This technique has been demonstrated repeatedly to provide an early warning sign of cerebral hypoperfusion during procedures with a high risk of adverse neurological outcomes [5]. Recent reports have suggested that cerebral oximetry monitoring with NIRS may be a useful indicator of cerebral hypoperfusion during shoulder surgery in the beach chair position [6,7].

The aim of this prospective, observational, blinded study was to evaluate the prevalence of regional cerebral oxygen desaturation in patients undergoing shoulder surgery in the beach chair position when routine anesthesia management and standard monitoring are used. We also aimed to identify potential physiological changes that might be associated with postural cerebral oxygen desaturation.

3.3.2 Methods

Ethical approval for this observational study (Ethical Committee N° 2008/191) was provided by the Ethical Committee of the Ghent University Hospital, Gent, Belgium (Chairperson Prof Dr R. Rubens) on 30 April 2008. After written informed consent, 20 consecutive unpremedicated adult patients scheduled for elective shoulder surgery in the beach chair position were included. Exclusion criteria were clinically apparent neurological or cognitive dysfunction.

Standard monitoring was used throughout the procedure, including ECG, pulse oximetry (S_pO_2), end-tidal oxygen, carbon dioxide and sevoflurane concentrations and non-invasive blood pressure measurement (AS3; Datex, Helsinki, Finland). Blood pressure measurements were performed at 3-min intervals with a non-invasive cuff placed on the arm opposite the operated side. Disposable NIRS sensors were applied on each side of the forehead for continuous registration of the regional cerebral oxygen saturation (rS_cO_2) of the corresponding brain hemisphere (INVOS 5100; Somanetics Corporation, Troy, MI, USA).

Anesthesia was induced with sufentanil (0.1-0.3 μg/kg), propofol (2-3 mg/kg) and cisatracurium (0.1 mg/kg). Anesthesia was maintained with sevoflurane (1.5-2.5% end-tidal concentration) in an oxygen/air mixture (50% oxygen) and additional doses of sufentanil (0.1-0.2 μg/kg), if needed. All patients were raised to a 60- to 70-degree sitting position. The head of the patient was fixed in the mid-line. Management of anesthesia and hemodynamics were left completely to the discretion of the attending anesthesiologist, who was blinded to the rS_cO_2 data, and who also was not informed about the purpose of the study. Routine clinical practice was used to maintain blood pressure. No deliberate hypotension was used. Systolic arterial pressure (SAP) of <80 mmHg or heart rate of <50 beats/min were usually treated.

Heart rate, non-invasive blood pressure, in- and end-expiratory gas tensions, S_pO_2 and bilateral rS_cO_2 were recorded continuously with RUGLOOP (Demed, Temse, Belgium). Blood loss was estimated and types and volumes of all fluids administered were recorded, as well as doses of all drugs given. At the postoperative visit by the responsible anesthesiologist on the evening of surgery, the patient was assessed neurologically with a gross motor and sensory neurological evaluation and a gross cognitive evaluation (orientation in time and space, recall of name, date of birth, and address). Any side-effects were recorded.

The rS_cO_2 values were compared at different time moments (awake, last value before position change from supine to upright position, 5 min after position change to beach chair, and at the minimum rS_cO_2). Changes in cerebral oxygen saturation were described in absolute terms (absolute rS_cO_2 <50%) and in relative terms (>20% decrease in rS_cO_2 compared to the value before position change). A rS_cO_2 desaturation score was calculated by multiplying rS_cO_2 below 50% with the duration of this event (in seconds) [8]. Hence, the rS_cO_2 desaturation score generated is an area under the curve measurement, which accounts for both severity and duration of desaturation.

Sample size calculation was based on the assumption that a relative decrease in saturation of 20% (the smallest effect to be clinically important [9]) would be detected. Based on the study of Kim et al. [10], a mean and standard deviation (SD) of 71% and 6% respectively were chosen. For a power of 0.8 and an α of 0.05, a sample size of 20 patients was calculated to be appropriate to detect a clinically relevant decrease in cerebral oxygen saturation. Statistical analysis was performed using the statistical software PASW Statistics 18 (SPSS Inc., Chicago, IL, USA). Data were tested for normal distribution using the Shapiro-Wilk test. Normally distributed continuous data are presented as mean ± SD.

The rS_cO_2 values at different time points were compared using an analysis of variance for repeated measurements (ANOVA). Post-test pairwise comparison was performed with the Tukey test. Possible relationships between rS_cO_2 and physiological variables were analyzed using linear regression analysis and quantified using the Spearman's correlation tests. A value of $P<0.05$ was considered statistically significant.

3.3.3 Results

Patient demographics are presented in Table 3.1. One patient had undergone a carotid endarterectomy 4 years earlier, and another patient suffered from a transient ischemic attack (TIA) 8 years earlier; neither patient had any residual symptoms.

Table 3.2 shows details of surgery and anesthesia. All patients received cristalloid solutions. If more than 1000 ml of cristalloids were needed, colloids were administered (four patients). The surgical procedures did not necessitate the use of deliberate hypotension and, therefore, routine clinical practice was used. Seven patients received ephedrine (5-10 mg) and one patient required phenylephrine 100 μg to correct a SAP of <80 mmHg. Three patients needed atropine 0.5 mg for bradycardia (heart rate <50 beats/min).

Table 3.1: Patient demographics

Sex, male/female (n)	5/15
Age, y	60.2 ± 13.4
Weight, kg	68.6 ± 17.6
Body mass index, kg/m^2	25.2 ± 4.8
Medical history, n	Hypertension: 11
	Neurological history: 2
	Cardiovascular medication: 11

Data are expressed as mean ± SD

Table 3.2: Details about surgery and anesthesia

Duration beach chair, min	78 ± 45 [20 - 151]
Blood loss, ml	186 ± 277 [5 - 1000]
Fluids before beach chair, ml	187 ± 186 [50 - 650]
Fluids during beach chair, ml	625 ± 444 [150 - 2100]
Sufentanil dose, μg/kg	0.24 ± 0.07 [0.1 - 0.38]
Drug use, n	Ephedrine: 7
	Atropine: 3
	Phenylephrine: 1
	Urapidil: 1

Data are expressed as mean ± SD [range]

The postural changes in cerebral oxygen saturation and blood pressure are shown in Table 3.3. When the beach chair position was adopted, rS_cO_2 decreased significantly from 79 ± 9% to 57 ± 9% on the left side and from 77 ± 10% to 59 ± 10% on the right side ($P<0.001$ for both sides compared with baseline, no significant difference between sides). A relative decrease in rS_cO_2 of >20% occurred in 80% of patients when the beach chair position was adopted. In 30% of patients, rS_cO_2 decreased to an absolute value below 50%. Desaturation scores ranged from 0 to 725%.sec (mean ± SD: 89 ± 221%.sec) on the left side and from 0 to 3360%.sec (178 ±

Table 3.3: Postural changes in cerebral oxygen saturation and in blood pressure

	LeftrS_cO_2 (%)	**RightrS_cO_2** (%)	**SAP/DAP** (mmHg)
Awake	69 ± 6	68 ± 6	156 ± 29/76 ± 20
Before position change	79 ± 9	77 ± 10	130 ± 32*/67 ± 20
5 min position change	65 ± 10‡	66 ± 11‡	110 ± 24*‡/64 ± 24
Minimum value	57 ± 9*‡	59 ± 10*‡	84 ± 22*‡/46 ± 11*‡

Data are expressed as mean ± SD. rS_cO_2: regional cerebral oxygen saturation. *p<0.05 vs awake value. ‡ p<0.05 *vs* value before position change.

750%.sec) on the right side. One patient had a desaturation score of more than 3000%.sec.

The patient who had undergone carotid endarterectomy had a maximum relative decrease in rS_cO_2 of 12.7% (minimum rS_cO_2 55%). The patient with a history of TIA had a relative decrease of 30.4% (minimum rS_cO_2 64%).

At all time points, rS_cO_2 was negatively correlated with age (Fig. 3.1 (upper panel)), but the magnitude of the decrease in rS_cO_2 with position change was independent of age (Fig. 3.1 (lower panel)).

Before the position change, there was a positive correlation between rS_cO_2 and end-tidal carbon dioxide ($EtCO_2$) (r = 0.53, P = 0.016). No correlation was found between rS_cO_2 and SAP (r = 0.28, P = 0.086). Five minutes after the change in position, a positive correlation was found between rS_cO_2 and $EtCO_2$ (r = 0.56, P = 0.013), but no correlation was found between rS_cO_2 and SAP (r = 0.29, P = 0.076). At the minimum rS_cO_2, there were positive correlations between rS_cO_2 and $EtCO_2$ (r = 0.47, P = 0.035) and between rS_cO_2 and SAP (r = 0.60, P = 0.007).

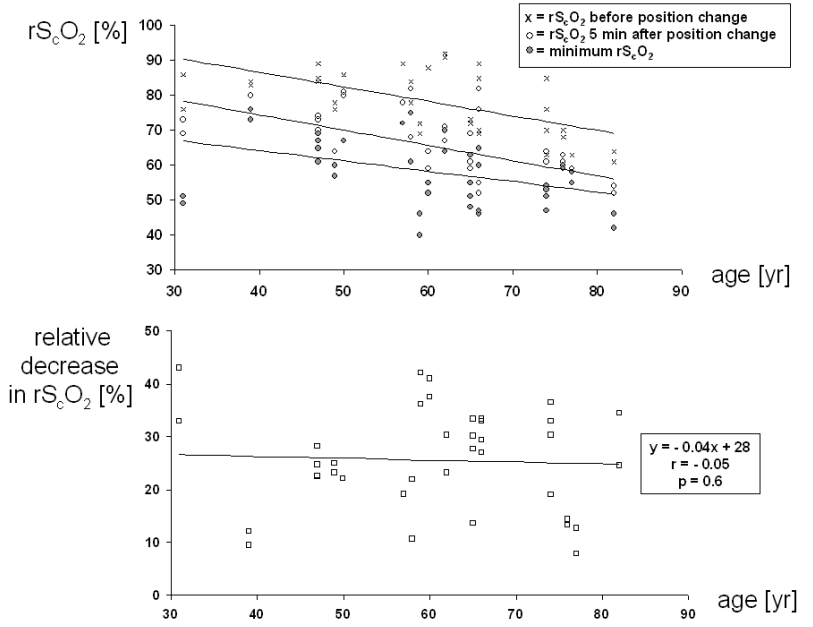

Figure 3.1: Upper panel: Correlation of age with regional cerebral oxygen saturation (rS_cO_2) before position change (crosslets) (y=-0.4x+103; r=-0.59; P<0.001), 5 minutes after position change (open circles) (y =-0.4x+92; r=-0.54; P<0.001), and minimum rS_cO_2 (closed circles) (y=-0.3x+76; r=-0.41; P=0.033). Lower panel: Correlation of age with magnitude of rS_cO_2 decrease after change to beach chair position.

A representative case is shown in Fig. 3.2. The rS_cO_2 decreased promptly when the position was changed from supine to the beach chair position and immediately recovered when the supine position was restored. Changes in rS_cO_2 closely paralleled changes in blood pressure, which is also apparent from the effects of ephedrine.

None of the patients developed gross neurological or cognitive dysfunction postoperatively.

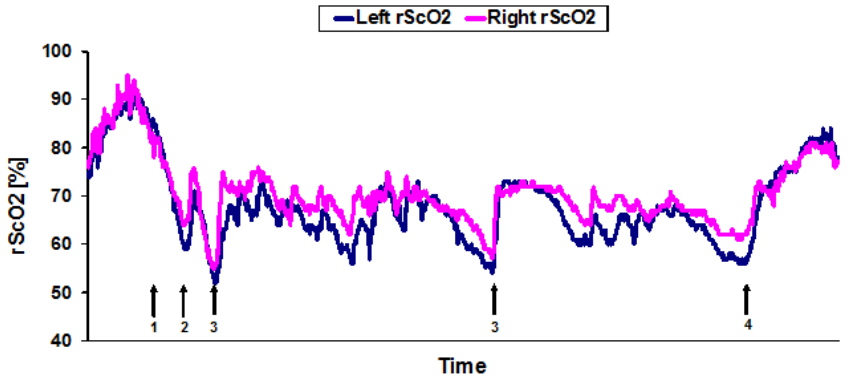

Figure 3.2: Representative case. Changes in regional cerebral oxygen saturation (rS_cO_2) at the start (1) and the end (4) of the beach chair position and after administration of atropine (2) and ephedrine (3).

3.3.4 Discussion

In the present study, we observed cerebral desaturation (a relative decrease in rS_cO_2 of >20%) in 80% of patients when an upright position was adopted during shoulder surgery. Postural decreases in cerebral oxygenation were consistent and related to blood pressure and $EtCO_2$.

Recently, three reports have described the value of NIRS in monitoring the adequacy of cerebral perfusion during shoulder surgery in the beach chair position. Fischer et al [6] reported a case showing causality between rS_cO_2, mean arterial pressure (MAP) and $EtCO_2$. Murphy et al. [7] evaluated the incidence of cerebral desaturation during shoulder surgery in the beach chair position compared to the lateral decubitus position. They used standardized anesthetic management and aimed to optimize cerebral perfusion by maintaining MAP within 20% of baseline values and controlling $EtCO_2$ between 30 and 34 mmHg. When cerebral oxygen desaturation was observed, they used a predetermined management protocol to increase rS_cO_2.

In the study of Tange et al. [11], perioperative management included support stockings, fluid administration at a rate of 10 ml/kg/h throughout the study period, gradual head-up tilt position, and careful blood pressure management to maintain MAP above 60 mmHg. All these measures aimed to minimize the impact of position change. Our study is different in that the objective was to evaluate the actual prevalence of regional cerebral oxygen desaturation in patients undergoing surgery in the beach chair position when standard anesthesia management and routine anesthesia monitoring (which currently does not include cerebral oximetry) were employed. For this reason, anesthetic management was left to the discretion of the attending clinicians who did not participate in the study and were blinded to the rS_cO_2 data.

It is assumed that the upright position induces significant hemodynamic changes that may impair cerebral circulation. Compared to the supine position, adopting an upright position has been shown to decrease systolic and mean arterial pressure, stroke volume and cardiac output, inducing a cerebral blood flow decrease of 12% [12]. In conscious individuals, these effects are compensated for by an increase in systemic vascular resistance, but during anesthesia this autonomic response may be attenuated or blocked. The combination of the sitting position and general anesthesia may, therefore, be potentially deleterious to cerebral perfusion. Reports describing cerebral ischemia in the beach chair position have, therefore, stressed the risk of hypotension [13]. It is often suggested that a systemic MAP between 50 and 150 mmHg lies within the range of cerebral autoregulation and, therefore, guarantees adequate cerebral perfusion. However this assumption has been challenged. First, the concept of cerebral autoregulation is questioned, because there seems to be a considerable individual variability in the autoregulation limits [14]. Second, it has been claimed that blood pressure measured at the brachial artery may overestimate the pressure at the level of the brain when the sitting position is adopted. Some authors, there-

fore, propose an arithmetic correction of blood pressure to determine pressure at the level of the brain (1 mmHg for each 1.25 cm difference in height between the external meatus and the middle of the blood pressure cuff) [13]. Applying this assumption to the present study, the mean difference between the brain and the site of the blood pressure cuff on the arm of 31 ± 3 (24-38) cm, would overestimate arterial pressure at the level of the head by 24 ± 2 (18-29) mmHg. Third, cerebral perfusion pressure (CPP) depends not only on inflow pressure but also on outflow pressure: CPP = MAP- central venous pressure (CVP) or CPP = MAP- intracranial pressure (ICP) if ICP is more than CVP. In the upright position, the jugular veins either partly or fully collapse, and the vertebral venous plexus becomes the main pathway for venous drainage [12]. Flow through this plexus might be impeded during head rotation and head tilt.

Although intuitively one would suppose that older patients have an increased risk of cerebral desaturation, our data showed no difference in the response to position change with age, which is consistent with the results of Gatto et al. [15] and Edlow et al. [16].

The cerebral circulation is very responsive to changes in CO_2. In a patient with normal CO_2 reactivity, cerebral blood flow changes 1-2 ml/100g/min per mmHg change in CO_2 [17]. This was also clear in our study, which showed a lower rS_cO_2 with lower $EtCO_2$.

Given the positive correlations between rS_cO_2 and blood pressure and $EtCO_2$, a simple recommendation could be to avoid hypotension and low $EtCO_2$. The study by Tange et al. [11] demonstrated that, with appropriate measures, cerebral desaturation can be avoided. However, three caveats should be considered. First, the ability of the circulatory system to compensate for sudden position changes varies considerably between patients and is unpredictable. Second, if deliberate hypotension is required, the impact on cerebral perfusion is unknown unless specific monitoring is employed. Finally, the high prevalence of cerebral desaturation in this study, together with the dramatic case reports, indicate that there is a compelling need for

more wariness and for more specific monitoring. Due to the advantage of simple, continuous and non-invasive monitoring, NIRS could have the potential to optimize patient care in these situations.

Several limitations should be considered. First, because NIRS technology does not distinguish between arterial and venous hemoglobin saturation, changes in the proportion of cerebral arterial and venous blood volume may confound measurements [18]. Changes in body position affect both arterial and venous pressures and can alter the ratio of arterial to venous compartments in the cerebral circulation. The measured changes in rS_cO_2 in the upright position may, therefore, be a consequence of true changes in tissue oxygen tension, or may be the effect of the changes in the relative fractions of arterial and venous blood in the cerebral tissue. Real-time measurements of changes in cerebral blood flow using transcranial Doppler might be helpful in solving this question, but is difficult to establish properly during head-up table tilting and during surgical manipulation of the patient. Second, the prevalence of desaturation is dependent on the baseline value and the threshold used to define cerebral desaturation. In most clinical studies, a 20% reduction from awake values or an absolute decrease below 50% oxygen saturation is used as the threshold [9]. Slater et al. [8] also took the duration of desaturation into account by introducing the term 'desaturation score'. Third, the relevance of the changes in cerebral oxygenation parameters might be questioned because of the absence of gross postoperative neurological dysfunction. However, without extensive neurocognitive monitoring, subtle changes induced by cerebral hypoxia may go unnoticed until functional organ damage becomes evident. Several randomized controlled trials have demonstrated that detection and treatment of cerebral oxygen desaturation results in better clinical outcome [8, 19-21].

Finally, there is the interesting controversy with regard to the exact determination of CPP and its relationship with flow. The practice of correcting the blood pressure for position (raising the

transducer or adjusting arterial pressure estimation to allow for the height between the heart and the brain) is dictated by the assumption that the heart lifts the blood to the elevated brain without a corresponding and equivalent venous return limb. In a closed loop system, such as the intact circulation, there is a continuous and balanced fluid column and no net work is performed against the effect of gravity [22]. Therefore, as long as the hydrostatic gradient from the measurement site to the brain remains the same for inflow and outflow pressures, there is no significant flow related pressure drop between the measurement site and the brain [23]. Hence, there is no need for adjustment of pressure measurements if the assumption is correct that venous outflow depends only on the outflow pressure, although this does not take into account the more complex nature of the venous resistance and the possibility of venous collapse when assuming the upright position. Therefore, it has been proposed that the CPP formula should be adapted to take into account the effect of atmospheric pressure on the jugular veins. It has been suggested that measurement level adjustments are probably not necessary if CVP can be maintained above 18 mmHg [24].

In conclusion, the results of the present study showed an incidence of 80% of cerebral oxygen desaturation when the beach chair position was adopted in patients undergoing shoulder surgery. Together with the high prevalence of cerebral desaturation also found in other studies, this underlines the need for awareness of this problem and suggests the need for perioperative monitoring of cerebral tissue oxygenation in this type of surgery. Monitoring, of course, should not preclude all customary measures being taken to avoid an abrupt decrease in blood pressure with position change.

3.3.5 References

1. Boisseau N, Rabarijaona H, Grimaud D, Raucoules-Aimé M. Tapia's syndrome following shoulder surgery. Br J Anaesth 2002 ; 88: 869-70
2. Bhatti MT, Enneking FK. Visual loss and ophthalmoplegia after shoulder surgery. Anesth Analg 2003; 96: 899-902
3. Pohl A, Cullen DJ. Cerebral ischemia during shoulder surgery in the upright position: a case series. J Clin Anesth 2005; 17: 463-9
4. Verbrugge SJ, Klimek M, Klein J. A cerebral watershed infarction after general anaesthesia in a patient with increased anti-cardiolipin antibody level. Anaesthesist 2004; 53: 341-6
5. Casati A, Spreafico E, Putzu M, Fanelli G. New technology for non-invasive brain monitoring: continuous cerebral oximetry. Minerva Anestesiol 2006; 72: 605-25
6. Fischer GW, Torrillo TM, Weiner MM, Rosenblatt MA. The use of cerebral oximetry as a monitor of the adequacy of cerebral perfusion in a patient undergoing shoulder surgery in the beach chair position. Pain Pract 2009; 9: 304-7
7. Murphy GS, Szokol JW, Marymont JH et al. Cerebral oxygen desaturation events assessed by near-infrared spectroscopy during shoulder arthroscopy in the beach chair and lateral decubitus positions. Anesth Analg 2010; 111: 496-505
8. Slater JP, Guarino T, Stack J et al. Cerebral oxygen desaturation predicts cognitive decline and longer hospital stay after cardiac surgery. Ann Thorac Surg 2009; 87: 36-45
9. Edmonds HL Jr, Ganzel BL, Austin EH. Cerebral oximetry for cardiac and vascular surgery. Semin Cardiothorac Vasc Anesth 2004; 8: 147-66
10. Kim MB, Ward DS, Cartwright CR, Kolano J, Chlebowski S, Henson LC. Estimation of jugular venous O2 saturation from cerebral oximetry or arterial O2 saturation during isocapnic hypoxia. J Clin Monit Comput 2000; 16: 191-9
11. Tange K, Kinoshita H, Minonishi T et al. Cerebral oxygenation in the beach chair position before and during general anesthesia. Minerva Anestesiol 2010; 76: 485-90

12. Alperin N, Hushek SG, Lee SH, Sivaramakrishnan A, Lichtor T. MRI study of cerebral blood flow and CSF flow dynamics in an upright posture: the effect of posture on the intracranial compliance and pressure. Acta Neurochir 2005; 95: 177-81
13. Cullen DJ, Kirby RR. Beach chair position may decrease cerebral perfusion; catastrophic outcomes have occurred. APSF Newsletter 2007; 22: 25, 27
14. Drummond JC. The lower limit of autoregulation: time to revise our thinking? Anesthesiology 1997; 86: 1431-1433.
15. Gatto R, Hoffman W, Paisansathan C, Mantulin W, Gratton E, Charbel FT. Effect of age on brain oxygenation regulation during changes in position. J Neurosci Methods 2007; 164: 308-11
16. Edlow BL, Kim MN, Durduran T et al. The effects of healthy aging on cerebral hemodynamic responses to posture change. Physiol Meas 2010; 31: 477-95
17. Brian JE, Jr. Carbon dioxide and the cerebral circulation. Anesthesiology 1998; 88: 1365-86
18. Pollard V, Prough DS, DeMelo AE, Deyo DJ, Uchida T, Widman R. The influence of carbon dioxide and body position on near-infrared spectroscopic assessment of cerebral hemoglobin oxygen saturation. Anesth Analg 1996; 82: 278-87
19. Goldman S, Sutter F, Ferdinand F, Trace C. Optimizing intraoperative cerebral oxygen delivery using noninvasive cerebral oximetry decreases the incidence of stroke for cardiac surgical patients. Heart Surg Forum 2004; 7: E376-81
20. Casati A, Fanelli G, Pietropaoli P et al. Continuous monitoring of cerebral oxygen saturation in elderly patients undergoing major abdominal surgery minimizes brain exposure to potential hypoxia. Anesth Analg 2005; 101: 740-7
21. Murkin JM, Adams SJ, Novick RJ et al. Monitoring brain oxygen saturation during coronary bypass surgery: a randomized, prospective study. Anesth Analg 2007; 104: 51-8
22. Munis JR, Lozada LJ. Giraffes, siphons, and Starling resistors: cerebral

perfusion pressure revisited. J Neurosurg Anesthesiol 2000; 12: 290-6
23. Munis J. The problems of posture, pressure, and perfusion: cerebral perfusion pressure defined. APSF Newsletter 2008; 22: 82-3
24. Pranevicius M, Pranevicius O. Modified calculation of the cerebral perfusion pressure in a sitting position: jugular Starling resistor and related clinical implications. APSF Newsletter 2008; 23: 32-3

3.4 NIRS monitoring in moyamoya disease

Value of cerebral oxygen saturation monitoring during cardiopulmonary bypass in an adult patient with moyamoya disease. De Buysscher P, Moerman A, Bové T, De Pauw M, Wouters P, De Hert S. J Cardiothor Vasc Anesth 2013, http://dx.doi.org/10.1053/j.jvca.2011.11.002

Abstract
Purpose: To describe the use of near-infrared spectroscopy (NIRS) to identify and reverse cerebral ischemia in a patient in whom the maintenance of adequate cerebral perfusion during cardiopulmonary bypass (CPB) was jeopardized severely because of moyamoya disease.
Case report: In an adult patient with moyamoya disease undergoing mitral valve repair, the use of NIRS provided real-time cerebral oxygenation monitoring and enabled close monitoring of all therapeutic actions taken. The decrease in rS_cO_2 with the initiation of CPB was reversed succesfully by the institution of pulsatile CPB flow, whereas other standard interventions, such as the increase of perfusion pressure and pump flow had failed, suggesting that these patients depending on extensive collateral network brain perfusion may benefit from preserved pulsatility during CPB.
Conclusion: This case report shows that real-time cerebral oxygenation monitoring during CPB provides a clinical useful additional monitoring tool, especially in patients at risk for neurological damage by a cerebrovascular disease like moyamoya.

3.4.1 Introduction

Moyamoya disease (MMD) is a progressive, chronic cerebrovascular occlusive disease occurring predominantly in the Asian population. As described by Suzuki and Takaku [1] in 1969, it affects the internal carotid arteries and anterior and middle cerebral arteries, resulting

in compensatory collateral networks at the base of the brain. These networks can be observed in cerebral angiography as a 'puff of smoke' (moyamoya means 'cloud' in Japanese). The clinical appearance is marked by various cerebrovascular incidents, including intracranial hemorrhage, transient ischemic attack (TIA), and recurrent small strokes [2].

In MMD, the blood supply to the brain is severely compromized, which represents a considerable challenge to the anesthesiologist during the perioperative period. Although the management of patients with MMD during cerebral revascularization surgery is described widely, reports on the management of patients with MMD undergoing cardiac surgery with cardiopulmonary bypass are limited [3-8]. The use of near-infrared spectroscopy (NIRS) as a monitoring tool of cerebral oxygen saturation during cardiac surgical procedures is gaining wide acceptance; however, its potential value in the perioperative management of MMD patients is unknown. In this case report, the use of NIRS to identify and reverse cerebral ischemia in a patient with MMD during cardiac surgery is described.

3.4.2 Case report

A 26-year-old man with MMD was referred to the authors' university center for the treatment of grade IV mitral valve insufficiency caused by anterior leaflet prolapse. His medical history included one TIA and recurrent episodes of transient headaches over the past ten years. His brother had a history of malignant hyperthermia. Because of increasing exercise intolerance and recent symptoms of congestive heart failure, he was proposed for mitral valve surgery. Echocardiography showed a significant prolapse of the anterior mitral valve leaflet, resulting in a huge eccentric jet with flow reversal into the pulmonary veins. Preoperative investigation of the associated cerebrovascular disease by brain magnetic resonance imaging (Fig. 3.3) showed bilateral distal occlusion of the internal carotid arteries, occlusion of the left ophthalmic artery, and a widely disrupted circle

of Willis with an extensive collateral network. Cerebral cortex perfusion seemed to be best compensated in the left occipital and left frontal cortex. Prophylactic cerebral revascularization surgery was not done, and cardiac surgery with mitral valve repair was chosen.

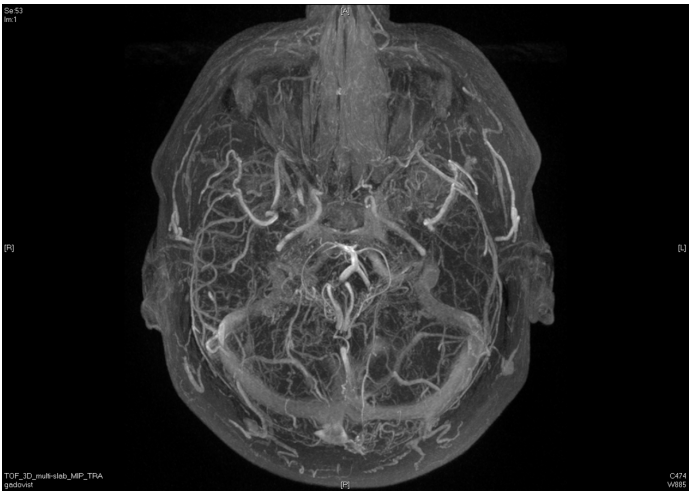

Figure 3.3: Cerebral angiography demonstrating abnormal collateral networks at the base of the brain.

Intraoperative monitoring included 5-lead ECG, invasive blood pressure measured in the right radial artery, central venous pressure measured via the right internal jugular vein, temperature (esophageal and rectal), capnography and regular arterial blood gas sampling. Additional transesophageal echocardiography completed the cardiovascular monitoring. We applied a bispectral index (BIS) electrode (BIS XP; Aspect Medical Systems, Newton, MA, USA) to monitor the depth of anesthesia and 2 NIRS sensors on the left and right forehead (INVOS 5100; Somanetics Corporation, Troy, MI, USA) to non-invasively measure regional cerebral oxygen saturation (rS_cO_2).

Before induction, awake rS_cO_2 values were 62% and 60% at the left and right side, respectively. With preoxygenation, rS_cO_2

increased to 70% on both sides (Fig. 3.4). Anesthesia was induced with diazepam 0.1 mg/kg and fentanyl 10 μg/kg. Intubation was facilitated with rocuronium 0.9 mg/kg and the lungs were ventilated with an air/oxygen mixture to keep arterial carbon dioxide partial pressure (P_aCO_2) around 40 mmHg. Anesthesia was maintained with additional fentanyl and diazepam doses (total dose 22 μg/kg and 10 mg, respectively) and a continuous infusion of propofol, of which the dosing was guided to maintain BIS values between 35 and 50 (dose range 3-5 mg/kg/h). Throughout surgery, the blood glucose level was kept between 80 and 120 mg/dl with a continuous insulin infusion. Between the induction of anesthesia and the initiation of cardiopulmonary bypass (CPB), NIRS indicated a bilateral rS_cO_2 between 57% and 75% (Fig. 3.4).

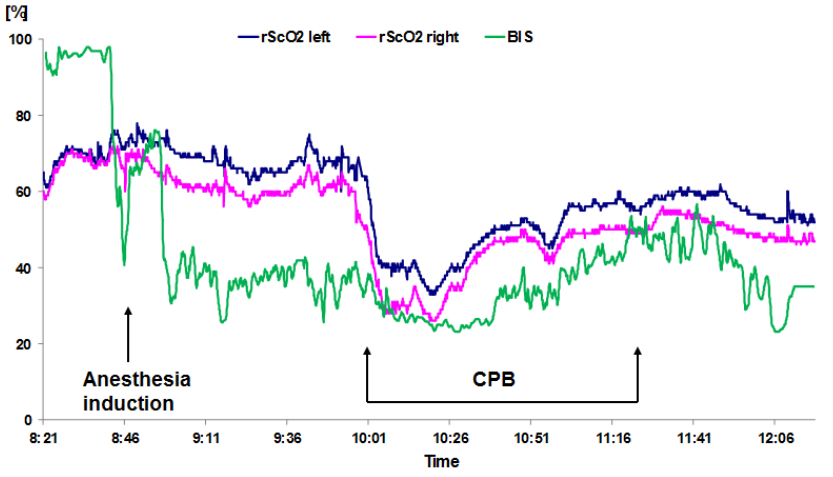

Figure 3.4: Intraoperative plot showing real-time readings of bilateral cerebral oxygen saturation and bispectral index. rS_cO_2: regional cerebral oxygen saturation, BIS: bispectral index.

CPB was performed with a nonpulsatile flow of 2.4 l/min/m^2, with hemodilution to a minimal hematocrit of 28%. Nasopharyngeal temperature was kept between 35°C and 36°C. P_aCO_2 and P_aO_2 were maintained at 40 mmHg and 350 mmHg, respectively. Alpha-stat regulation of pH values was adopted.

A few minutes after starting CPB, a sudden decrease in rS_cO_2 was observed on both sides to 25 to 40% (Fig. 3.5). BIS values showed a parallel decrease, but to a lesser extent (Fig. 3.4). Mechanical causes were ruled out, and intended values of hematocrit, BIS, P_aCO_2, and P_aO_2 were confirmed. Increases in CPB flow as well as increases in perfusion pressure with phenylephrine failed to raise rS_cO_2. Therefore we decided to decrease nasopharyngeal temperature to 33°C. Initially, rS_cO_2 seemed to improve; however, this was very short-lasting. Finally, we converted from nonpulsatile flow to pulsatile flow, which resulted in a gradual rS_cO_2 increase (Fig. 3.5).

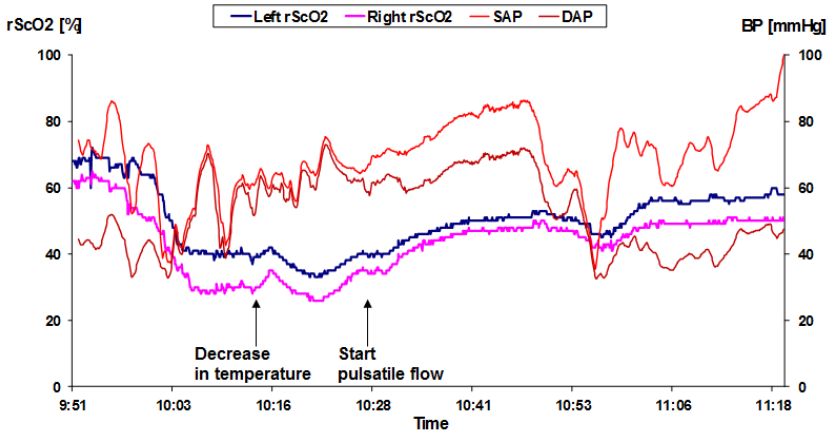

Figure 3.5: Real-time readings of bilateral cerebral oxygen saturation and arterial blood pressure during cardiopulmonary bypass. Institution of pulsatile flow resulted in gradual increase in cerebral oxygen saturation. rS_cO_2: regional cerebral oxygen saturation, BP: blood pressure, SAP: systolic arterial blood pressure, DAP: diastolic arterial blood pressure.

After successful weaning from CPB, bilateral rS_cO_2 values stabilized around 50 to 60%. Postoperatively, the patient suffered from prolonged somnolence and a transient paresis of the left arm, which improved over the following days without any sequelae. At postoperative day 10, magnetic resonance imaging of the brain revealed no new defects.

3.4.3 Discussion

This case report shows the utility of NIRS monitoring in a MMD patient in whom the maintenance of adequate cerebral perfusion during CPB was jeopardized severely because of the underlying pathology.

Denault et al. [9] introduced a useful treatment algorithm to correct decreases in cerebral saturation values, which the authors have adopted for many years. When rS_cO_2 decreased, technical or mechanical causes (eg, adhesion of the NIRS sensors, head position, and positioning of the arterial and venous cannulae) were first ruled out. Then, those factors that affect cerebral oxygen balance, such as blood pressure [10], P_aCO_2 [10], temperature [11], hematocrit [12], depth of anesthesia [13] and pump flow, were verified and optimized. Real-time cerebral oxygenation monitoring enabled us to monitor closely the effects of each therapeutic action. Despite correction for all possible confounding factors, a dramatic decrease in rS_cO_2 values during CPB was still observed. Finally, the decrease in rS_cO_2 was reversed successfully by initiating pulsatile CPB flow, as suggested by Denault et al. [9].

The benefit of pulsatile versus nonpulsatile flow during CPB remains an intensely debated topic. The controversy is likely because of the heterogeneity of the study populations and the lack of quantification of generated pressure-flow waveforms [14]. A series of studies have documented that at the same flow and pressure conditions pulsatile perfusion generates more hemodynamic energy in the blood flow than nonpulsatile perfusion. This additional energy resulted in

better vital organ perfusion [15,16]. Pulsatile CPB has been shown to improve cerebral blood flow and brain tissue oxygenation [17]. Only 3 clinical reports documented the influence of pulsatile CPB on rS_cO_2 measured with NIRS. Zhao et al. [18] and Su et al. [19] showed smaller decreases in rS_cO_2 levels in the pulsatile versus non-pulsatile group during pediatric CPB. In contrast, Grubhofer et al. [20] found no benefit of pulsatile perfusion on cerebral oxygenation during hypothermic CPB in adult patients. In the present case, a steady increase in rS_cO_2 was observed when pulsatile flow was initiated, supporting the observations of Zhao et al. [18] and Su et al. [19].

Considering the family history of malignant hyperthermia, we avoided the use of volatile anesthetics. Several studies showed no significant difference in outcome or perioperative complications of inhaled anesthesia versus total intravenous anesthesia. However, two studies [21,22] compared the effect of sevoflurane and propofol on regional cortical blood flow and intracranial pressure during revascularization procedures in patients with MMD and concluded that with propofol cortical blood flow was significantly higher and intracranial pressure was lower.

Two case reports in which BIS monitoring was applied [3,4] and one report with NIRS monitoring [5] during cardiac surgery in patients suffering from MMD were found, yet none used both BIS and NIRS. In this case, dramatic decreases in NIRS values were found, which was only mildly reflected in the associated BIS values. Although BIS and NIRS offer distinct indices for perioperative neurological monitoring, both are actually complementary. BIS reflects the functional state of the brain, and therefore BIS could help to determine the significance of a rS_cO_2 decrease. By contrast, because rS_cO_2 assesses cerebral oxygen balance, it helps to identify the cause of a BIS change. In this case report, the decrease of BIS values could have been interpreted as an increase in depth of anesthesia or as a decrease in cerebral metabolic rate by lowering body

temperature. However, the associated decrease in NIRS suggested that the reduction in BIS was caused by a cerebral oxygenation deficit.

The limitations of NIRS are inherent to its underlying technology and are described in detail elsewhere [23,24]. Specifically for this case, some limitations of NIRS are highlighted. First, although the algorithm used to calculate oxygen saturation assumes a fixed distance for light to travel through the sampled area (the optical path length), its validity remains questionable in the rapidly changing condition occurring during CPB (eg, a decrease in hematocrit or a change in viscosity). Second, Tyree et al. [25] showed that measurements based on hemoglobin saturation (which is the case for NIRS) do not always accurately reflect oxygenation at the cellular level, providing a false sense of safety. Finally, the measurements obtained with NIRS are regional and strictly confined to the zone underneath the sensor. Consequently, clinically relevant focal ischemia in a brain area remote from the monitored area may stay unnoticed, in particular in patients with a diffuse occlusive cerebrovascular disease like MMD.

This case report shows that real-time cerebral oxygenation monitoring during CPB provides a clinical useful additional monitoring tool, especially in patients at risk for neurological damage by a cerebrovascular disease like MMD. The successful reversal of rS_cO_2 decrease by the institution of pulsatile CPB flow, whereas other standard interventions, such as the increase of perfusion pressure and pump flow had failed, suggests that these patients depending on extensive collateral network brain perfusion may benefit from preserved pulsatility during CPB.

3.4.4 References

1. Suzuki J, Takaku A. Cerebrovascular "moyamoya" disease. Disease showing abnormal net-like vessels in base of brain. Arch Neurol 1969; 20: 288-99
2. Burke GM, Burke AM, Sherma AK, et al. Moyamoya disease: a summary. Neurosurg Focus 2009; 26: E11
3. Al-Naimi KT, Mediratta NK, Pennefather SH. Hypothermic cardiopulmonary bypass in a patient with moyamoya disease. J Cardiothorac Vasc Anesth 2009; 23: 206-7
4. Han SH, Kim SD, Ham BM, et al. Normothermic cardiopulmonary bypass in a patient with moyamoya disease. J Cardiothorac Vasc Anesth 2005; 19: 499-500
5. Jimi N, Shin T. Anesthetic management of a patient with Moyamoya disease undergoing open heart surgery. Pediatr Anesth 2006; 16: 1195-6
6. Gatti G, Benussi B, Gon L, et al. Aortic valve replacement in an adult white male with moyamoya disease and coronary artery fistulas. J Cardiothorac Vasc Anesth 2007; 21: 166-8
7. Wang N, Kuluz J, Barron M, et al. Cardiopulmonary bypass in a patient with moyamoya disease. Anesth Analg 1997; 84: 1160-3
8. Kashima I, Inoue Y, Takahashi R. The use of intra-aortic balloon pump as cerebral protection in a patient with moyamoya disease undergoing coronary artery bypass grafting. Interact Cardiovasc Thorac Surg 2008; 7: 522-3
9. Denault A, Deschamps A, Murkin JM. A proposed algorithm for the intraoperative use of cerebral near-infrared spectroscopy. Semin Cardiothorac Vasc Anesth 2007; 11: 274-81
10. Iwama T, Hashimoto N, Yonekawa Y. The relevance of hemodynamic factors to perioperative ischemic complications in childhood moyamoya disease. Neurosurgery 1996; 38: 1120-6
11. Parray T, Martin TW, Siddiqui S. Moyamoya disease: a review of the disease and anesthetic management. J Neurosurg Anesthesiol 2011; 23: 100-9
12. Sato K, Shirane R, Yoshimoto T. Perioperative factors related to the

development of ischemic complications in patients with moyamoya disease. Childs Nerv System 1997; 13: 68-72
13. Kansha M, Irita K, Takahashi S, et al. Anesthetic management of children with Moyamoya disease. Clin Neurol Neurosurg 1997; 99: S110-3
14. Ündar A. Benefits of pulsatile flow during and after cardiopulmonary bypass procedures. Artif Organs 2005; 29: 688-90
15. Haines N, Wang S, Ündar A, et al. Clinical outcomes of pulsatile and non-pulsatile mode of perfusion. J Extra Corpor Technol 2009; 41: 26-9
16. Akçevin A, Alkan-Bozkaya T, Qiu F, et al. Evaluation of perfusion modes on vital organ recovery and thyroid hormone homeostasis in pediatric patients undergoing cardiopulmonary bypass. Artif Organs 2010; 34: 879-84
17. Ündar A. Pulsatile versus nonpulsatile cardiopulmonary bypass procedures in neonates and infants: from bench to clinical practice. ASAIO J 2005; 51: VI-X
18. Zhao J, Yang J, Liu J, et al. Effects of pulsatile and nonpulsatile perfusion on cerebral regional oxygen saturation and endothelin-1 in tetralogy of fallot infants. Artif Organs 2011; 35: E54-8
19. Su XW, Guan Y, Barnes M, et al. Improved cerebral oxygen saturation and blood flow pulsatility with pulsatile perfusion during pediatric cardiopulmonary bypass. Pediatr Res 2011; 70: 181-5
20. Grubhofer G, Mares P, Rajek A, et al. Pulsatility does not change cerebral oxygenation during cardiopulmonary bypass. Acta Anaesthesiol Scand 2000; 44: 586-91
21. Sato K, Shirane R, Kato M, et al. Effect of inhalation anesthesia on cerebral circulation in moyamoya disease. J Neurosurg Anesthesiol 1999; 11: 25-30
22. Kikuta K, Takagi Y, Nozaki K, et al. Effects of intravenous anesthesia with propofol on regional cortical blood flow and intracranial pressure in surgery for moyamoya disease. Surg Neurol 2007; 68: 421-4
23. Edmonds HL Jr, Ganzel BL, Austin EH 3rd. Cerebral oximetry for cardiac and vascular surgery. Semin Cardiothorac Vasc Anesth 2004; 8: 147-66

24. Murkin JM, Arango M. Near-infrared spectroscopy as an index of brain and tissue oxygenation. Br J Anaesth 2009; 103 Suppl 1:i3-i13
25. Tyree K, Tyree M, DiGeronimo R. Correlation of brain tissue oxygen tension with cerebral near-infrared spectroscopy and mixed venous oxygen saturation during extracorporeal membrane oxygenation. Perfusion 2009; 24: 325-31

Chapter 4

NIRS for monitoring regional tissue perfusion

4.1 Background

The amount of blood delivered to an organ determines oxygen delivery to that particular organ. Under physiological conditions, different organs receive a relatively predictable blood flow depending on their metabolic demand. However, when cardiac output decreases, the sympathetic stress response raises vascular resistance, diverting blood flow from less important tissues (skin, muscle, gastrointestinal tract, kidneys) to vital organs (the brain and the heart). Monitoring the macrocirculation using measures of blood pressure and arterial oxygen saturation, do not necessarily predict adequate perfusion and oxygenation of individual tissues. The use of NIRS for monitoring regional oxygen saturation at somatic sites has been advocated as an early warning system for changes in the oxygen supply-demand balance, thereby allowing an early marker of silent regional hypoperfusion.

4.2 Objective

The aim of the present studies was to explore the potential of NIRS to monitor regional organ perfusion. In the first study, the effect of aortic cross-clamping on cerebral, renal, and muscle oxygen saturation was evaluated in children undergoing aortic coarctation repair. In the second study, the applicability of NIRS to estimate oxygen saturation of the spinal cord was explored during aortic cross-clamping in a patient undergoing thoracoabdominal aneurysm repair.

4.3 NIRS during aortic coarctation repair

The effect of blood pressure regulation during aortic coarctation repair on brain, kidney and muscle oxygen saturation measured by near-infrared spectroscopy: a randomized, clinical trial. Moerman A, Bové T, François K, Jacobs S, Deblaere I, Wouters P, De Hert S. Anesth Analg 2013; 116: 760-6

Abstract

Background. In this study, we compared the effects of three frequently used blood pressure-regulating agents on brain (rS_cO_2), renal (S_rO_2), and muscle (S_mO_2) oxygen saturation, during aortic coarctation repair in children. Based on the reported adverse effect of sodium nitroprusside (SNP) on left-sided rS_cO_2 during aortic coarctation repair, we tested the hypothesis that the alterations in left rS_cO_2 occurring with SNP would not be present with sevoflurane and nitroglycerin (NTG). Additionally, we explored the effects of blood pressure regulation with SNP, NTG or sevoflurane on right-sided rS_cO_2, S_rO_2, and S_mO_2.

Methods. Children with isolated aortic coarctation undergoing surgical repair through a left thoracotomy without the use of cardiopulmonary bypass were considered eligible for the study.

During aortic cross-clamping, control of mean arterial blood pressure (MAP) was conducted according to randomization by the use of SNP, NTG or sevoflurane, to obtain a mean target right brachial blood pressure of 120 to 150% of the MAP value before cross-clamping. Bilateral rS_cO_2, S_rO_2 and S_mO_2 were recorded continuously with near-infrared spectroscopy. As a primary endpoint, the maximal relative change in left-sided rS_cO_2 in response to aortic cross-clamping was compared among treatment groups.

Results. Ten patients per group were included. No significant difference among treatment groups was observed in maximal relative change in left-sided rS_cO_2 (SNP *vs* sevoflurane: mean difference -0.7%, 99% confidence interval (CI) -31 to 29%, P=1.0; SNP *vs* NTG: mean difference -1.8%, 99% CI -32 to 28%, P=1.0; sevoflurane *vs* NTG: mean difference -1.1%, 99% CI -31 to 29%, P=1.0). Additional analyses also detected no difference between groups in right rS_cO_2 (P=0.4). Compared with NTG, treatment with SNP resulted in a significantly larger (-64 ± 17 *vs* -34 ± 25%, P=0.01) and faster (-9 ± 4%.min^{-1} *vs* -4 ± 3%.min^{-1}, P=0.004) decrease in S_mO_2. Right-sided rS_cO_2 and MAP showed a poor correlation for NTG (r=-0.2, P=0.93), whereas borderline for sevoflurane (r=0.44, P=0.09) and SNP (r=0.56, P=0.04).

Conclusions. The mean differences in left-sided rS_cO_2 among the patients treated with SNP, NTG, or sevoflurane for proximal hypertension during aortic cross-clamping were no more than 32%. Additional analysis demonstrated a low MAP-rS_cO_2 dependence with the use of NTG. Because NTG also resulted in a smaller and slower decrease of oxygen saturation in peripheral tissues, our data suggest that its use might be preferable for proximal blood pressure control during surgical procedures involving aortic cross-clamping.

4.3.1 Introduction

Surgical repair of aortic coarctation through left thoracotomy involves proximal aortic arch cross-clamping, resulting in temporary hypoperfusion of the tissues distal to the cross-clamp. This manoeuver may also be associated with an abrupt increase in ventricular afterload and immediate proximal (to the aortic cross-clamp) hypertension, often necessitating pharmacologic control [1]. Currently, the use of potent and short-acting vasodilators such as sodium nitroprusside (SNP) and nitroglycerin (NTG) is preferred for treating hypertension during aortic cross-clamping for this procedure. However, Azakie et al. [2] have raised concerns regarding the effect of SNP on left-sided cerebral oxygen saturation (rS_cO_2) during aortic coarctation repair. In addition, it has been demonstrated that SNP may worsen the already impaired oxygen balance of tissues below the aortic cross-clamp during surgery on the thoracic aorta [3-5].

The effects of different antihypertensive agents on tissue oxygen saturation during aortic cross-clamping remain largely unexplored. The purpose of the present study was to test the hypothesis that the alterations in left rS_cO_2 described with SNP would not be present with other blood pressure-regulating agents. Second, we wanted to compare the effects of blood pressure-regulating drugs during aortic coarctation repair on the oxygen saturation of the right-sided brain and the peripheral tissues.

Three agents frequently used for perioperative blood pressure control during cardiac surgery [6] were included: SNP and NTG as intravenous vasodilating agents, and sevoflurane as an inhaled anesthetic with vasodilating effect. We hypothesized that the alterations in oxygen saturation of the brain and peripheral tissues reported with SNP would represent an agent-specific phenomenon that is not present with NTG or sevoflurane.

4.3.2 Methods

This study was a single-center, prospectively randomized, controlled trial, conducted from October 2007 to March 2011. The trial was registered at ClinicalTrials.gov, on September 25, 2007 (NCT00535808). After Institutional Review Board approval, written informed consent was obtained from the parents or legal guardian of the child.

All children with isolated aortic coarctation undergoing surgical correction through a left thoracotomy without the use of cardiopulmonary bypass were considered eligible. Patients with associated cardiac defects resulting in a hemodynamically significant intracardiac shunt were excluded. To assure uniformity of the impact of aortic cross-clamping on cerebral perfusion, the experimental protocol involved cross-clamping of the left carotid artery in all patients. If cross-clamping of the left carotid artery was surgically not indicated, patients were excluded from the study protocol. Assignment to the groups was determined by random drawing of sealed envelopes containing the labels 'sevoflurane', 'sodium nitroprusside' or 'nitroglycerin'.

On the morning of the surgery, patients were allowed to take their normal daily medication. The uniform protocol of anesthesia included induction with sufentanil 0.5 μg/kg, midazolam 100 μg/kg, and rocuronium 0.9 mg/kg. Anesthesia was maintained with sevoflurane inhalation (1 MAC) and additional doses of sufentanil. Mechanical ventilation was adjusted in order to obtain an arterial carbon dioxide partial pressure (P_aCO_2) of 40 mmHg. Fractional inspired oxygen (F_iO_2) was set at 0.5. The body temperature was kept constant at 35.0-36.0 °C by using a warming mattress underneath the patient (Blanketrol® II, Cincinnati Sub-Zero Products Inc., Cincinnati, OH) and a pediatric forced-air warming blanket surrounding the patient (Bair Hugger® Therapy, Arizant Healthcare Inc., Eden Prairie, MN).

Two disposable near-infrared spectroscopy (NIRS) sensors were applied on each side of the forehead for continuous registration of the rS_cO_2 of the corresponding brain hemisphere (INVOS 5100, Somanetics Corporation, Troy, MI). Additionally, a NIRS sensor was placed over the right flank below the costovertebral angle overlying the kidney (T10-L2) to estimate renal oxygen saturation (S_rO_2), and one over the right thigh to measure muscle oxygen saturation (S_mO_2). Arterial blood pressure was recorded continuously via an arterial line in the right brachial artery. A blood pressure cuff was placed on the left lower extremity. Central venous pressure was monitored through right internal jugular vein access.

The surgical procedure was performed in a standardized manner, with the patient in the right lateral decubitus position, using a left lateral thoracotomy approach. After extensive dissection of the aortic arch, supra-aortic vessels and descending aorta down to four intercostal levels, the ductus arteriosus or ligament was ligated. Subsequent to systemic heparin administration (1 mg/kg), the aortic arch was cross-clamped proximally between the innominate artery and the left carotid artery, and distally on the descending aorta below the first intercostal artery. Surgical repair consisted of resection of the coarctation segment and direct end-to-end anastomosis.

Control of blood pressure during aortic cross-clamping was performed according to the randomization sequence by the use of sevoflurane, SNP or NTG. Drug dose was titrated to obtain a mean target right brachial blood pressure of 120 to 150% of the mean blood pressure value before aortic cross-clamping. The vasodilator therapy was started immediately after heparin administration (start of administration of SNP/NTG in the SNP and NTG groups, respectively, or increasing the concentration of sevoflurane in the sevoflurane group). Two minutes before anticipated completion of the anastomosis, administration of the vasoactive treatment was stopped to attenuate the hypotensive response upon clamp release.

Heart rate, invasive systemic blood pressure and central venous pressure, in- and end-expiratory gas tensions, pulse oximetry and NIRS data (bilateral rS_cO_2, S_rO_2, S_mO_2) were recorded continuously and integrated digitally with the RUGLOOP software (Demed, Temse, Belgium). Analysis of hematocrit, arterial and venous blood gas partial pressures, and lactate levels was performed just before surgical incision, after heparin administration, 5 min after aortic cross-clamping, 5 min after aortic declamping, and postoperatively at arrival in the intensive care unit. Types and volumes of all fluids administered, doses of any drugs given, and blood loss were recorded.

Data description

In the present study, we compared the effects of three blood pressure-regulating agents on rS_cO_2, S_rO_2, and S_mO_2. Because no data from the literature were available allowing sample size calculation for changes in S_rO_2 and S_mO_2 during aortic cross-clamping, we had to rely for the expected treatment effects and the sample size calculation on reported rS_cO_2 changes during aortic cross-clamping. Azakie et al. [2] demonstrated a relative decrease of left-sided rS_cO_2 of 10.4% with the use of SNP during aortic cross-clamping. Assuming a baseline mean rS_cO_2 and standard deviation of 71% and 6%, respectively [7], a sample size of 7 patients per group was calculated to detect a minimal difference of 10% in left rS_cO_2 among treatment groups with a power of 0.8 and an α of 0.05. To account for possible dropouts, 10 patients per group were included.

Absolute NIRS values have a wide range of variability among patients when measured with the INVOS technology [8]. Therefore, only measures of the relative changes in NIRS variables were analyzed, defined as the relative percentage of the lowest (in case of decrease) or highest (in case of increase) value during the cross-clamp period versus the value just before aortic cross-clamping.

The primary outcome variable of the present study was the maximal relative change in left rS_cO_2 after aortic cross-clamping.

Secondary NIRS variables included the maximal relative change in right rS_cO_2, S_rO_2 and S_mO_2 after aortic cross-clamping. Further secondary analyses included the rate of decrease in S_rO_2 and S_mO_2 in each treatment group, and the integrated rS_cO_2, S_rO_2, and S_mO_2 for each treatment group. The rate of decrease in S_rO_2 and S_mO_2 was determined by the average rate of decay, calculated by dividing the maximal change in S_rO_2 or S_mO_2 by the time to reach its nadir, expressed in % per minute. The integrated rS_cO_2, S_rO_2, or S_mO_2, or area under the curve (AUC), was calculated with reference to the value just before aortic cross-clamping, using measurement intervals of 5 seconds, and is expressed in %.second. Subsequently, the AUC accounts for both depth and duration of change in oxygen saturation.

Since rS_cO_2 and blood pressure have been reported to be correlated [9], we also evaluated the relationship between right-sided rS_cO_2 and MAP in the 3 treatment groups.

The extent of collateral circulation has been shown to be age-related [10], therefore the relationship between age and changes in S_rO_2 and S_mO_2 was also evaluated.

Statistical analysis

Statistical analysis was performed using the statistical software SPSS Statistics 20 (SPSS Inc., Chicago, IL). The raw data were tested for normality using the Shapiro-Wilk test and were considered normally distributed if $P > 0.05$. Homogeneity of variances was tested with Levene's test. Additionally, residuals were tested as well, and normality has been confirmed. Normally distributed continuous data are presented as mean $\pm$ SD. Non-parametric data are presented as median [range].

Comparison of demographic data among the 3 treatment groups was performed with the Kruskal-Wallis test for continuous data and with the chi-square test for categorical data.

Intraoperative data, absolute rS_cO_2, S_rO_2 and S_mO_2 values, and blood gas values among the 3 treatment groups were compared with analysis of variance. For pairwise comparisons among groups, Tukey correction was used with 99% confidence intervals (CIs).

Between-group comparisons of maximal relative changes in rS_cO_2, S_rO_2, and S_mO_2 were done in a general linear model with adjustment for baseline oxygen saturations, and Bonferroni correction for multiple comparisons (3 in the Bonferroni denominator). The same statistical method was applied for analysis of the rate of decay for S_rO_2 and S_mO_2.

AUCs for rS_cO_2, S_rO_2 and S_mO_2 were analyzed with the Kruskal-Wallis test. Pairwise differences in AUC among treatment groups were examined for significance by using Mann-Whitney U test.

For the correlation between changes in right rS_cO_2 and MAP, Kendall's tau test of concordance was used. The relationship between age and changes in S_rO_2 and S_mO_2 was evaluated by simple linear regression analysis.

The level of statistical significance was set at corrected 2-sided P-value <0.05 for the primary analyses. A P-value of <0.01 was considered significant for secondary endpoints regarding multiple comparisons after Bonferroni correction with denominator 3.

4.3.3 Results

Thirty-one patients were considered eligible. One patient was excluded before randomization to a treatment group because cross-clamping of the left carotid artery was surgically not indicated. Patient characteristics are summarized in Table 4.1. There were no differences among groups in the listed variables.

Table 4.1: Patient characteristics for the three randomized groups

	Sevo	**SNP**	**NTG**	**P-value**
Gender (M/F)	7 / 3	8 / 2	6 / 4	0.62
Age (days)	12 [4–193]	20 [3–77]	90 [5–568]	0.36
Weight (kg)	3.3 [2.0–8.6]	3.6 [1.4–5.7]	5.1 [3.2–11.3]	0.22
BSA (m^2)	0.21 [0.15–0.39]	0.22 [0.12–0.28]	0.27 [0.20–0.49]	0.20
ASA 1/2/3 (n)	0/5/5	0/6/4	1/4/5	0.92

Data are expressed as median [range]. M/F: Male/Female, ASA: American Society of Anesthesiology, BSA: body surface area, NTG: Nitroglycerin, Sevo: sevoflurane, SNP: Sodium Nitroprusside.

Intraoperative data are reported in Table 4.2. As expected, during aortic cross-clamping, the mean end-tidal sevoflurane concentration was higher in the sevoflurane group compared with the SNP group and the NTG group (P=0.01 for each). There was no difference in sevoflurane concentration between the SNP and NTG groups. Sufentanil total dose and arterial and venous blood gas results were similar among the three groups. The mean total doses of SNP and NTG necessary for maintaining the target MAP were 14.3 $\pm$ 11.2 μg/kg and 18.6 $\pm$ 14.5 μg/kg, respectively.

No significant differences in MAP were observed among the 3 groups at any time of measurement, indicating that the different blood pressure-regulating strategies allowed for a comparable proximal blood pressure control during aortic cross-clamping.

Table 4.2: Intraoperative data for the three randomized groups

	Sevo	**SNP**	**NTG**	**P-value**
Duration of CX (min)	15 ± 5	13 ± 5	15 ± 10	0.79
Total sufentanil dose (μg/kg)	1.5 ± 0.3	1.7 ± 0.6	1.9 ± 0.8	0.34
Mean ETsevo during CX (%)	3.1 ± 1.1	1.8 ± 0.6*	1.8 ±0.5*	0.01
Mean MAP during CX (mmHg)	61 ± 11	69 ± 15	70 ± 19	0.43
Mean HR during CX (beats/min)	123 ± 10	128 ± 17	126 ± 17	0.73
Hct during CX (%)	31 ± 4	32 ± 4	31 ± 6	0.94
P_aO_2 during CX (mmHg)	145 ± 42	151 ± 67	156 ± 67	0.93
P_vO_2 during CX (mmHg)	41 ± 14	46 ± 11	50 ± 14	0.34
P_aCO_2 during CX (mmHg)	44 ± 5	47 ± 8	44 ± 9	0.76
Lactate during CX (mg/dl)	19 ± 5	18 ± 4	15 ± 4	0.35

Data are expressed as mean ± SD. Analysis of hematocrit, blood gas partial pressures and lactate was performed 5 minutes after start of aortic cross-clamping (CX). *P=0.01 for the difference with the sevoflurane group. CX: aortic cross-clamping, ETsevo: end-tidal concentration of sevoflurane, Hct: hematocrit, HR: heart rate, MAP: mean arterial pressure, NTG: Nitroglycerin, Pa: arterial partial pressure, Pv: venous partial pressure, Sevo: sevoflurane, SNP: Sodium Nitroprusside.

No difference among groups was observed in mean left-sided rS_cO_2 values before aortic cross-clamping (72 ± 10%, 77 ± 13%, and 77 ± 11% for sevoflurane, SNP and NTG, respectively, P=0.57). Three possible responses to aortic cross-clamping were observed in left rS_cO_2 measurements: a decrease of left rS_cO_2 in 2 patients of each group (maximal relative decrease of -5 and -17% for sevoflurane, -5 and -47% for SNP, -28 and -33% for NTG, P=0.58 between groups), no change in left rS_cO_2 in 1 patient in the sevoflurane group, 2 patients in the SNP group, and in 2 patients in the NTG group, whereas an increase in left rS_cO_2 was observed in the remaining patients (sevoflurane, n= 7, 10 ± 7%; SNP, n=6, 13 ± 4%; NTG, n=6, 17 ± 19%, P=0.32 between groups). No differences among groups were observed in the maximal relative changes in left rS_cO_2 values in response to aortic cross-clamping (SNP *vs* sevo: mean difference -0.7%, 99% CI -31 to 29%, P=1.0; SNP *vs* NTG: mean difference -1.8%, 99% CI -32 to 28%, P=1.0; sevo *vs* NTG: mean difference -1.1%, 99% CI -31 to 29%, P=1.0).

The following additional observations were made regarding changes in right rS_cO_2, S_rO_2 and S_mO_2. No differences among groups were observed in mean right rS_cO_2 values before aortic cross-clamping (P=0.69) and in maximal relative change in right rS_cO_2 values in response to aortic cross-clamping (P=0.4) (Table 4.3). S_rO_2 and S_mO_2 showed a rapid and significant decrease after aortic cross-clamping in all groups, reaching a plateau phase for S_rO_2 within 8.6 minutes, 7.4 minutes and 10.0 minutes for sevoflurane, SNP, and NTG, respectively (P=0.08 among groups) and within 9.4 minutes, 6.8 minutes and 9.9 minutes for S_mO_2 for sevoflurane, SNP, and NTG, respectively (P=0.02 among groups). All tissue oxygen saturations recovered promptly after release of the aortic cross-clamp. For S_mO_2, the maximal relative changes were larger and the rate of decay was faster in the SNP group compared to the NTG group (Table 4.3).

Table 4.3: Absolute values before aortic cross-clamping and maximal relative change during aortic cross-clamping for right cerebral (rS_cO_2), renal (S_rO_2) and muscle oxygen saturation (S_mO_2) for the three randomized groups. Rate of decay during aortic cross-clamping for S_rO_2 and S_mO_2 for the three randomized groups

	Sevo	**SNP**	**NTG**	**P-value**
Absolute right rS_cO_2 value (%) before CX	70 ± 13	72 ± 12	74 ± 8	0.69
Maximal relative change in right rS_cO_2 (%)	18 ± 18	21 ± 14	14 ± 12	0.40
Absolute S_rO_2 value (%) before CX	77 ± 8	82 ± 9	70 ± 16	0.13
Maximal relative change in S_rO_2 (%)	-43 ± 19	-59 ± 13	-33 ± 22	0.04
Rate of decay S_rO_2 (%.min^{-1})	-6 ± 3	-8 ± 3*	-4 ± 3	0.01
Absolute S_mO_2 value (%) before CX	81 ± 13	78 ± 13	79 ± 16	0.92
Maximal relative change in S_mO_2 (%)	-55 ± 19	-64 ± 17*	-34 ± 25	0.01
Rate of decay S_mO_2 (%.min^{-1})	-6 ± 2	-9 ± 4*	-4 ± 3	0.004

Data are expressed as mean ± SD. CX: aortic cross-clamping, NTG: Nitroglycerin, Sevo: sevoflurane, SNP: Sodium Nitroprusside.
*Significantly different ($p<0.01$) from NTG group.

AUC for oxygen saturation from each site is depicted in Fig. 4.1. No differences were observed among the 3 treatment groups in AUC for left-sided and right-sided rS_cO_2 (P=0.74 and P=0.17, respectively). For renal AUC, there was a difference between the NTG and the SNP group (P=0.009). There were no differences in muscle AUC among the treatment groups (P=0.05 for NTG vs sevoflurane, and P=0.03 for NTG vs SNP).

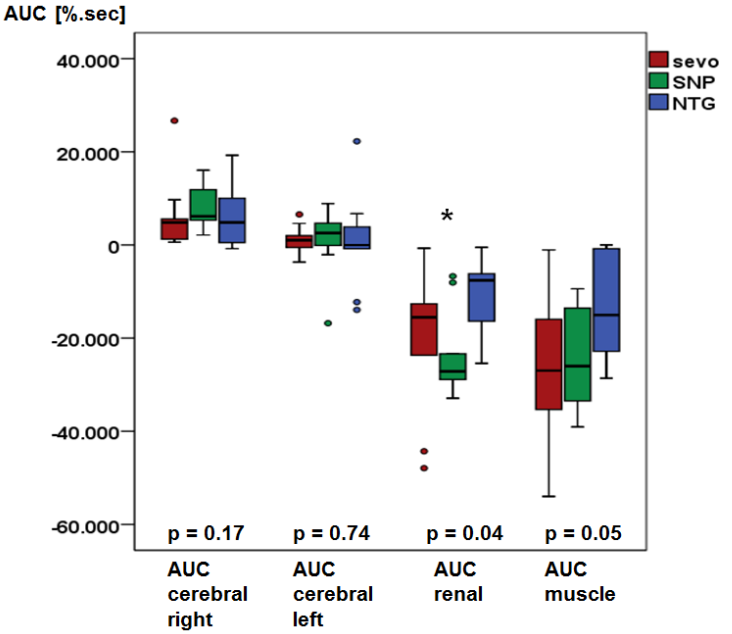

Figure 4.1: Box-and-whisker plots of the area under the curve (AUC) for cerebral, renal and muscle oxygen saturation. NTG: Nitroglycerin, Sevo: sevoflurane, SNP: Sodium Nitroprusside. °: outliers of the 5% and 95%-centiles. P-values presented in the figure below each measurement indicate between groups differences analyzed with the Kruskal-Wallis test. Pairwise differences between treatment groups were analyzed with Mann-Whitney U test (*SNP *vs* NTG, p=0.009).

Right-sided rS_cO_2 and MAP showed a poor correlation for NTG (r=-0.2, P=0.93), whereas the correlation was borderline for sevoflurane (r=0.44, P=0.09) and SNP (r=0.56, P=0.04).

An effect of age was observed on the maximal relative decrease of S_rO_2 (unstandardized β=0.06, CI 99% -0.02 to 0.14, P=0.06) and S_mO_2 (unstandardized β=0.07, CI 99% 0.01 to 0.13, P=0.03). This effect was independent of the study product used (unstandardized β=1.5, CI 99% -12.4 to 15.4, P=0.76 for S_rO_2 and unstandardized β=6.3, CI 99% -7.9 to 20.6, P=0.23 for S_mO_2).

Analysis of hematocrit, blood gas partial pressures, and lactate levels performed 5 minutes after aortic cross-clamp removal is presented in Table 4.4. There were no differences among the treatment groups. In all patients, clinical recovery was uneventful. Postoperative lactate levels and blood creatinine levels were comparable among groups.

Table 4.4: Analysis of blood gas values performed 5 minutes after aortic cross-clamp removal for the three randomized groups

	Sevo	**SNP**	**NTG**	**P-value**
pH	7.26 ± 0.07	7.27 ± 0.12	7.33 ± 0.09	0.24
Base excess (mmol/L)	-4.4 ± 2.3	-3.2 ± 4.0	-2.5 ± 3.3	0.45
Bicarbonate (mmol/L)	22.1 ± 1.2	23.9 ± 3.3	23.3 ± 2.9	0.31
Hct (%)	31 ± 4	32 ± 3	32 ± 5	0.78
P_aO_2 (mmHg)	172 ± 89	175 ± 88	164 ± 63	0.95
P_vO_2 (mmHg)	51 ± 8	49 ± 6	47 ± 8	0.54
P_aCO_2 (mmHg)	51 ± 6	55 ± 15	46 ± 9	0.20
Lactate (mg/dl)	29 ± 8	24 ± 8	21 ± 7	0.11

Data are expressed as mean ± SD. Hct: hematocrit, NTG: Nitroglycerin, P_aO_2: partial pressure of oxygen, arterial, P_vO_2: partial pressure of oxygen, venous, Sevo: sevoflurane, SNP: Sodium Nitroprusside.

4.3.4 Discussion

In this randomized, clinical study, the effects of blood pressure-regulating strategies with SNP, NTG, or sevoflurane on cerebral, renal and muscle oxygen saturation were investigated during aortic cross-clamping in children undergoing aortic coarctation repair. No significant differences in cerebral oxygen saturation values were observed among the three strategies. Decreases in renal and muscle oxygen saturation were larger and had a faster rate of decay in SNP-treated patients. For both SNP and sevoflurane MAP-rS_cO_2 dependence was higher than for NTG.

Effects on cerebral oxygen saturation

In this study, aortic cross-clamping always involved temporary occlusion of the left carotid artery. This manoeuver was associated with a variable response of the left-sided rS_cO_2, ranging from a decrease to an increase in rS_cO_2. Confidence intervals for pairwise comparisons between groups were wide. Although our study design did not allow us to comment on possible underlying mechanisms, it is conceivable that this phenomenon merely reflects the functional adequacy of the circle of Willis.

In a study on 18 patients undergoing aortic coarctation repair, Azakie et al. [2] observed a pronounced decrease in left rS_cO_2 in 2 patients treated with SNP, in whom the left carotid artery was clamped during the intervention. They attributed this finding to a SNP-induced disruption of cerebral autoregulation. However, because in that study no simultaneous recording of both left and right hemispheres was obtained, it cannot be determined whether this rS_cO_2 decrease is the result of an agent-specific effect or rather a deficient circle of Willis.

We observed no significant differences in right rS_cO_2 values among the different blood pressure-regulating strategies; however, with NTG treatment, changes in rS_cO_2 were less dependent on changes in MAP than with SNP and sevoflurane. A higher correlation between MAP

and rS_cO_2 has been reported to be indicative of impaired cerebral autoregulation, whereas values around zero and negative values could be considered as representative of intact autoregulation [11,12]. In line with this reasoning, the higher correlation between MAP and rS_cO_2 in the SNP and sevoflurane groups compared with the NTG group would suggest that SNP and sevoflurane may interfere to a larger extent with cerebral autoregulation than NTG. This is in accordance with previous work reporting on dose-dependent impairment of cerebral autoregulation with SNP [13], whereas there was no significant impairment with NTG [14,15]. Data on the effect of sevoflurane on cerebral autoregulation are controversial. It is generally assumed that cerebral autoregulation is maintained at low concentrations of sevoflurane, whereas higher doses seem to decrease autoregulatory capacity [16].

Effects on renal and muscle oxygen saturation

Concerning the effects on peripheral tissue oxygen saturation, a larger and faster decrease in both renal and muscle oxygen saturation was observed in children treated with SNP. Previous studies have suggested that SNP-induced hypotension might worsen the impaired oxygen balance of tissues below the aortic cross-clamp [3-5]. These findings could not be readily explained. Of interest, an experimental study on striated hamster muscle conducted by Endrich et al. [17] demonstrated that SNP dilated preferentially precapillaries and caused a consistent increase in intravascular pressure within the venules. Consequently, the arteriolar-venular pressure gradient was reduced and functional capillary density decreased, leading to skeletal muscle tissue hypoxia. In contrast, NTG dilated both arterioles and venules, leaving the functional capillary density and local pO_2 unchanged. Our findings are in accordance with the results of Endrich et al. [17] and suggest that NTG may be preferable to SNP in terms of tissue oxygenation.

In all patients, both S_rO_2 and S_mO_2 declined to a plateau phase, which indicated that oxygen delivery no longer met metabolic oxygen requirements, likely resulting in anaerobic metabolism. The duration of the nadir of oxygenation has been demonstrated to be directly related to the extent of tissue injury [18,19]. Sakamoto et al.[18] demonstrated that nadir times of less than 25 minutes did not induce tissue injury. It can therefore be expected that the nadir times in our study were too short to translate into changes of biomarkers indicative for tissue injury, such as serum lactate, base excess, and creatinine levels.

Study limitations

The results of the present study should be interpreted within the constraints of the methodology. First, because of absence of evident adverse clinical events due to the short aortic cross-clamp times, the clinical implications of the current study on outcome remain to be determined. Second, the current study population comprised only young patients. Because the extent of collateral circulation has been shown to be age-related [10], the validity of the current results in older patients with a possibly more developed collateral circulation needs to be confirmed. Third, the reliability of NIRS to measure specific renal oxygen saturation can be questioned because of the uncertainty related to the depth of penetration of the near-infrared light in relation to the kidney. However, a number of studies have suggested that placement of a NIRS sensor over the flank might indeed reflect renal oxygen saturation. Ortmann et al. [20] demonstrated a strong correlation between flank NIRS values and renal vein saturation in children weighing <10 kg. Also, low renal tissue oxygen saturations measured with NIRS were associated with renal dysfunction after pediatric cardiac surgery [21] and after aortic coarctation repair [22].

In conclusion, no differences were observed in rS_cO_2 values between the different blood pressure regulating strategies. However, with NTG treatment, changes in rS_cO_2 were less dependent on changes in MAP than with SNP and sevoflurane. Decreases in S_rO_2 and S_mO_2 were larger and had a faster rate of decay in SNP-treated patients. Based on the lower MAP-rS_cO_2 dependence and the smaller and slower decreases in S_rO_2 and S_mO_2, our data suggest that NTG might be preferable for blood pressure control during surgical procedures involving aortic cross-clamping.

4.3.5 References

1. Gelman S. The pathophysiology of aortic cross-clamping and unclamping. Anesthesiology 1995; 82: 1026-60

2. Azakie A, Muse J, Gardner M, Skidmore KL, Miller SP, Karl TR, McQuillen PS. Cerebral oxygen balance is impaired during repair of aortic coarctation in infants and children. J Thorac Cardiovasc Surg 2005; 130: 830-6

3. Gelman S, Reves JG, Fowler K, Samuelson PN, Lell WA, Smith LR. Regional blood flow during cross-clamping of the thoracic aorta and infusion of sodium nitroprusside. J Thorac Cardiovasc Surg 1983; 85: 287-91

4. Marini CP, Grubbs PE, Toporoff B, Woloszyn TT, Coons MS, Acinapura AJ, Cunningham JN. Effect of sodium nitroprusside on spinal cord perfusion and paraplegia during aortic cross-clamping. Ann Thorac Surg 1989; 47: 379-83

5. Cernaianu AC, Olah A, Cilley JH Jr, Gaprindashvili T, Gallucci JG, DelRossi AJ. Effect of sodium nitroprusside on paraplegia during cross-clamping of the thoracic aorta. Ann Thorac Surg 1993; 56: 1035-8

6. Vuylsteke A, Feneck RO, Jolin-Mellgard A, Latimer RD, Levy JH, Lynch C 3rd, Nordlander ML, Nystrom P, Ricksten SE. Perioperative blood pressure control: a prospective survey of patient management in cardiac surgery. J Cardiothorac Vasc Anesth 2000; 14: 269-73

7. Kim MB, Ward DS, Cartwright CR, Kolano J, Chlebowski S, Henson LC. Estimation of jugular venous O2 saturation from cerebral oximetry or arterial O2 saturation during isocapnic hypoxia. J Clin Monit Comput 2000; 16: 191-9
8. McNeill S, Gatenby JC, McElroy S, Engelhardt B. Normal cerebral, renal and abdominal regional oxygen saturations using near-infrared spectroscopy in preterm infants. J Perinatol 2011; 31: 51-7
9. Moerman A, De Hert S, Jacobs T, De Wilde L, Wouters P. Cerebral oxygen desaturation during beach chair position. Eur J Anaesthesiol 2012; 29: 82–7
10. Berens RJ, Stuth EA, Robertson FA, Jaquiss RD, Hoffman GM, Troshynski TJ, Staudt SR, Cava JR, Tweddell JS, Bert Litwin S. Near infrared spectroscopy monitoring during pediatric aortic coarctation repair. Paediatr Anaesth 2006; 16: 777-81
11. Steiner LA, Pfister D, Strebel SP, Radolovich D, Smielewski P, Czosnyka M. Near-infrared spectroscopy can monitor dynamic cerebral autoregulation in adults. Neurocrit Care 2009; 10: 122-8
12. Brady K, Joshi B, Zweifel C, Smielewski P, Czosnyka M, Easley RB, Hogue CW Jr. Real-time continuous monitoring of cerebral blood flow autoregulation using near-infrared spectroscopy in patients undergoing cardiopulmonary bypass. Stroke 2010; 41: 1951-6
13. Stånge K, Lagerkranser M, Sollevi A. Nitroprusside-induced hypotension and cerebrovascular autoregulation in the anesthetized pig. Anesth Analg 1991; 73: 745-52
14. Endoh H, Honda T, Ohashi S, Hida S, Shibue C, Komura N. The influence of nicardipine-, nitroglycerin-, and prostaglandin E(1)-induced hypotension on cerebral pressure autoregulation in adult patients during propofol-fentanyl anesthesia. Anesth Analg 2002; 94: 169-73
15. Moppett IK, Sherman RW, Wild MJ, Latter JA, Mahajan RP. Effects of norepinephrine and glyceryl trinitrate on cerebral haemodynamics: transcranial Doppler study in healthy volunteers. Br J Anaesth 2008; 100: 240-4

16. Conti A, Iacopino DG, Fodale V, Micalizzi S, Penna O, Santamaria LB. Cerebral haemodynamic changes during propofol-remifentanil or sevoflurane anaesthesia: transcranial Doppler study under bispectral index monitoring. Br J Anaesth 2006; 97: 333-9
17. Endrich B, Franke N, Peter K, Messmer K. Induced hypotension: action of sodium nitroprusside and nitroglycerin on the microcirculation. Anesthesiology 1987; 66: 605-13
18. Sakamoto T, Hatsuoka S, Stock UA, Duebener LF, Lidov HG, Holmes GL, Sperling JS, Munakata M, Laussen PC, Jonas RA. Prediction of safe duration of hypothermic circulatory arrest by near-infrared spectroscopy. J Thorac Cardiovasc Surg 2001; 122: 339-50
19. Huang JH, Su ZK, Wang SM. Near-infrared spectroscopy monitoring of brain oxygen in infant cardiac surgery. Asian Cardiovasc Thorac Ann 2007; 15: 194-9
20. Ortmann LA, Fontenot EE, Seib PM, Eble BK, Brown R, Bhutta AT. Use of near-infrared spectroscopy for estimation of renal oxygenation in children with heart disease. Pediatr Cardiol 2011; 32: 748-53
21. Owens GE, King K, Gurney JG, Charpie JR. Low renal oximetry correlates with acute kidney injury after infant cardiac surgery. Pediatr Cardiol 2011; 32: 183-8
22. Fuentes-Garcia D, Carceles-Baron MD, Lopez-Lopez R, Roques-Escolar V. Non-invasive oximetry for early detection of cerebral and somatic ischaemia during corrective surgery for aortic coarctation in paediatric patients. Br J Anaesth 2010; 104: 780-2

4.4 NIRS during aortic aneurysm repair

Near-Infrared Spectroscopy for Monitoring Spinal Cord Ischemia during Hybrid Thoracoabdominal Aortic Aneurysm Repair. Moerman A, Van Herzeele I, Vanpeteghem C, Vermassen F, François K, Wouters P. J Endovasc Ther 2011; 18: 91-5

Abstract

Purpose: To describe a simple, non-invasive technique to detect changes in oxygen saturation at the level of the spinal cord and to suggest its suitability for individualized blood pressure management during and after thoracoabdominal aneurysm repair.
Case report: Near-Infrared Spectroscopy (NIRS) sensors were applied over the tenth thoracic vertebra for continuous monitoring of tissue oxygen saturation (S_sO_2) during endovascular repair of a post-dissection aneurysm of the aortic arch and descending aorta. After stent-graft deployment mean S_sO_2 decreased significantly. Moreover the relationship between S_sO_2 and arterial blood pressure became linear, reflecting pressure-dependency of spinal cord perfusion after stent deployment.
Conclusion: These data show that NIRS monitors changes in S_sO_2 after aortic endograft deployment which were strongly related to arterial blood pressure. Regional NIRS monitoring at the vertebral level may function as a valuable non-invasive guide to the management of blood pressure during thoracoabdominal aneurysm repair, both intra- and postoperatively.

4.4.1 Introduction

During thoracoabdominal aortic aneurysm (TAAA) repair, spinal cord perfusion is precarious and vulnerable to hemodynamic compromise, eventually leading to neurologic injury [1,2]. Close monitoring is mandatory to detect spinal cord ischemia in time to treat it. Near-Infrared Spectroscopy (NIRS) is a non-invasive continuous monitoring technique to measure tissue oxygen saturation [3]. Whereas initial research focused on the use of NIRS for monitoring cerebral saturation, interest has now extended to evaluating the oxygenation of tissues other than the brain. To date, research on the use of NIRS to monitor spinal cord oxygenation is scarce: Only animal studies [4,5] and 3 clinical reports [6-8] have examined the feasibility of NIRS to monitor spinal cord perfusion.

We present a case where tissue oxygen saturation at the level of the spinal cord (S_sO_2) decreased significantly after aortic endograft deployment and became strongly related to arterial blood pressure.

4.4.2 Case report

A 53-year old man with an extensive medical history, including replacement of the aortic valve and ascending aorta (Bentall procedure) for acute aortic dissection in 1998 and replacement of the ascending aorta and proximal aortic arch for acute aortic dissection in 2008, presented with a large TAAA due to chronic dissection from the distal aortic arch into the iliac arteries. The patient was scheduled for a staged hybrid repair. In the first phase, extra-anatomical revascularization of the supra-aortic arteries from the proximal ascending aorta was done, followed by placement of endografts in the distal ascending aorta, aortic arch, and descending aorta. In the second phase, open abdominal repair with retrograde perfusion of the celiac, mesenteric, and renal arteries was planned, with further exclusion of the TAAA by stent-grafting. Local Ethics' Committee approval and written informed consent from the patient were obtained.

The hybrid arch procedure was performed under general anesthesia with full hemodynamic monitoring. A cerebrospinal fluid (CSF) drain was positioned at a height of 13.5 cmH_2O above the external meatus, which equated to a pressure of 10 mmHg within the spinal canal. CSF was allowed to drain continuously. Disposable NIRS sensors were applied to the right and the left side of the forehead, over the tenth thoracic vertebra (T10), and over the right calf, and tissue oxygen saturation was monitored continuously during the entire procedure (INVOS 5100; Somanetics Corporation, Troy, MI, USA). All hemodynamic, respiratory and tissue oxygen saturation data were recorded continuously with RUGLOOP (Demed, Temse, Belgium).

The extra-anatomical revascularization of the arch vessels was carried out through a median sternotomy. The arch vessels were anastomosed to a bifurcated graft that was sewn proximally onto the ascending aortic tube graft. Epicardial ventricular pacemaker wires were placed to allow induction of hypotension by rapid ventricular pacing during deployment of the stent-grafts. Subsequently, the Excluder TAG devices (W. L. Gore & Associates, Inc, Flagstaff, AZ, USA) were delivered via the right common femoral artery. A TAG (37×200 mm) was introduced and deployed distal to the arch vessels origin; a second stent-graft (37×150 mm) was deployed with sufficient overlap in the descending thoracic aorta, but during removal of the delivery device, this stent-graft was accidentally withdrawn. Retrieval of the misdeployed stent-graft (still connected to the release wire and the inner shaft of the delivery device) was accomplished via an infrarenal aortotomy. The infrarenal abdominal aortic aneurysm was repaired with a bifurcation graft (Dacron 18×9 mm) connected to both common iliac arteries. Finally, a TAG (37×150 mm) was deployed uneventfully in the residual descending thoracic aorta with sufficient overlap, terminating proximal to the diaphragm.

Mean S_sO_2 decreased significantly from $76 \pm 2.6\%$ (from start of measurement until deployment of first stent-graft) to $61 \pm 5.6\%$ (from deployment of last stent-graft until the end of the operation) (P<0.001) (Fig. 4.2).

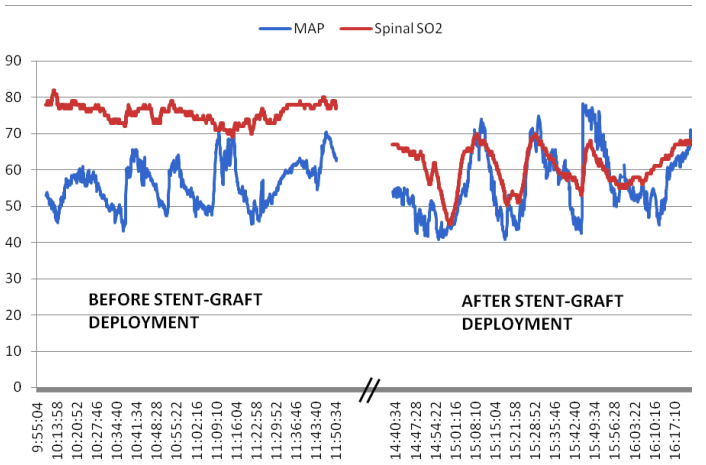

Figure 4.2: Relationship between spinal saturation (S_sO_2) and mean arterial blood pressure (MAP) before and after stent-graft deployment during first operation.

Prior to stent-graft deployment, mean S_sO_2 fluctuated only mildly with mean arterial blood pressure (MAP), while after stent-graft deployment, small decreases in arterial blood pressure provoked major decreases in S_sO_2. This pressure dependency is quantified in Figure 4.3: the correlation between MAP and S_sO_2 was clearly linear after deployment of the devices, whereas there was no correlation before stent-graft deployment.

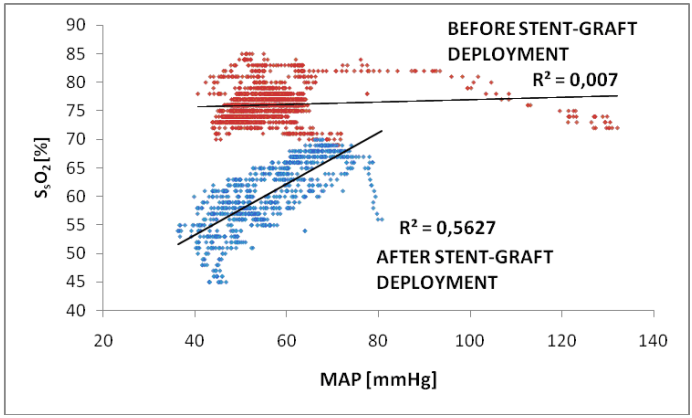

Figure 4.3: Correlation between spinal saturation (S_sO_2) and mean arterial blood pressure (MAP) before and after stent-graft deployment during first operation.

Twelve days later, the second part of the hybrid procedure was performed. A spinal drain was inserted and NIRS sensors were placed over the left and right forehead and at 2 locations over the spinal column: at T10 and at the second lumbar vertebra (L2). The visceral vessels were revascularized by the implantation of a bifurcated Dacron graft anastomosed to the previously implanted bifurcated graft. The right limb was connected to the common hepatic artery and tunnelled behind the pancreas; the left limb was anastomosed to the superior mesenteric trunk. Finally, a Dacron graft originating from the right limb was connected in an end-to-end fashion to the right renal artery. The remaining TAAA was excluded by deployment of 3 stent-grafts with sufficient overlap (TAG 28×150 mm, 31×150 mm and 37×150 mm). Hypotension to prevent movement of the stent-grafts during deployment was accomplished with nitroprusside. The devices were deployed in a retrograde fashion and positioned proximal to the bifurcated graft perfusing the visceral arteries.

Correlation between MAP and S_sO_2 revealed that spinal cord perfusion had become less pressure dependent in the days following the first operation (r^2=0.29 vs r^2=0.56 immediately after first operation) (Fig. 4.4).

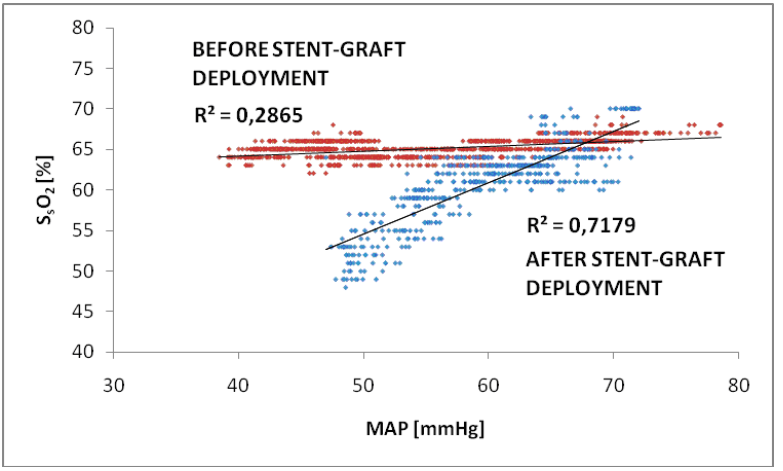

Figure 4.4: Correlation between spinal saturation (S_sO_2) at T10 level and mean arterial blood pressure (MAP) before and after stent-graft deployment during second operation.

Despite very low systemic blood pressures, S_sO_2 at the T10 and L2 levels remained unaffected before stent-graft deployment (Fig. 4.5). After endograft release, the pressure dependency of spinal cord perfusion was again manifested at the T10 level, consistent with the observation made in the first operation. However, this time an additional measurement at L2 served as control; at the L2 level, this phenomenon was not seen.

The patient recovered without any neurological dysfunction and his TAAA has been succesfully excluded over 9 months of follow-up.

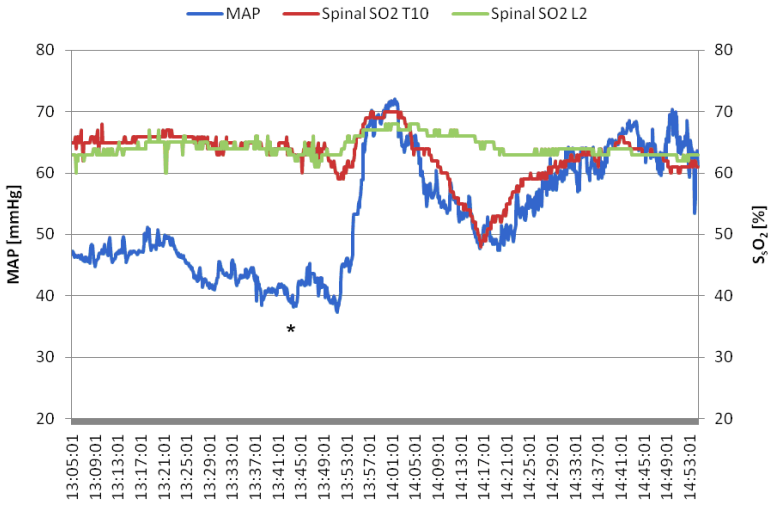

Figure 4.5: Relationship between spinal saturation (S_sO_2) at the T10 and L2 level and mean arterial blood pressure (MAP) during second operation. Asterisk (*) represents stent-graft deployment.

4.4.3 Discussion

During endovascular TAAA repair, tissue oxygen saturation at the T10 level dropped significantly after endograft deployment. Furthermore, a significant linear relationship was noted between S_sO_2 and arterial blood pressure after stent-graft deployment, which was not present before stent-graft deployment. As NIRS seems to reflect pressure dependence of spinal cord perfusion, its utility as a guide to optimize perioperative blood pressure management during TAAA repair deserves further investigation.

NIRS exploits the fact that biological tissues, including bone, are transparent in the near-infrared range [3]. Specific wavelengths of near-infrared light are emitted through the tissues lying below a sensor. Depending on the amount of light reflected back to light

detectors built into the same sensor, regional oxygen saturation of the underlying tissue can be determined. The mean depth of light transmission is proportional to the emitter-detector separation by a factor of approximately one third [9]. The use of 2 photodetectors allows selective measurement of deeper tissue, a process known as spatial resolution: the closer receiver measures superficial tissue while the distal optode measures both superficial and deeper tissue. After adjusting for interference from the superficial tissues, oxygenation of deeper tissues is derived.

Initial animal studies demonstrated the feasibility of NIRS to monitor the spinal cord. Macnab et al. [4] exposed the posterior elements of the spine in 3 pigs; they sutured NIRS optodes directed toward the spinal cord over the T9 laminae or on the spinous processes of T9 and T10. Interventions included decreasing the arterial oxygen saturation and distracting the spine at T9-T10, which reduced blood flow to the spinal cord. Each intervention resulted in NIRS changes that were observed immediately and resolved promptly, independent of the position of the optodes. LeMaire et al. [5] sequentially ligated segmental arteries from T6 through L1 in pigs, while regional oxygen saturation was monitored with NIRS in the upper (T6-T7) and lower cord (T9-T11). After ligation, regional oxygen saturation in the lower cord was significantly less than in the upper cord. This regional difference in the degree of ischemia was confirmed microscopically, with significantly more pronounced ischemic changes and more ischemic neurons in the lower-cord sections.

To date, 3 reports have described the use of NIRS for monitoring spinal cord oxygenation in humans. Macnab et al. [6] used NIRS in an infant requiring release of a congenitally tethered spinal cord. Subsequently, in a series of 9 patients undergoing TAAA repair, Edmonds and Ganzel [7] observed a greater decline in spinal saturation measured at T10 in patients who experienced lower limb motor deficit compared to patients without deficit. This decline was consistent with the results of simultaneously performed spinal

cord transmission measurements. Mitchell et al. [8] noted a significant drop in perispinal regional oxygen saturation at the T10 level during coarctation repair in neonates. Removal of the aortic clamp immediately restored the perispinal saturation to baseline values.

In NIRS monitoring of spinal cord ischemia, the optically interrogated region is not well-defined, which may pose a problem. One concern is that oxygenation in the surrounding tissues, such as muscle and subcutaneous tissue, is measured instead of oxygenation in the spinal cord. Although the spatial resolution reduces the influence of outer layers, not all extraspinal structures may have been excluded. Nevertheless, NIRS data on regional oxygenation may adequately reflect spinal cord perfusion, albeit indirectly, as a collateral network ensures the shared blood supply between the spinal cord and the surrounding tissues [10]. In order to prove this concept, LeMaire et al. [5] injected indocyanine green dye into the subarachnoid space and found an immediate change in light absorption, suggesting that at least some of the photons were reaching the spinal cord.

In our case, 2 observations support the viewpoint that saturation at the spinal cord level measured by NIRS (directly or indirectly) reflects spinal cord perfusion. First, S_sO_2 at T10, which was initially pressure independent, became strongly influenced by arterial blood pressure after endograft deployment. This is consistent with published reports that have described the treatment of spinal cord ischemia after endovasculair repair by increasing the arterial pressure [2,11]. In addition, spinal cord perfusion became less pressure dependent in the days following the first operation, which Etz et al. [12] also observed in their study. Spinal cord perfusion pressure spontaneously returned to baseline values after $\sim$ 48 hours.

Second, after deployment of stent-grafts from the diaphragm to the level of the bifurcated graft perfusing the visceral arteries, NIRS values at T10 were significantly decreased by changes in arterial blood pressure, whereas at the L2 level, S_sO_2 remained stable (Fig. 4.5). This may be explained by the segmental nature of spinal

perfusion and may suggest that S_sO_2 measurement includes the spinal vasculature.

Somatosensory-evoked potentials (SSEPs) and motor-evoked potentials (MEPs) monitoring are primarily used to monitor spinal cord perfusion, although no prospective studies have proven its efficacy to reduce spinal cord injury. Nevertheless, several reports have demonstrated that spinal cord ischemia detected with SSEPs and/or MEPs could be corrected with appropriate interventions [13,14]. Still, SSEPs and MEPs monitoring is not widely used because of its limitations. NIRS could be useful as an adjunctive tool to assess the entire spinal cord perfusion. Or, it may offer a simple alternative for monitoring spinal cord ischemia when SSEPs and/or MEPs are unavailable, especially in the postoperative period in which SSEP/MEP monitoring is generally impractical or impossible.

Conclusion

To our knowledge, no one has demonstrated the dependence of oxygen saturation at the level of the spinal cord on blood pressure after thoracic stent-graft deployment. These preliminary data suggest that NIRS may be employed for individualized management of blood pressure during TAAA repair, both intra- and postoperatively. Further investigations are required to compare NIRS with SSEPs and MEPs monitoring and to evaluate whether measuring and intervening on the values obtained by NIRS make a difference in the neurological outcome of patients who undergo repair of extensive thoracoabdominal aneurysms.

4.4.4 References

1. Etz CD, Luehr M, Kari FA, et al. Paraplegia after extensive thoracic and thoracoabdominal aortic aneurysm repair: Does critical spinal cord ischemia occur postoperatively? J Thorac Cardiovasc Surg 2008; 135: 324-30
2. Azizzadeh A, Huynh TT, Miller CC III, et al. Postoperative risk factors for delayed neurologic deficit after thoracic and thoracoabdominal aortic aneurysm repair: A case-control study. J Vasc Surg 2003; 37: 750-4
3. Murkin JM, Arango M. Near-infrared spectroscopy as an index of brain and tissue oxygenation. Br J Anaesth 2009; 103 (Suppl. 1): i3-i13
4. Macnab AJ, Gagnon RE, Gagnon FA. Near Infrared Spectroscopy for intraoperative monitoring of the spinal cord. Spine 2002; 27: 17-20
5. LeMaire SA, Ochoa LN, Conklin LD, et al. Transcutaneous near-infrared spectroscopy for detection of regional spinal ischemia during intercostal artery ligation: Preliminary experimental results. J Thorac Cardiovasc Surg 2006; 132: 1150-5
6. Macnab AJ, Gagnon RE, Gagnon FA, et al. NIRS monitoring of brain and spinal cord – detection of adverse intraoperative events. Spectroscopy 2003; 17: 483-90
7. Edmonds Jr H, Ganzel B. Spinal oximetry for ischemia detection during thoracoabdominal aneurysm repair [abstract]. Anesth Analg 2004; 98: SCA 72
8. Mitchell ME, Sehic A, Edmonds Jr HL, et al. Non-invasive peri-spinal oximetry for aortic coarctation repair [abstract]. Clinical Neurophysiology 2006; 117: S238
9. Germon TJ, Evans PD, Barnett NJ, et al. Cerebral near infrared spectroscopy: emitter-detector separation must be increased. Br J Anaesth 1999; 82: 831-7
10. Griepp RB, Griepp EB. Spinal cord perfusion and protection during descending thoracic and thoracoabdominal aortic surgery: The collateral network concept. Ann Thorac Surg 2007; 83: S865-9
11. Cheung AT, Pochettino A, McGarvey ML, et al. Strategies to manage paraplegia risk after endovascular stent repair of descending thoracic aortic aneurysms. Ann Thorac Surg 2005; 80: 1280-9

12. Etz CD, Homann TM, Plestis KA, et al. Spinal cord perfusion after extensive segmental artery sacrifice: can paraplegia be prevented? Eur J Cardiothorac Surg 2007; 31: 643-8
13. Jacobs MJ, de Mol BA, Elenbaas Ted, et al. Spinal cord blood supply in patients with thoracoabdominal aortic aneurysms. J Vasc Surg 2002; 35: 30-7
14. Schurinck GW, Nijenhuis RJ, Backes WH, et al. Assessment of spinal cord circulation and function in endovascular treatment of thoracic aortic aneurysms. Ann Thorac Surg 2007; 83: S877-81

Chapter 5

NIRS as an estimate of venous oxygen saturation

5.1 Background

Initially, the interest in the use of cerebral oximetry focused on the detection of asymmetric changes, indicating a potentially catastrophic cerebral event. In recent years, a growing understanding of the physiological principles of NIRS led to a more complete appreciation of its potential.

NIRS measures regional oxygen saturation in the cerebral cortex, which is a predominantly venous bed [1,2]. Therefore, cerebral oxygen saturation measured with NIRS primarily reflects venous oxygen saturation. When cardiac output decreases progressively, cerebral autoregulation and preferential distribution of cardiac output to the brain preserves perfusion to the brain longer than perfusion to any other organ system. Consequently, decreases in cerebral venous oxygen saturation usually occur when global venous oxygen saturation is also deteriorating. Not surprisingly, NIRS-measured cerebral oxygen saturation was shown not only to correlate with oxygen saturation in blood obtained from the internal jugular vein

[3], but also from the pulmonary artery [4] and superior caval vein [3,4].

Even though perfusion of the brain is momentarily preserved when cardiac output declines, the brain appears to offer a "window" on global hemodynamics and NIRS seems to provide a non-invasive monitoring tool to assess global tissue perfusion. This notion is supported by the results of Murkin [5] who showed that optimizing cerebral NIRS also enhanced global tissue oxygenation, resulting in significantly less major (non-cerebral) organ morbidity. Recently, NIRS has been suggested as a potentially valuable biomarker in tracking the status of heart failure patients [6]. Heringlake et al. demonstrated that preoperative cerebral oxygen saturation is reflective of global cardiopulmonary function, associated with short- and long-term mortality and morbidity in cardiac surgery patients [7].

Mixed venous oxygen saturation ($S_{mv}O_2$) is generally accepted as an indicator of adequacy of systemic oxygen balance, and its use for guidance of therapy has been demonstrated to improve outcome [8]. However, its obligatory need for more invasive instrumentation precludes its use as a standard routine monitoring in perioperative care. The availability of an easy to use, reliable, and non-invasive monitor of global oxygen balance would benefit a much wider spectrum of patients at risk for anesthesia and surgery.

References

1. Ito H, Kanno I, Fukuda H. Human cerebral circulation: positron emission tomography studies. Ann Nucl Med 2005; 19: 65-74

2. Watzman HM, Kurth CD, Montenegro LM, Rome J, Steven JM, Nicolson SC. Arterial and venous contributions to near-infrared cerebral oximetry. Anesthesiology 2000; 93: 947-53

3. Nagdyman N, Ewert P, Peters B, Miera O, Fleck T, Berger F. Comparison of different near-infrared spectroscopic cerebral oxygenation indices with central venous and jugular venous oxygenation saturation in children. Paediatr Anaesth 2008; 18: 160-6
4. Tortoriello TA, Stayer SA, Mott AR, et al. A noninvasive estimation of mixed venous oxygen saturation using near-infrared spectroscopy by cerebral oximetry in pediatric cardiac surgery patients. Paediatr Anaesth 2005; 15: 495-503
5. Murkin JM, Adams SJ, Novick RJ, et al. Monitoring brain oxygen saturation during coronary bypass surgery: a randomized, prospective study. Anesth Analg 2007; 104: 51-8
6. Rifai L, Winters J, Friedman E, Silver MA. Initial description of cerebral oximetry measurement in heart failure patients. Congest Heart Fail 2012; 18: 85-90
7. Heringlake M, Garbers C, Kabler JH. Preoperative cerebral oxygen saturation and clinical outcomes in cardiac surgery. Anesthesiology 2011; 114: 58-69
8. Pölönen P, Ruokonen E, Hippeläinen M, Pöyhönen M, Takala J. A prospective, randomized study of goal-oriented hemodynamic therapy in cardiac surgical patients. Anesth Analg 2000; 90: 1052-9

5.2 Objective

The aim of the study was to evaluate the feasibility of NIRS as a non-invasive monitor of global oxygen balance, providing a reliable estimate of systemic venous oxygen saturation.

5.3 NIRS as an estimate of venous saturation

Relation between mixed venous oxygen saturation and cerebral oxygen saturation measured by absolute and relative near-infrared spectroscopy during off-pump coronary artery bypass grafting. Moerman A, Vandenplas G, Bové T, Wouters P, De Hert S. Br J Anaesth 2013; 110: 258-65

Abstract

Background. We hypothesized that previously reported contradictory results regarding the equivalence of mixed venous ($S_{mv}O_2$) and cerebral (rS_cO_2) oxygen saturation might be related to time delay issues and to measurement technology. In order to explore these two factors, we designed a prospective clinical study comparing $S_{mv}O_2$ with relative (INVOS) and absolute (Foresight) rS_cO_2 measurements.

Methods. Forty-two consenting patients undergoing elective off-pump coronary artery bypass grafting were included. Two INVOS and two Foresight sensors continuously registered rS_cO_2. $S_{mv}O_2$ was measured continuously via a pulmonary artery catheter. Data were assessed by within- and between-group comparisons and correlation analysis.

Results. A similar time delay of 19 (4) and 18 (4) s was found for $S_{mv}O_2$ compared with rS_cO_2 measurements by Foresight and INVOS, respectively, during hemodynamic changes. After adjusting for this time delay, the correlation between $S_{mv}O_2$ and rS_cO_2 increased from r=0.25 to 0.75 (P<0.001) for Foresight, and from r=0.28 to 0.73 (P<0.001) for INVOS. Comparison of Foresight and INVOS revealed significant differences in absolute rS_cO_2 values (range 58–89% for Foresight and 28–95% for INVOS). Changes in rS_cO_2 in response to acute hemodynamic alterations were significantly more pronounced with INVOS compared with Foresight (P<0.001).

Conclusions. Considering the important time delay with $S_{mv}O_2$, rS_cO_2 seems to reflect more appropriately acute hemodynamic

alterations. This might suggest its use as a valid alternative to invasive monitoring of tissue oxygen saturation. Relative and absolute rS_cO_2 measurements demonstrated significant differences in measured rS_cO_2 values and in the magnitude of rS_cO_2 changes during hemodynamic alterations.

5.3.1 Introduction

A primary goal of hemodynamic management of patients undergoing surgery is to provide adequate tissue oxygenation. Mixed venous oxygen saturation ($S_{mv}O_2$) is generally accepted as an indicator of adequacy of systemic oxygen balance, and its use for guidance of therapy has been demonstrated to improve outcome [1]. Owing to its invasiveness, this variable is not commonly incorporated into routine anesthesia monitoring. The availability of an easy to use, reliable, and non-invasive monitor of global oxygen balance would benefit a much wider spectrum of patients at risk for anesthesia and surgery.

Near-infrared spectroscopy (NIRS) measures regional cerebral oxygen saturation (rS_cO_2) in the cerebral cortex, which is a predominantly venous bed [2]. The findings of Murkin and colleagues [3] suggest that cerebral oximetry might be useful as an index for global oxygen delivery and consumption, indicating that NIRS might offer a continuous, non-invasive alternative for $S_{mv}O_2$.

Previous studies found contradictory results regarding the equivalence and interchangeability of $S_{mv}O_2$ and rS_cO_2 data [4-12]. We hypothesized that this inconsistency might be related to two factors. First, $S_{mv}O_2$ values were recorded intermittently, providing only isolated epochs for comparison such that time delay issues may not have been taken into account. Secondly, rS_cO_2 measurements were all performed with the INVOS cerebral oximeter (Somanetics Corporation, Troy, MI, USA), which is approved by the Food and Drug Administration (FDA) as a relative cerebral oximeter or a trend monitor [K051274 FDA 510(k) premarket notification]. Hence, the reported poor correlations might be the result of inherent limitations

of the measurement technology.

In order to explore these two hypotheses, we designed a prospective observational clinical study comparing continuously measured $S_{mv}O_2$ with both relative and absolute rS_cO_2 measurements. Because we wanted to evaluate both experimental questions in a wide range of hemodynamic changes, we chose a model of off-pump coronary artery bypass (OPCAB) surgery, as the course of this procedure entails significant hemodynamic alterations during surgical exposure and cardiac manipulation. The Foresight cerebral oximeter (CAS Medical Systems, Branford, CT, USA) was chosen as comparative NIRS technology, since it claims to be an absolute cerebral oximeter (www.casmed.com), providing absolute rS_cO_2 values [13,14].

5.3.2 Methods

This trial is registered at ClinicalTrials.gov (NCT01673841). After Institutional Ethics Committee approval and written informed consent, 42 patients undergoing elective OPCAB surgery for at least three-vessel coronary artery disease were included. Patients with arteriovenous shunts, intracardiac shunts, a previous history of cerebrovascular accident, or stenosis of the internal carotid artery of >60% were excluded.

Description of NIRS devices

The physical principles upon which NIRS is based have been described [15]. In general terms, NIRS utilizes the absorption and reflectance spectra of near-infrared light to quantify oxygenation of tissues underlying the sensor. Both INVOS and Foresight use the Modified Beer-Lambert law to measure tissue oxygen saturation, and eliminate the contribution of extracerebral tissue by using the principle of spatial resolution (depth of photon penetration proportional to the source-detector separation). However, some important technical differences exist. The INVOS 5100 generates two wavelengths of light at 730 and 810 nm from light emitting diodes, while Foresight uses

laser-emitting diodes to generate light at four different wavelengths (690, 778, 800 and 850 nm). The spacing of the light detectors from the light emitter, which influences the sample volume and depth of penetration, is at 3 and 4 cm distance for INVOS 5100, and at 1.5 and 5 cm for Foresight. There is also a difference in assumed cerebral arterial:venous ratio upon which the oximetry values are calculated (assumed ratio of 25:75 for INVOS and 30:70 for Foresight). Owing to the technical differences and the different computational algorithms for the calculation of tissue saturation, the comparability between INVOS 5100 and Foresight is not clear.

Study design

On the morning of surgery, subjects were allowed to take their routine medication, except for angiotensin-converting enzyme inhibitors. Four disposable oxygenation sensors [two INVOS sensors (INVOS 5100, Somanetics Corporation) and two Foresight sensors (CAS Medical Systems)] were applied bilaterally on the forehead for continuous registration of rS_cO_2. The sensors of one monitor were placed just above the eyebrows, and the sensors of the other monitor were placed just above the former sensors. Sensor placement was determined at random by a computerized randomization list. Baseline values were obtained at least 1 minute after placement of sensors until values were stabilized. Anesthesia was induced with diazepam 0.1 mg/kg, fentanyl 5 μg/kg, propofol 1 mg/kg, and rocuronium 1 mg/kg. The lungs were ventilated mechanically with oxygen enriched air (fractional inspired oxygen 0.6) adjusted to keep the end-tidal carbon dioxide ($EtCO_2$) around 4.7 kPa. Anesthesia was maintained with boluses of fentanyl up to a total dose of 25-35 μg/kg and sevoflurane at a minimum concentration of 1.5 vol%. Standard monitoring was used throughout the procedure, including ECG, pulse oximetry, capnography, invasive arterial, central venous and pulmonary artery pressure monitoring, continuous $S_{mv}O_2$ monitoring [Swan-Ganz CCOmbo pulmonary artery catheter (Edwards lifesciences,

Irvine, CA, USA)], and transoesophageal echocardiography.

Hemodynamic management was at the discretion of the attending anesthetist. All variables were recorded continuously with RUGLOOP (Demed, Temse, Belgium) and were analysed at two seconds intervals. Types and volumes of all fluids were recorded, as well as doses of any drugs given.

To explore interference when Foresight and INVOS were operating simultaneously, we included a methodological evaluation of the reliability of our data. During preparation of the internal thoracic artery - which includes a hemodynamic stable period - the monitors were switched off one at a time for 5 min. During these periods, the mean rS_cO_2 and standard deviation (SD) were measured for each monitor separately and compared with mean (SD) obtained during the 5 min preceding this intervention when both monitors were operating simultaneously.

The response of rS_cO_2 to major hemodynamic disturbances was explored during placement of deep pericardial stitches. During every heart retraction, which induced a substantial decrease in mean arterial pressure (MAP), relative changes in MAP, rS_cO_2 and $S_{mv}O_2$ were calculated at 5 (T1) and 10 s (T2) after start of heart retraction, at the minimum value of MAP (T3), and at 5 (T4), 10 (T5), 15 (T6) and 20 (T7) s after release of heart retraction. Relative change was defined as the percentage difference between the value just before heart retraction and the value at the different time moments. The integrated value or area under the curve (AUC) for rS_cO_2 during placement of the pericardial stitches was also explored to evaluate the response of rS_cO_2 to major hemodynamic disturbances . The AUC was calculated by taking the difference between the current values and the value just before heart retraction, multiplied by the corresponding time in seconds, and is expressed in %.sec.

Statistical analysis

Sample size calculation was based on an aimed correlation coefficient of 0.5 between $S_{mv}O_2$ and rS_cO_2 values [5,6]. Accepting a two-tailed α error of 0.01 and a β error of 0.8, 42 subjects were required. Statistical analysis was performed using SPSS Statistics 20 (SPSS Inc., Chicago, IL, USA). Distribution of data was tested for normality using the Shapiro-Wilk test. Normally distributed continuous data are presented as mean (SD). Non-parametric data are presented as median [range]. Comparison of data between Foresight and INVOS were performed by the Mann-Whitney U analysis. Correlation analysis was performed by the Pearson or Spearman's ρ testing as appropriate. P-values <0.05 were considered significant.

5.3.3 Results

Thirty male and 12 female subjects with an average age of 72 (8) yr, weight of 78 (16) kg, and height of 166 (8) cm were included. Awake rS_cO_2 values were 70 (4)% and 69 (3)% for Foresight on the left and right side, respectively, and 64 (10)% and 64 (9)% for INVOS on the left and right side, respectively (P<0.001 between Foresight and INVOS). For further analysis, right and left cerebral saturations of the corresponding monitoring system were averaged.

Mutual interference of monitors

With both monitors running simultaneously, Foresight exhibited more variability in rS_cO_2 than when INVOS was switched off (0.9 (0.4)% compared with 0.5 (0.2)%, P=0.004) (Fig. 5.1). INVOS performance was not affected by the presence of Foresight (0.6 (0.2)% *vs* 0.7 (0.2)% Foresight on-off, respectively, n.s.). Simultaneous operation did not affect the mean rS_cO_2 values for either monitor (INVOS mean values 72 (9)% compared with 70 (15)% with Foresight on and off, respectively; Foresight mean values 70 (4)% compared with 70 (4)% with INVOS on and off, respectively).

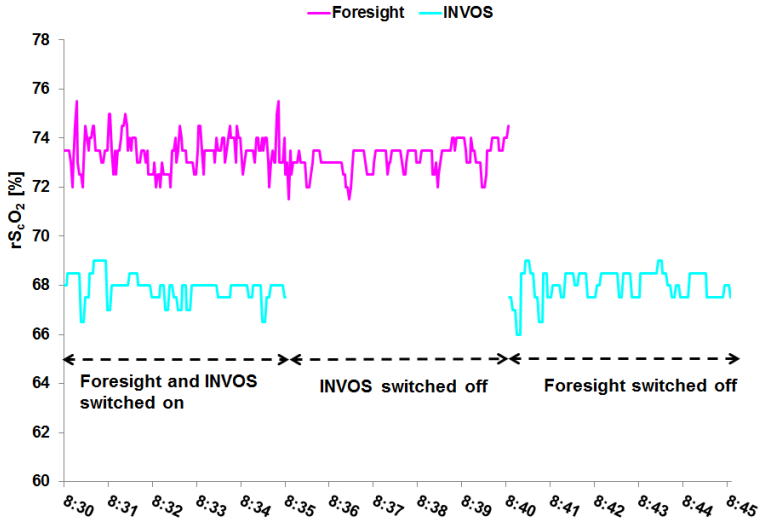

Figure 5.1: Representative example illustrating higher variability of Foresight regional cerebral oxygen saturation (rS_cO_2) values when Foresight and INVOS monitors were operating simultaneously.

Hypothesis 1: time delay issues are responsible for reported poor correlations

To explore this hypothesis, $S_{mv}O_2$, rS_cO_2 and MAP were displayed graphically for each subject separately. Figure 5.2 illustrates a representative case during the placement of deep pericardial stitches, which was associated with substantial hemodynamic alterations. MAP decreased briefly every time the heart was retracted to allow the placement of the pericardial stitches. NIRS values followed immediately, while $S_{mv}O_2$ values obviously lagged behind. This resulted in a poor correlation between $S_{mv}O_2$ and rS_cO_2 at the moment of placement of the pericardial stitches: r=0.25 [0.01-0.67] for Foresight and r=0.28 [0.10-0.63] for INVOS, with no significant difference between monitors.

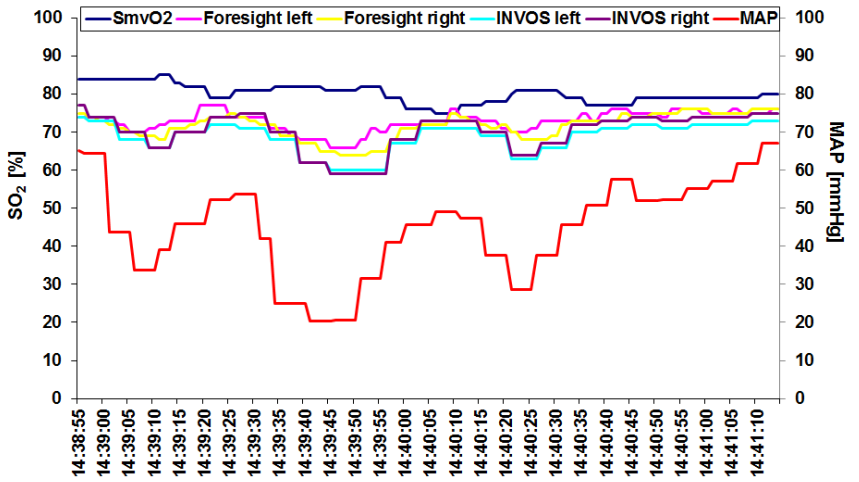

Figure 5.2: Representative case showing substantial changes in mean arterial blood pressure (MAP) (red line) associated with retraction of the heart during placement of deep pericardial stitches. Changes in MAP were closely followed by changes in cerebral oxygen saturation measured by Foresight (pink and yellow lines) and INVOS (light blue and violet lines), while mixed venous oxygen saturation ($S_{mv}O_2$) (dark blue line) obviously lagged behind.

The mean time delay between $S_{mv}O_2$ and MAP or rS_cO_2 (calculated as the number of seconds between minimum $S_{mv}O_2$ and minimum MAP or minimum rS_cO_2) was 18 (4), 19 (4) and 18 (4) seconds for MAP, Foresight and INVOS respectively. After adjusting for this time delay, taking the nadir value for each variable, the correlation between $S_{mv}O_2$ and rS_cO_2 increased from r=0.25 to r=0.75 [0.15-0.88] (P<0.001) for Foresight, and from r=0.28 to r=0.73 [0.30-0.87] (P<0.001) for INVOS, with no significant difference between monitors.

Hypothesis 2: role of the NIRS measurement technology

In order to investigate the hypothesis that the measurement technology might be responsible for the conflicting results reported in previous studies [4-12], we determined whether the absolute (Foresight) and relative (INVOS) NIRS monitors reported identical rS_cO_2 values, and whether relationships between rS_cO_2 and $S_{mv}O_2$ were similar. We also analyzed the differences in response to important hemodynamic disturbances.

The mean Foresight values were significantly higher (70 (4)%) than the mean INVOS values (66 (10)%) (P<0.001). A histogram of the distribution of all rS_cO_2 data (9604 data pairs) is presented in figure 5.3, indicating that INVOS measurements showed a wider range of values [28-95%] than corresponding Foresight measurements [58-89%]. As a consequence, the correlation between the individual Foresight and INVOS rS_cO_2 values was poor (r = 0.31).

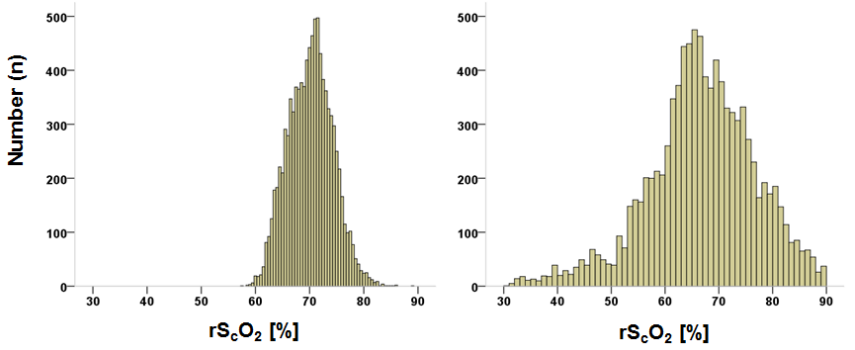

Figure 5.3: Frequency distribution of the regional cerebral oxygen saturation (rS_cO_2) data measured with Foresight (left panel) and with INVOS (right panel) (n=9604), demonstrating a wider range of absolute rS_cO_2 values with INVOS [28-95%] than with Foresight [58-89%].

Correlation analysis of all collected data pairs (n = 8338) revealed a poor correlation between $S_{mv}O_2$ and rS_cO_2 for both devices (r=0.37 for Foresight and r=0.39 for INVOS) (Fig. 5.4). The linear regression was described by $y = 0.22x + 53$ for Foresight, and $y = 0.62x + 20$ for INVOS, indicating that for each % change in $S_{mv}O_2$, there is a 0.22% change in rS_cO_2 for Foresight and a 0.62% change in rS_cO_2 for INVOS (P<0.001 between monitors). However, this analysis includes an unequal number of data pairs per subject, which could potentially result in an imbalanced statistical weight of subjects with exceedingly good or bad correlations between $S_{mv}O_2$ and rS_cO_2. Therefore, we also calculated the correlation between $S_{mv}O_2$ and rS_cO_2 for each subject individually, resulting in a median correlation coefficient of r=0.73 [0.05-0.92] and r=0.72 [0.12-0.92] for Foresight and INVOS, respectively (no significant difference between monitors).

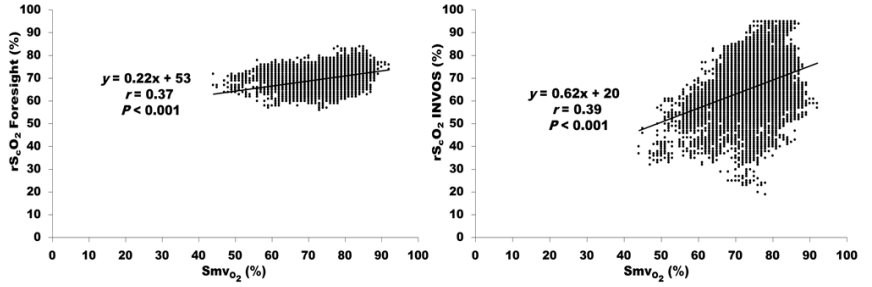

Figure 5.4: Correlation analysis of all collected data pairs (n=8338) demonstrating a poor correlation between mixed venous oxygen saturation ($S_{mv}O_2$) and regional cerebral oxygen saturation (rS_cO_2) for Foresight (r=0.37) (left panel) and INVOS (r=0.39) (right panel). The slope of rS_cO_2 versus $S_{mv}O_2$ was significantly more positive for INVOS (P<0.001 versus Foresight).

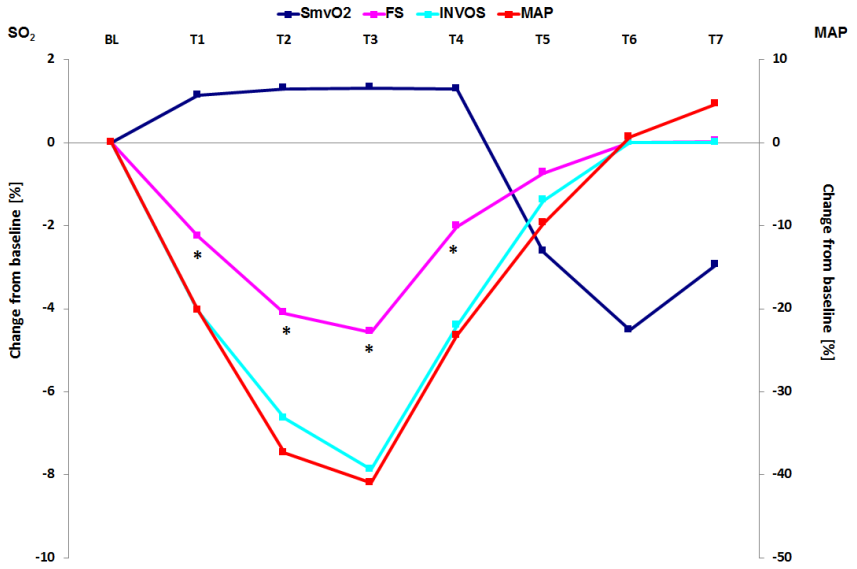

Figure 5.5: Relative changes in mean arterial pressure (MAP) (red line), mixed venous oxygen saturation ($S_{mv}O_2$) (dark blue line) and regional cerebral oxygen saturation (rS_cO_2) measured with Foresight (FS) (pink line) and INVOS (light blue line) during placement of the pericardial stitches (96 data sets). Changes in MAP are immediately followed by changes in rS_cO_2, while changes in $S_{mv}O_2$ lagged behind. Changes in rS_cO_2 were significantly more pronounced when measured with INVOS compared to Foresight (* Significant difference between Foresight and INVOS, $p<0.001$). BL: baseline, just before heart retraction, T1: 5 seconds after start of heart retraction, T2: 10 seconds after start of heart retraction, T3: at the minimum value of MAP, T4: at 5 seconds after release of heart retraction, T5: at 10 seconds after release of heart retraction, T6: at 15 seconds after release of heart retraction, T7: at 20 seconds after release of heart retraction.

The response of rS_cO_2 to major hemodynamic disturbances was explored during placement of deep pericardial stitches. There were a total of 96 data sets corresponding to pericardial stitch placement. Relative changes of MAP, rS_cO_2 and $S_{mv}O_2$ during these events are displayed in Figure 5.5, demonstrating significantly more pronounced changes in rS_cO_2 when measured with INVOS compared to Foresight (P<0.001). The ratio of changes in rS_cO_2 to changes in MAP was 21 (0.7)% and 11 (1.5)% for INVOS and Foresight, respectively (P<0.001). Accordingly, AUC was also significantly greater for rS_cO_2 when measured with INVOS, that is, -68%.sec (range -3 to -345%.sec) (=18% of AUC MAP) compared with -39%.sec (range -1 to -285%.sec) (=10% of AUC MAP) for Foresight, P<0.001. Correlation analysis between MAP and rS_cO_2 demonstrated a median correlation coefficient of r=0.72 [0.06-0.98] and 0.77 [0.49-0.96] for Foresight and INVOS, respectively (P=0.39 between Foresight and INVOS) (Fig. 5.6). Despite similar correlation coefficients, linear regression analysis demonstrated a significantly more positive slope of rS_cO_2 *vs* MAP for INVOS compared with Foresight (P=0.001 between Foresight and INVOS).

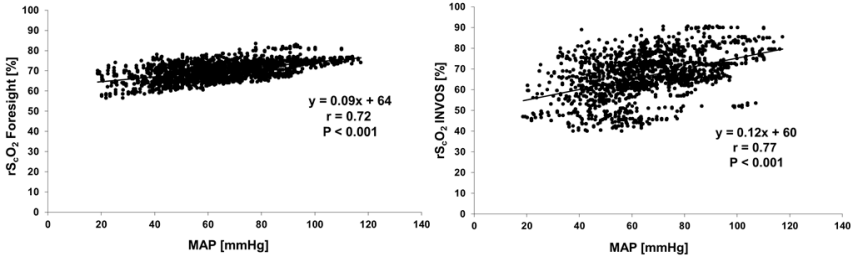

Figure 5.6: Correlation analysis demonstrating significant correlation between mean arterial blood pressure (MAP) and regional cerebral oxygen saturation (rS_cO_2) for Foresight (r=0.72) (left panel) and INVOS (r=0.77) (right panel). The slope of rS_cO_2 versus MAP was significantly more positive for INVOS (P=0.001 compared to Foresight).

5.3.4 Discussion

Our results indicate a substantial time delay between $S_{mv}O_2$ and rS_cO_2 measurements during hemodynamic alterations, which is responsible for a poor correlation between the individual values of these two variables. Comparison of data obtained with Foresight and INVOS cerebral oximetry revealed a similar correlation between $S_{mv}O_2$ and rS_cO_2. However, the devices demonstrated significant differences in measured rS_cO_2 values and in the magnitude of rS_cO_2 changes during hemodynamic alterations.

We also evaluated mutual interference by examining the variability of rS_cO_2 values when both monitors were running simultaneously compared with the values when each monitor was working separately. Our data demonstrated that INVOS performance was not affected by the presence of Foresight, whereas Foresight rS_cO_2 values exhibited significant higher variability when INVOS was also switched on, indicating interference of the Foresight measurements by the beam of light coming from the INVOS device. However, because the induced variability was very small and the mean Foresight rS_cO_2 values did not change when both devices were operating simultaneously, we considered the observed interference as clinically irrelevant and our data acquisition to be reliable to address the experimental question.

$S_{mv}O_2$ is often used in anesthesia and in intensive care to evaluate the balance between tissue oxygen delivery and oxygen consumption. However, its obligatory need for more invasive instrumentation precludes its use as a standard routine measurement. Since it can be expected that measurements of brain and systemic tissue oxygen balances vary in a similar direction, the measurement of rS_cO_2 by NIRS could offer a promising non-invasive alternative [3]. Several authors have compared rS_cO_2 and $S_{mv}O_2$ by focusing on interchangeability, using $S_{mv}O_2$ as the standard reference [4-10]. However, rS_cO_2 and $S_{mv}O_2$ measure different entities, and we should not expect that both methods are interchangeable. While rS_cO_2 reflects oxygen saturation in a small region of the frontal cortex, $S_{mv}O_2$ repre-

sents a measure of venous blood oxygen saturation from all organs. This notion is supported by the observation that $S_{mv}O_2$ primarily represents oxygen status in the lower body and poorly reflects brain oxygenation [16]. Therefore, in the present study, we did not focus on interchangeability, but on the ability of $S_{mv}O_2$ and rS_cO_2 to reflect hemodynamic changes in a similar way.

In accordance with our data, Paarmann and colleagues [4] also demonstrated poor correlation between $S_{mv}O_2$ and rS_cO_2 during periods of hemodynamic instability compared to hemodynamic stable periods. They attributed this finding to retention of CO_2, leading to an increase in rS_cO_2, without a concomitant change in $S_{mv}O_2$. The importance of CO_2 in the correlation analysis of $S_{mv}O_2$ and rS_cO_2 has been demonstrated during moderate hypothermic cardiopulmonary bypass [5]. The present study design does not allow to comment on potential influences of CO_2 on $S_{mv}O_2$ and rS_cO_2. Throughout the study, $EtCO_2$ was maintained at 4.7 kPa and one can assume that the hemodynamic disturbances occurring were too short-lasting to result in effective alterations in arterial CO_2 concentrations.

We hypothesized that time delay issues might contribute to the poor correlation between $S_{mv}O_2$ and rS_cO_2. We demonstrated a substantial time delay between changes in MAP and concomitant changes in $S_{mv}O_2$ of 18 (4) seconds, while no time delay was observed between changes in MAP and changes in rS_cO_2. After adjusting for the time delay, the correlation between $S_{mv}O_2$ and rS_cO_2 increased significantly for both Foresight and INVOS, confirming our hypothesis.

Most monitors use a time-weighted average to compute the value displayed, and each device updates and displays the value at a different rate, which might confound time delay analyses. In the present study, MAP was displayed beat-to-beat, Foresight and $S_{mv}O_2$ both had a data update rate of 2 s, while the INVOS monitor had the slowest data update rate (3.3 s). Therefore, the time delay observed with $S_{mv}O_2$ compared with MAP and rS_cO_2 cannot be attributed

to inherent device-related time delays. We speculate that the 18 s delay in $S_{mv}O_2$ compared with rS_cO_2 reflects the circulation time. rS_cO_2 directly measures regional oxygen balance, whereas $S_{mv}O_2$ is a reflection of the global oxygen balance, from venous blood returning from the superior and inferior cavae and from the coronary sinus, and is therefore subject to time delay due to the circulation time. Of interest, the time delay between $S_{mv}O_2$ and rS_cO_2 found in our study perfectly accords with previously described circulation times [17]. Our data imply that rS_cO_2 might represent a prompter more reliable variable than $S_{mv}O_2$ to assess the effect of changes in MAP on tissue perfusion, because it can be assumed that when hemodynamic deterioration leads to impaired brain perfusion, other vital organs will also be compromized [18].

The range of rS_cO_2 values is significant larger when measured with INVOS compared with Foresight. This can be related to the use of four narrow laser wavelengths (bandwidth <1 nm) in the Foresight technology compared with the use of two broader wavelengths (bandwidth 30-40 nm) in the INVOS technology (www.perfusion.com/cgi-bin/absolutenm/articlefiles/chen2008/chen2008.pdf), improving measurement accuracy [19]. However, the differences in absolute values might also be due to different computational algorithms for the calculation of rS_cO_2 of both NIRS devices. Similarly, penetration depth could differ depending on the wavelength and intensity of the emitted light, the sensitivity of the light detector, and the spacing between the light emitter and light detectors. Variable sensitivity to extracranial tissue contamination is another possibility for the observed differences [20].

We demonstrated an identical correlation between rS_cO_2 and both $S_{mv}O_2$ and MAP for the two NIRS devices. However, despite similar correlation coefficients, the slopes of rS_cO_2 *vs* $S_{mv}O_2$ or MAP were significantly more positive for INVOS, suggesting a better reflection of $S_{mv}O_2$ and MAP changes. Likewise the response of rS_cO_2 to acute hemodynamic alterations was more pronounced when

measured with INVOS.

The underlying reasons for the differences between INVOS and Foresight measurements cannot be identified from the present study. Either INVOS data show a greater variability due to less accurate measurement technology, or alternatively, Foresight data show less variability because of a more pronounced signal attenuation technology, providing rS_cO_2 values that do not as readily reflect true physiological changes. Clearly, more studies are needed to clarify this issue.

In summary, our data suggest that the conflicting and poor results described previously when comparing rS_cO_2 with $S_{mv}O_2$ can to some extent be attributed to a time delay between measurements. rS_cO_2 might represent a prompter more reliable variable than $S_{mv}O_2$ to assess the effect of changes in MAP on tissue perfusion. We could not confirm that the type of cerebral oximeter also contributed to the poor correlation as previously reported. Both technologies responded similar to hemodynamic changes, although responses of rS_cO_2 to changes in MAP seemed to be more pronounced when measured with INVOS compared to Foresight.

5.3.5 References

1. Pölönen P, Ruokonen E, Hippeläinen M, Pöyhönen M, Takala J. A prospective, randomized study of goal-oriented hemodynamic therapy in cardiac surgical patients. Anesth Analg 2000; 90: 1052-9

2. Watzman HM, Kurth CD, Montenegro LM, Rome J, Steven JM, Nicolson SC. Arterial and venous contributions to near-infrared cerebral oximetry. Anesthesiology 2000; 93: 947-53

3. Murkin JM, Adams SJ, Novick RJ, et al. Monitoring brain oxygen saturation during coronary bypass surgery: a randomized, prospective study. Anesth Analg 2007; 104: 51-8

4. Paarmann H, Heringlake M, Heinze H, et al. Non-invasive cerebral oxygenation reflects mixed venous oxygen saturation during the varying haemodynamic conditions in patients undergoing transapical transcatheter

aortic valve implantation. Interact Cardiovasc Thorac Surg 2012; 14: 268-72
5. Baraka A, Naufal M, El-Khatib M. Correlation between cerebral and mixed venous oxygen saturation during moderate versus tepid hypothermic hemodiluted cardiopulmonary bypass. J Cardiothorac Vasc Anesth 2006; 20: 819-25
6. Dullenkopf A, Baulig W, Weiss M, Schmid ER. Cerebral near-infrared spectroscopy in adult patients after cardiac surgery is not useful for monitoring absolute values but may reflect trends in venous oxygenation under clinical conditions. J Cardiothorac Vasc Anesth 2007; 21: 535-9
7. Tortoriello TA, Stayer SA, Mott AR, et al. A noninvasive estimation of mixed venous oxygen saturation using near-infrared spectroscopy by cerebral oximetry in pediatric cardiac surgery patients. Paediatr Anaesth 2005; 15: 495-503
8. Bhutta AT, Ford JW, Parker JG, et al. Noninvasive cerebral oximeter as a surrogate for mixed venous saturation in children. Pediatr Cardiol 2007; 28: 34-41
9. Paarmann H, Schön J, Schmidt W, et al. Agreement of noninvasive cerebral oxygenation with mixed venous oxygen saturation in patients undergoing ECMO-therapy. Appl Cardiopulm Pathophysiol 2011; 15: 55-61
10. Schön J, Heringlake M, Berger K, Volker Groesdonk H, Sedemund-Adib B, Paarmann H. Relationship between mixed venous oxygen saturation and regional cerebral oxygenation in awake, spontaneously breathing cardiac surgery patients. Minerva Anestesiol 2011; 77: 952-8
11. Tyree K, Tyree M, DiGeronimo R. Correlation of brain tissue oxygen tension with cerebral near-infrared spectroscopy and mixed venous oxygen saturation during extracorporeal membrane oxygenation. Perfusion 2009; 24: 325-31
12. Cua CL, Hoffman TM, Taeed R, et al. Cerebral saturations trend with mixed venous saturations in patients undergoing extracorporeal life support. Perfusion 2004; 19: 171-6
13. Hemmerling TM, Bluteau MC, Kazan R, Bracco D. Significant decrease of cerebral oxygen saturation during single-lung ventilation measured using absolute oximetry. Br J Anaesth 2008; 101: 870-5

14. Tang L, Kazan R, Taddei R, Zaouter C, Cyr S, Hemmerling TM. Reduced cerebral oxygen saturation during thoracic surgery predicts early postoperative cognitive dysfunction. Br J Anaesth 2012; 108: 623-9
15. Moerman A, Wouters P. Near-infrared spectroscopy (NIRS) monitoring in contemporary anesthesia and critical care. Acta Anaesth Belg 2010; 61: 185-94
16. Redlin M, Koster A, Huebler M, et al. Regional differences in tissue oxygenation during cardiopulmonary bypass for correction of congenital heart disease in neonates and small infants: relevance of near-infrared spectroscopy. J Thorac Cardiovasc Surg 2008; 136: 962-7
17. Pearce ML, Lewis AE, Kaplan MR. The factors influencing the circulation time. Circulation 1952; 5: 583-8
18. McDaniel LB, Zwischenberger JB, Vertrees RA, et al. Mixed venous oxygen saturation during cardiopulmonary bypass poorly predicts regional venous saturation. Anesth Analg 1995; 80: 466-72
19. Fischer GW, Silvay G. Cerebral oximetry in cardiac and major vascular surgery. HSR Proceedings in Intensive Care and Cardiovascular Anesthesia 2010; 2: 249-56
20. Davie SN, Grocott HP. Impact of extracranial contamination on regional cerebral oxygen saturation: a comparison of three cerebral oximetry technologies. Anesthesiology 2012; 116: 834-40

Chapter 6

NIRS to assess the physiological determinants of tissue oxygen saturation

6.1 Background

Vasopressors are frequently used during anesthesia when blood pressure is challenged. However, vasoconstrictors may impair regional organ perfusion, which will go unnoticed when relying solely on blood pressure, until functional organ damage becomes evident. Both pressure and flow are considered important variables for prevention of perfusion deficit and the resulting end organ failure. However, the relative importance of each is less established.

Since NIRS provides an estimation of systemic venous saturation, its use offers the opportunity to evaluate physiological determinants of global tissue perfusion.

6.2 Objective

The aim of the present study was to determine the effect of flow and pressure on tissue oxygen saturation.

6.3 NIRS to assess physiology of perfusion

Influence of variations in systemic blood flow and pressure on cerebral and systemic oxygen saturation in cardiopulmonary bypass patients. Moerman A, Denys W, De Somer F, Wouters P, De Hert S. Br J Anaesth 2013, in press

Abstract
Background. Although both pressure and flow are considered important determinants of regional organ perfusion, the relative importance of each is less established. The aim of the present study was to evaluate the impact of variations in flow and/or pressure on cerebral and whole-body oxygen saturation.
Methods. Thirty-four consenting patients undergoing elective cardiac surgery on cardiopulmonary bypass were included. Using a randomized cross-over design, four different hemodynamic states were simulated: 1) 20% flow decrease, 2) 20% flow decrease with phenylephrine to restore baseline pressure, 3) 20% pressure decrease with sodium nitroprusside (SNP) under baseline flow, and 4) increased flow with baseline pressure. The effect of these changes was evaluated on cerebral (S_cO_2) and systemic (S_vO_2) oxygen saturation, and on systemic oxygen extraction ratio (OER). Data were assessed by within- and between-group comparisons.
Results. Decrease in flow was associated with a decrease in S_cO_2

(from 63.5 (7.4) to 62.0 (8.5)%, P<0.001). When blood pressure was restored with phenylephrine during low flow, S_cO_2 further decreased from 61.0 (9.7) to 59.2 (10.2)%, P<0.001. Increase in flow was associated with an increase in S_cO_2 from 62.6 (7.7) to 63.6 (8.9)%, P=0.03, while decreases in pressure with the use of SNP did not affect S_cO_2. S_vO_2 was significantly lower (P<0.001) and OER was significantly higher (P<0.001) in the low flow arms.
Conclusions. In the present elective cardiac surgery population, S_cO_2 and S_vO_2 were significantly lower with lower flow, regardless of systemic blood pressure. Moreover, phenylephrine administration was associated with a reduced cerebral and systemic oxygen saturation.

6.3.1 Introduction

Decreases in blood pressure during anesthesia are often managed by vasopressor use. However, vasoconstrictors may impair regional organ perfusion, which might go undetected when monitoring solely blood pressure [1]. Cerebral oximetry, a noninvasive technology using near infrared spectroscopy (NIRS), enables an estimation of systemic venous saturation, thereby providing a means for real-time monitoring of adequacy of organ perfusion [2,3].

In a proposed algorithm to correct for decreases in NIRS-derived cerebral oxygen saturation (S_cO_2), increasing mean arterial pressure (MAP) with the use of vasopressors was suggested as one of the initial measures to correct for low S_cO_2 [4]. However, recent published data demonstrated that vasopressors such as phenylephrine may negatively affect S_cO_2 [5-9]. This negative effect on S_cO_2 was not observed when increase in blood pressure was obtained by vasopressor agents which also increase cardiac output, such as ephedrine [6,10]. Also, studies in healthy subjects demonstrated an increase in S_cO_2 during exercise [7,11], whereas in patients not capable of increasing cardiac output, such as in patients with heart failure, the ability to augment S_cO_2 during exercise was limited [12]. These data suggest that cardiac

output might contribute to the preservation of cerebral oxygenation.

The aim of the present study was to determine the impact of variations in flow, in pressure, and in both variables at the same time on cerebral and whole-body oxygen saturation. We hypothesized that not only pressure, but also flow would have a major contribution in preservation of cerebral and systemic oxygenation.

A major problem in evaluating physiologic processes is that pressure and flow are intertwined and modifications to one also alter the other. Cardiopulmonary bypass (CPB) represents a unique clinical circumstance in which different aspects of perfusion can be modified independently and in a controlled manner. Therefore we chose CPB as the model to test our hypothesis. To separate the effect of flow and pressure on cerebral and systemic oxygenation, we independently modified these parameters in patients on CPB.

6.3.2 Methods

This prospective clinical study was approved by the Institutional Ethics Committee and written informed consent was obtained from all subjects. The trial is registered at ClinicalTrials.gov (NCT01424800). Thirty-four adult patients scheduled for elective cardiac surgery (coronary artery bypass grafting and/or valve surgery) on moderately hypothermic CPB without blood transfusion were recruited. Patients with history of cerebrovascular disease or significant carotid artery stenosis (>60%) and patients necessitating vasopressor or inotropic therapy before surgery were excluded.

On the morning of surgery, patients were allowed to take their routine medication, except for angiotensin-converting enzyme inhibitors. Patients were premedicated with oral diazepam (5-10 mg). Standard monitoring was used throughout the procedure, including ECG, pulse oximetry, end-tidal oxygen, carbon dioxide and sevoflurane concentrations, bispectral index (BIS), invasive arterial and central venous pressure measurement, and temperature measurement (AS3; Datex, Helsinki, Finland). Arterial blood pressure was

recorded continuously via the right radial artery catheter. Two disposable NIRS sensors were applied on each side of the forehead for continuous registration of S_cO_2 of the corresponding brain hemisphere (INVOS 5100; Somanetics Corporation, Troy, MI, USA). All data were recorded continuously and integrated digitally with the RUGLOOP (Demed, Temse, Belgium).

Anesthesia was induced with fentanyl 5 μg/kg, diazepam 0.1 mg/kg, and rocuronium 1 mg/kg. The lungs were ventilated mechanically with oxygen-enriched air (fractional inspired oxygen 0.6) adjusted to keep the end-tidal carbon dioxide ($EtCO_2$) around 5 kPa. Anesthesia was maintained with boluses of fentanyl up to a total dose of 25-35 μg/kg and sevoflurane at a minimum concentration of 1.5 vol%.

CPB was performed with a roller pump (Stöckert S5; Sorin group, München, Germany) providing non-pulsatile flow. The priming consisted of 1200 ml colloids (Geloplasma®, Fresenius Kabi, Schelle, Belgium), heparin 5000 IU and mannitol 0.5 g/kg. Systemic heparinization maintained an activated clotting time of >480 seconds. Moderately hypothermic CPB (blood temperature 30 °C) was initiated at flow rates of 2.5 L/min/m^2. During CPB P_aO_2 and P_aCO_2 were maintained around 25 kPa and 5 kPa respectively. Arterial blood gases were measured at 37 °C, independent of body temperature (alpha-stat blood gas management). Blood was sampled from the pump oxygenator after 3 minutes during steady state, I1 and I3. Temperature, P_aCO_2, P_aO_2, haemoglobin and sevoflurane concentrations were kept constant during the measurements.

Interventions

The study used a randomized cross-over design where the subjects served as their own controls. Subjects were randomly allocated, based on computer generated codes, to start with the flow related interventions or with the pressure related interventions. In all subjects, response to variations in flow, in pressure, and to the combined

variation of flow and pressure was investigated. With the interventions, a change of 20% in pressure and/or flow was aimed. Changes in blood pressure were obtained by the use of vasoactive agents, sodium nitroprusside (SNP) for blood pressure decrease and phenylephrine for blood pressure increase. Flow was regulated by control of the pump flow.

Baseline (BL) values of mean arterial blood pressure (MAP), flow, S_cO_2 and systemic oxygen saturation (S_vO_2) were determined at steady state. Steady state was defined as the presence of a stable (<10% change) MAP over a period of 5 minutes on CPB. After reaching steady state, four different hemodynamic states were simulated: 20% flow decrease (I1), 20% flow decrease with administration of phenylephrine to restore baseline MAP (I2); then hemodynamics were allowed to return to BL values after which SNP was administered until 20% MAP decrease under baseline flow (I3), followed by restoration of baseline MAP by increasing pump flow (I4). The order of variations in pressure and flow was assigned randomly by the use of a computer generated randomization code. Subjects were randomly assigned to undergo first the flow related interventions and then the pressure related interventions (group F), or first the pressure related interventions and then the flow related interventions (group P). All changes were sustained for 5 minutes. In group F the sequence of changes was BL, I1, I2, BL, I3, I4. In group P the sequence of changes was BL, I3, I4, BL, I1, I2 (Fig. 6.1). Interventions were separated by a time period of about 2 minutes for finalizing computer data registration and preparation of the next intervention.

Outcome variables

To analyze the changes in S_cO_2, right and left S_cO_2 were averaged. We calculated both the change in absolute values in S_cO_2, as the relative change in S_cO_2, defined as the percentage difference between the S_cO_2 value at the start of the intervention and the value exactly 5 minutes later, at the end of the intervention. To account for both

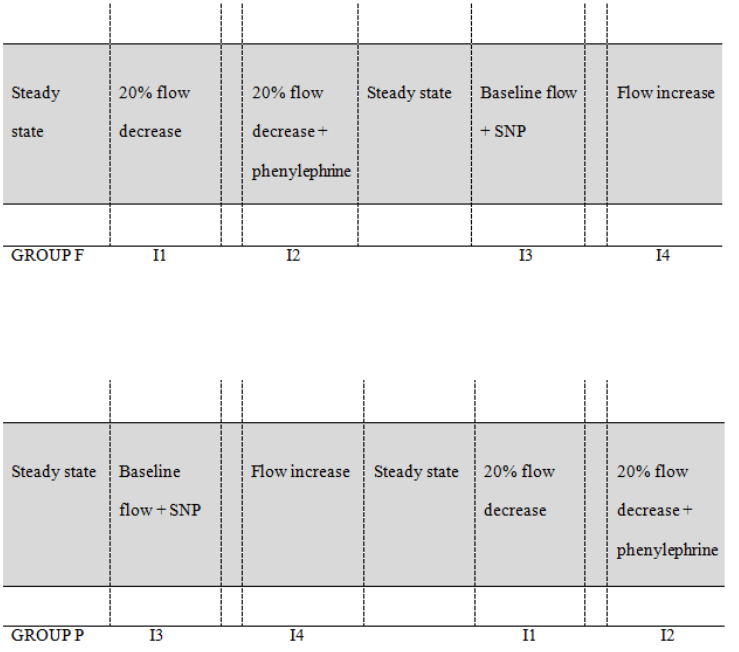

Figure 6.1: Graphic presentation of the study design. Sequence of interventions in group F (first the flow related interventions) and group P (first the pressure related interventions).

magnitude and duration of changes in S_cO_2, the area under the curve (AUC) was also calculated (expressed in %.sec).

To evaluate the effect of changes in flow and pressure on whole-body oxygen balance, S_vO_2 was measured, and systemic oxygen delivery (DO_2) and oxygen extraction ratio (OER) were calculated according to standard formulae. Arterial oxygen content: $C_aO_2 = 1.34 * Hb * S_aO_2 + 0.003 * P_aO_2$, where Hb = hemoglobin concentration, S_aO_2 = arterial oxygen saturation, P_aO_2 = arterial partial pressure of oxygen. $DO_2 = Q * C_aO_2$, where Q = pump flow. $OER =$

$(S_aO_2 - S_vO_2)/S_aO_2$, where S_vO_2 = venous oxygen saturation.

Statistical analysis

Lucas and co-workers assessed the influence of pharmacological-induced changes in blood pressure on cerebral oxygenation, and indicated an absolute change in S_cO_2 of -1.8% per 10 mmHg change in MAP, with a reduction approximating 14% during the higher range of MAP [8]. In the present protocol we aimed at a change of 20% in pressure with the interventions. We therefore accepted an absolute change in rS_cO_2 of 5% with alterations in pressure or flow as a clinically relevant change. Based on the reported mean S_cO_2 of 64% with a SD of 10% [3], and accepting a two-tailed α error of 0.05 and a β error of 0.8, 34 patients were calculated to be required. Statistical analysis was performed using the statistical software SPSS Statistics 20 (SPSS Inc., Chicago, IL, USA). Distribution of the data was tested for normality using the Shapiro-Wilk test. The assumption of normality was fulfilled and data are presented as mean (SD). Comparisons between group F and group P were made with Student's t-test. Variables during the different interventions were compared using repeated measures analysis of variance (ANOVA), with Tukey correction for multiple post-hoc comparisons. For each intervention, differences between pre- and post-intervention S_cO_2 values were tested using a paired data Student's t-test. A value of $P<0.05$ was taken as the level of significance.

6.3.3 Results

Nine female and 25 male subjects with an average age of 62 (14) years, weight of 80 (16) kg and height of 171 (9) cm were enrolled in the study. Demographics did not differ between the F and the P group.

Temperature, sevoflurane concentrations, P_aO_2, P_aCO_2 and hemoglobin showed no differences between the different interventions, neither between the F and the P group (Table 6.1).

	BL	**I1**	**I2**	**I3**	**I4**
Temp (°C)					
F group	30.5 (1.3)	30.7 (1.4)	31.0 (1.1)	30.7 (1.3)	30.7 (1.3)
P group	30.0 (1.5)	30.1 (1.2)	30.2 (1.6)	30.3 (1.4)	30.5 (1.4)
Sevo (%)					
F group	1.1 (0.5)	1.2 (0.5)	1.2 (0.5)	1.2 (0.5)	1.3 (0.5)
P group	1.0 (0.3)	1.4 (0.7)	1.3 (0.7)	1.1 (0.4)	1.1 (0.4)
$\mathbf{P_aO_2}$ (kPa)					
F group	33 (9)	30 (5)		30 (6)	
P group	30 (7)	28 (7)		27 (7)	
$\mathbf{P_aCO_2}$ (kPa)					
F group	5.8 (0.5)	5.5 (0.6)		5.7 (0.2)	
P group	5.6 (0.6)	5.0 (0.4)		5.0 (0.5)	
Hb (g/dl)					
F group	9.8 (0.9)	9.9 (1.1)		10.1 (0.9)	
P group	9.5 (1.4)	10.0 (1.2)		9.5 (1.3)	

Table 6.1: Blood temperature, sevoflurane concentration, and blood gas values during the different interventions, demonstrating no differences between the interventions, neither between the F group (flow related interventions were performed before the pressure related interventions) and the P group (pressure related interventions were performed before the flow related interventions). Data are presented as mean (SD). P-value between F and P group >0.05; P-value between interventions >0.05. BL: baseline, (I1) 20% flow decrease, (I2) 20% flow decrease with administration of phenylephrine to restore baseline MAP, (I3) baseline flow with administration of sodium nitroprusside until 20% MAP decrease, (I4) restoration of baseline MAP by increasing pump flow; P_aO_2: arterial oxygen partial pressure, P_aCO_2: arterial carbon dioxide partial pressure, Hb: hemoglobin.

The intended targets of changes in flow and MAP were reached in all subjects (Table 6.2). The changes in flow and MAP were not different between the F and the P group, indicating that the sequence of interventions did not bias the data. Therefore, in order to analyze the effect of changes in flow and pressure, we pooled the data of both groups.

	BL	**I1**	**I2**	**I3**	**I4**
Flow (L/min)					
F group	4.5 (0.5)	3.6 (0.4)	3.6 (0.4)	4.5 (0.5)	5.0 (0.5)
P group	4.4 (0.4)	3.6 (0.3)	3.6 (0.3)	4.4 (0.4)	4.9 (0.5)
MAP (mmHg)					
F group	67 (5)	57 (8)	69 (8)	57 (7)	65 (8)
P group	70 (9)	63 (9)	71 (9)	57 (7)	68 (8)

Table 6.2: Endpoints of changes in flow and pressure during the different interventions, indicating that the intended targets of changes in flow and pressure were reached in all subjects. Data are presented as mean (SD). P-value between F and P group >0.05; P-value between interventions <0.001. BL: baseline, (I1) 20% flow decrease, (I2) 20% flow decrease with administration of phenylephrine to restore baseline MAP, (I3) baseline flow with administration of sodium nitroprusside until 20% MAP decrease, (I4) restoration of baseline MAP by increasing pump flow.

DO_2 was significantly lower during low flow (I1) (263 (62) ml/min/m^2) compared to normal flow (I3) (320 (63) ml/min/m^2), P=0.001.

The changes in MAP and flow with their concomitant effects on S_cO_2 are illustrated in Figure 6.2. The changes in S_cO_2 and systemic oxygen balance parameters between the interventions are displayed in Table 6.3.

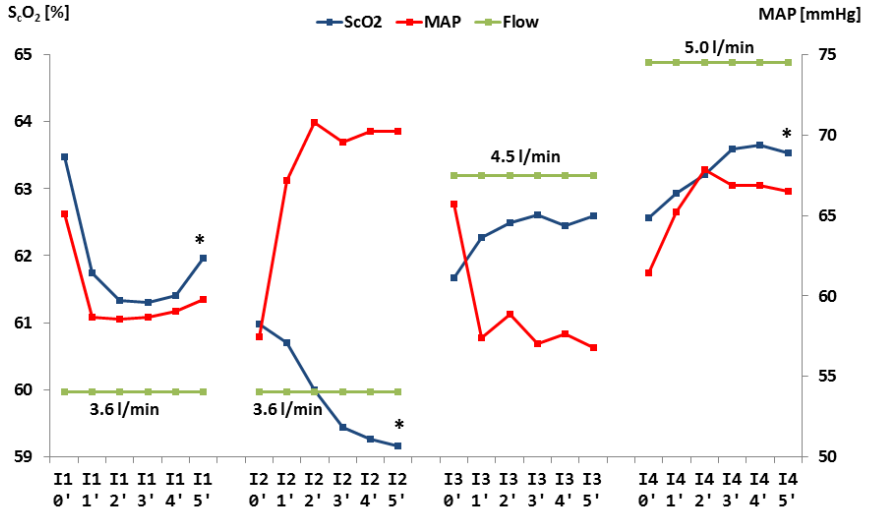

Figure 6.2: Changes in MAP and flow with their concomitant effects on S_cO_2 for each intervention: (I1) 20% flow decrease, (I2) 20% flow decrease with administration of phenylephrine to restore baseline MAP, (I3) baseline flow with administration of sodium nitroprusside until 20% MAP decrease, (I4) restoration of baseline MAP by increasing pump flow. Data are presented as mean values. *p<0.05 between pre- and postintervention S_cO_2.

	BL	I1	I2	I3	I4
AUC rS_cO_2 (%.sec)	N.A.	-522(323)*	-249(424)*	145(687)	232(379)
Rel. change in rS_cO_2 (%)	N.A.	-2.8(3.7)*	-3.2(3.8)*	1.5(5.1)	1.6(3.3)
S_vO_2 (%)	86(3)	82(4)‡	82(5)‡	85(4)	87(4)
OER	0.14(0.03)	0.18(0.04)‡	0.17(0.05)‡	0.14(0.04)	0.12(0.04)

Table 6.3: Cerebral oxygen saturation and oxygen consumption parameters during the different interventions, demonstrating lower cerebral (S_cO_2) and systemic (S_vO_2) oxygen saturation and a higher oxygen extraction ratio (OER) during low flow (I1 and I2) compared to baseline (BL), normal flow (I3), and high flow (I4). Data are presented as mean (SD). *Significantly different from I3 and I4; ‡ Significantly different from BL, I3 and I4. (I1) 20% flow decrease, (I2) 20% flow decrease with administration of phenylephrine to restore baseline MAP, (I3) baseline flow with administration of sodium nitroprusside until 20% MAP decrease, (I4) restoration of baseline MAP by increasing pump flow. AUC S_cO_2: area under the curve for cerebral oxygen saturation, N.A.: not applicable.

Responses to decrease in flow

Intervention 1: With 20% flow decrease, MAP decreased from 65 (9) to 60 (11), indicating the accompanying decrease in MAP with flow decrease. S_cO_2 decreased from 63.5 (7.4) to 62.0 (8.5)%, P<0.001 (Fig. 6.2). Decreases in S_cO_2 were significantly more pronounced compared to interventions with normal (I3) and high flow (I4) (Table 6.3). S_vO_2 was significantly lower and OER was significantly higher compared to baseline and compared to interventions with normal and high flow (Table 6.3).

Intervention 2: With 20% flow decrease and administration of phenylephrine to restore baseline MAP, MAP increased from 57 (10) to 70 (8). S_cO_2 decreased from 61.0 (9.7) to 59.2 (10.2)%, P<0.001 (Fig. 6.2). Decreases in S_cO_2 were significantly more pronounced compared to interventions with normal (I3) and high flow (I4) (Table 6.3). S_vO_2 was significantly lower and OER was significantly higher

compared to baseline and compared to interventions with normal and high flow (Table 6.3).

Responses to decrease in pressure

Intervention 3: With 20% MAP decrease (from 66 (12) to 57 (7)), obtained by administration of SNP while maintaining baseline pump flow, S_cO_2 did not change significantly (61.7 (8.4) to 62.6 (8.4)%, P=0.13) (Fig. 6.2). S_vO_2 was significantly higher and OER was significantly lower in conditions with low blood pressure obtained by SNP (I3) compared to low blood pressure caused by low flow (I1) (Table 6.3).

Responses to increase in flow

Intervention 4: When increasing pump flow until restoration of baseline MAP (from 61 (11) to 67 (8)), the increase in flow was 11% (from 4.5 (0.5) to 5.0 (0.5) L/min). S_cO_2 increased from 62.6 (7.7) to 63.6 (8.9)%, P=0.03) (Fig. 6.2). S_cO_2 values were not different between conditions with high flow and baseline pressure (I4) compared to baseline flow and low pressure by SNP (I3) (Table 6.3). S_vO_2 was significantly higher and OER was significantly lower compared to conditions with low flow (I1 and I2) (Table 6.3).

6.3.4 Discussion

The debate on the best strategies for prevention of perfusion deficit and the resulting end organ failure is ongoing. Both pressure and flow are considered important variables [13]. However, the relative importance of each is less established. Under the conditions of the present study, changes in flow affected cerebral and systemic venous oxygen saturations more than changes in MAP. S_cO_2 and S_vO_2 were significantly higher at normal to high flow than at reduced flow, regardless of systemic blood pressure.

In the elective cardiac surgery population, used in this study, maintaining flow and thus DO_2 seemed to be more important than

maintaining pressure. This finding is in accordance with data demonstrating that organ injury can be prevented by targeting DO_2 levels above a critical threshold during cardiopulmonary bypass [14,15]. However, the obtained results do not exclude perfusion pressure as an important variable. It is important to note that even during low pressure, our lowest value of 60 mmHg is higher than the critical value of 50 mmHg as reported in other studies [16].

In the present study increasing blood pressure with phenylephrine induced a decrease in S_cO_2. This is in accordance with a number of recently published studies [5-9]. The mechanism of this phenomenon is still unknown. Cardiac output has been proposed as the most important factor in preserving S_cO_2 [5]. However in our study, pump flow was kept constant during administration of phenylephrine, indicating that other factors than cardiac output or pump flow contribute to the decrease in S_cO_2. Some authors relate the decrease in S_cO_2 with phenylephrine to direct α-1 adrenergic receptor activation [17] or to indirect cerebral vasoconstriction via reflexively increased sympathetic nerve activity [18]. Others refute this mechanism by stating that the cerebral vasculature lacks significant α- and β-adrenoceptors [19]. Recently it has been suggested that the S_cO_2 decrease with administration of phenylephrine indicates a functional pressure autoregulation mechanism [20]. The phenylephrine-induced increase in perfusion pressure provokes vasoconstriction of the cerebral arterioles in order to prevent abrupt cerebral hyperperfusion. NIRS calculates the oximetry values based on an assumed cerebral arterial to venous blood volume ratio [21]. Autoregulatory vasoconstriction of the cerebral arterioles induces a smaller arterial and relatively larger venous contribution to the NIRS signal, causing a decrease in S_cO_2. This hypothesis is supported by the study of Ogoh and colleagues who evaluated arterial and venous cerebral blood flow, and demonstrated an elevated arterial tone and reduced cerebral venous tone during phenylephrine administration, indicating cerebral autoregulation [9].

The S_cO_2 increase with SNP-induced hypotension could be readily

explained by the same mechanisms. Either nitrates reduce the resistance in the cerebral vessels, allowing more blood flow to the brain [22], or the S_cO_2 increase with administration of SNP could be considered as a functional pressure autoregulation mechanism, provoking vasodilation of the cerebral arterioles in order to prevent cerebral hypoperfusion.

It might be argued that the cerebral autoregulation-induced altered A:V ratio accounts for the observed changes in S_cO_2, without a genuine change in cerebral oxygenation. However, the consistent and concordant changes in both S_cO_2 and systemic oxygen balance parameters during the different interventions, suggest that S_cO_2 changes actually reflect oxygen balance changes.

The magnitude of changes in S_cO_2 in this study was very small ($\sim$ 0.9-1.8% absolute change depending on the intervention) and although statistically significant, the clinical relevance of these changes in the present study may be debatable. However, our results cannot be implicitly extrapolated to any other clinical situation. First, our measurements were done during moderate hypothermia which reduces oxygen consumption, with consequently smaller changes in S_cO_2. Second, we used sevoflurane for maintenance of anesthesia, which might have blunted the decrease in S_cO_2 with administration of phenylephrine by its cerebral vasodilatory effect [23,24]. Based on the same mechanism, the decrease in S_cO_2 with phenylephrine will be intensified in case of hypocapnia [20]. Third, flow and pressure were manipulated within physiological ranges for short periods of time. In clinical practice larger changes for a longer period are often - deliberately or not - the case.

The results of the present study should be interpreted within the constraints of the methodology. First, to explore the relative contribution of flow and pressure on cerebral oxygenation, and with the aim to separate the effects of both parameters, the present study was performed in patients on CPB where both the flow and the pressure component of perfusion can be modified in a controlled manner.

However, as was to be expected, changes in flow were accompanied by changes in pressure (I1 and I4) (Fig. 6.2). Secondly, based on the principle of spatially resolved spectroscopy, NIRS devices should theoretically distinguish between absorption of photons returning from deep rather than from superficial tissue. However, recently 2 reports demonstrated that extracranial contamination significantly influences the NIRS signal [25,26]. Because both vasodilators and vasoconstrictors might affect skin flow directly, changes in skin blood flow might have influenced the NIRS measurements of cerebral oxygenation. It has been suggested that the cerebral oximeter used in the present study is more prone to extracranial contamination [25]. Therefore, administration of vasoactive medication might result in more pronounced artifactual measurements compared to cerebral oximeters with less extracranial contribution. Interestingly, we recently demonstrated that S_cO_2 responses to acute haemodynamic alterations were also more pronounced when measured with INVOS [3]. It is unclear whether this has to be explained by a less accurate measurement technology of INVOS, or whether the other cerebral oximetry devices use a more pronounced signal attenuation technology, resulting in more stable -but less representative- values for both intra- and extracranial measurements. Third, NIRS measures oxygen saturation in a superficial area of the brain directly below the sensors, but does not examine the deep brain. As recently demonstrated, though a low NIRS value predicts brain hypoperfusion, a normal NIRS value may not always imply that perfusion is adequate [27]. Therefore, the utility of NIRS for individualization of perioperative pressure and blood flow management awaits testing in properly designed and executed clinical trials [28].

In conclusion, in the elective cardiac surgery population used in this study, cerebral saturation seemed to be more dependent on flow than on pressure maintenance. Moreover, blood pressure increase with phenylephrine elicited reduced cerebral and systemic oxygen saturation.

6.3.5 References

1. O'Dwyer C, Woodson LC, Conroy BP, et al. Regional perfusion abnormalities with phenylephrine during normothermic bypass. Ann Thorac Surg 1997; 63: 728-35
2. Murkin JM, Adams SJ, Novick RJ, et al. Monitoring brain oxygen saturation during coronary bypass surgery: a randomized, prospective study. Anesth Analg 2007; 104: 51-8
3. Moerman A, Vandenplas G, Bové T, Wouters P, De Hert S. Relation between mixed venous oxygen saturation and cerebral oxygen saturation measured by absolute and relative near-infrared spectroscopy during off-pump coronary artery bypass grafting. Br J Anaesth 2013; 110: 258-65
4. Denault A, Deschamps A, Murkin JM. A proposed algorithm for the intraoperative use of cerebral near-infrared spectroscopy. Semin Cardiothorac Vasc Anesth 2007; 11: 274-81
5. Meng L, Cannesson M, Alexander BS, et al. Effect of phenylephrine and ephedrine bolus treatment on cerebral oxygenation in anaesthetized patients. Br J Anaesth 2011; 107: 209-17
6. Nissen P, Brassard P, Jorgensen TB, Secher NH. Phenylephrine but not ephedrine reduces frontal lobe oxygenation following anesthesia-induced hypotension. Neurocrit Care 2010; 12: 17-23
7. Brassard P, Seifert T, Wissenberg M, Jensen PM, Hansen CK, Secher NH. Phenylephrine decreases frontal lobe oxygenation at rest but not during moderately intense exercise. J Appl Physiol 2010; 108: 1472-8
8. Lucas SJ, Tzeng YC, Galvin SD, Thomas KN, Ogoh S, Ainslie PN. Influence of changes in blood pressure on cerebral perfusion and oxygenation. Hypertension 2010; 55: 698-705
9. Ogoh S, Sato K, Fisher JP, Seifert T, Overgaard M, Secher NH. The effect of phenylephrine on arterial and venous cerebral blood flow in healthy subjects. Clin Physiol Funct Imaging 2011; 31: 445-51
10. Moerman A, De Hert S, Jacobs T, De Wilde L, Wouters P. Cerebral oxygen desaturation during beach chair position. Eur J Anaesthesiol 2012; 29: 82-7
11. Secher NH, Seifert T, Van Lieshout JJ. Cerebral blood flow and

metabolism during exercise: implications for fatigue. J Appl Physiol 2008; 104: 306-14
12. Koike A, Itoh H, Oohara R, et al. Cerebral oxygenation during exercise in cardiac patients. Chest 2004; 125: 182-90
13. Murphy GS, Hessel EA 2nd, Groom RC. Optimal perfusion during cardiopulmonary bypass: an evidence-based approach. Anesth Analg 2009; 108: 1394-417
14. Ranucci M, Romitti F, Isgro G, et al. Oxygen delivery during cardiopulmonary bypass and acute renal failure after coronary operations. Ann Thorac Surg 2005; 80: 2213-20
15. Bastien O, Piriou V, Aouifi A, Flamens C, Evans R, Lehot JJ. Relative importance of flow versus pressure in splanchnic perfusion during cardiopulmonary bypass in rabbits. Anesthesiology 2000; 92: 457-64
16. Schell RM, Kern FH, Greeley WJ, et al. Cerebral blood flow and metabolism during cardiopulmonary bypass. Anesth Analg 1993; 76: 849-65
17. Purkayastha S, Raven PB. The functional role of the alpha-1 adrenergic receptors in cerebral blood flow regulation. Indian J Pharmacol 2011; 43: 502-6
18. Van Lieshout JJ, Secher NH. Point:counterpoint: Sympathetic activity does/does not influence cerebral blood flow. Point: Sympathetic activity does influence cerebral blood flow. J Appl Physiol 2008; 105: 1364-6
19. Strandgaard S, Sigurdsson ST. Point:counterpoint: Sympathetic activity does/does not influence cerebral blood flow. Counterpoint: Sympathetic nerve activity does not influence cerebral blood flow. J Appl Physiol 2008; 105: 1366-7
20. Meng L, Gelb AW, Alexander BS, et al. Impact of phenylephrine administration on cerebral tissue oxygen saturation and blood volume is modulated by carbon dioxide in anaesthetized patients. Br J Anaesth 2012; 108: 815-22
21. Watzman HM, Kurth CD, Montenegro LM, Rome J, Steven JM, Nicolson SC. Arterial and venous contributions to near-infrared cerebral oximetry. Anesthesiology 2000; 93: 947-53

22. Moppett IK, Sherman RW, Wild MJ, Latter JA, Mahajan RP. Effects of norepinephrine and glyceryl trinitrate on cerebral haemodynamics: transcranial Doppler study in healthy volunteers. Br J Anaesth 2008; 100: 240-4
23. Conti A, Iacopino DG, Fodale V, Micalizzi S, Penna O, Santamaria LB. Cerebral haemodynamic changes during propofol-remifentanil or sevoflurane anaesthesia: transcranial Doppler study under bispectral index monitoring. Br J Anaesth 2006; 97: 333-9
24. Reinsfelt B, Westerlind A, Ricksten S-E. The effects of sevoflurane on cerebral blood flow autoregulation and flow-metabolism coupling during cardiopulmonary bypass. Acta Anaesthesiol Scand 2011; 55: 118-23
25. Davie SN, Grocott HP. Impact of extracranial contamination on regional cerebral oxygen saturation: a comparison of three cerebral oximetry technologies. Anesthesiology 2012; 116: 834-40
26. Sorensen H, Secher NH, Siebenmann C, et al. Cutaneous Vasoconstriction Affects Near-infrared Spectroscopy Determined Cerebral Oxygen Saturation during Administration of Norepinephrine. Anesthesiology 2012; 117: 263-70
27. Allen BS, Ko Y, Buckberg GD, Tan Z. Studies of isolated global brain ischaemia: II. Controlled reperfusion provides complete neurologic recovery following 30 min of warm ischaemia - the importance of perfusion pressure. Eur J Cardiothorac Surg 2012; 41: 1147-54
28. Grocott HP. Avoid hypotension and hypoxia: an old anesthetic adage with renewed relevance from cerebral oximetry monitoring. Can J Anaesth 2011; 58: 697-702

Chapter 7

General discussion

The treatment objective for any anesthetist is to provide the best and most safe treatment with the best possible outcome. Over the last 25-50 years the incidence of death directly attributable to anesthesia has fallen from 1 in 2500 in the mid-1950s to 1 in 200 000 nowadays [1]. Several authors suggested that the incidence of death and complications could be further reduced by deliberately enhancing the balance between tissue oxygen delivery and tissue oxygen consumption, thereby preventing perioperative tissue oxygenation debt (Goal Directed Therapy) [2,3]. However, current standard anesthesia monitoring does not give an early indication of impending and developing tissue oxygen debt. Improving outcome in our patients will require that anesthetists become more proactive in their monitoring techniques.

Near-infrared spectroscopy (NIRS) is a non-invasive technology that continuously monitors regional tissue oxygenation. Originally used for assessment of oxygen saturation of the brain, its use has now been expanded to evaluation of oxygenation of tissues other than the brain. There is also growing evidence for the larger applicability of NIRS as an estimate of systemic venous saturation in correspondence

with the adequacy of the circulatory status. New and promising advances may further this technology to become part of our standard armamentarium, in order to optimize patient care in daily anesthesia practice.

The present thesis describes and discusses the feasibility of clinical monitoring with NIRS to counter the current shortcomings in anesthesia monitoring. This thesis reports the potential of NIRS to assess the oxygen balance in patient groups vulnerable to global or regional perfusion deficits, thereby enabling optimization of hemodynamic management.

Chapter 1 summarizes the different technical issues of NIRS and highlights the clinical considerations in cerebral NIRS monitoring. Following that, it is always useful to remember that no monitoring device - no matter how insightful its data - will improve patient outcome unless used with a comprehensive monitoring strategy (Fig. 7.1).

Figure 7.1

Applicability of NIRS to assess perioperative global and regional cerebral perfusion

Dramatic case reports of adverse neurological outcome after minor surgery in relatively healthy patients indicate the shortcomings of current routine anesthesia monitoring. The technical difficulties and/or invasiveness of brain monitoring preclude its use as a standard routine monitoring in perioperative care. As NIRS offers simple, non-invasive, real-time monitoring of cerebral oxygen saturation, its utility as an additional anesthesia monitoring tool deserves further investigation. In this thesis we investigated the use of NIRS for detection of cerebral perfusion deficit, both global and regional, and we assessed the physiological determinants that influence cerebral oxygen saturation.

The surgical and anesthetic communities have been recently alarmed by a series of dramatic neurological outcomes in patients after shoulder surgery in the upright position. Although the exact pathogenesis of these events was unknown, malrotation of the head and perioperative hypotension were intuitively implicated as the causal factors. We hypothesized that cerebral hypoperfusion might go unnoticed when relying solely on blood pressure. Therefore we evaluated the prevalence of cerebral oxygen desaturation in 20 consecutive adult patients undergoing shoulder surgery in the upright position. Routine anesthesia management and standard anesthesia monitoring were used. The responsible anesthetist was not informed about the purpose of the study and was blinded for the rS_cO_2 data. The study is presented in **chapter 3.3**. We observed a relative decrease in rS_cO_2 of more than 20% in 80% of patients when the beach chair position was adopted, underlining the need for awareness of this problem and indicating the need for perioperative monitoring of cerebral oxygen saturation in this type of surgery. In the same study, we identified blood pressure and carbon dioxide concentration as physiological determinants for cerebral desaturation.

In **chapter 3.4**, we demonstrate the utility of NIRS in the management of a patient with moyamoya disease, which is a chronic cerebrovascular occlusive disease, severely compromizing blood supply to the brain. The use of real-time cerebral oxygenation monitoring with NIRS identified a severe decrease in rS_cO_2 with the initiation of cardiopulmonary bypass. By the use of NIRS, which enabled close monitoring of all therapeutic actions taken, the decrease in rS_cO_2 could finally be reversed by initiating pulsatile bypass flow.

During repair of aortic coarctation through left thoracotomy, cross-clamping of the left carotid artery is often indicated. This might result in temporary hypoperfusion of the left brain. Since it has been reported that sodium nitroprusside (a blood pressure regulating agent) has an adverse effect on left-sided rS_cO_2 during aortic coarctation repair, we aimed to compare the effect of three different blood pressure regulating agents on left-sided rS_cO_2. This study is presented in **chapter 4.3**. We observed a variable response of the left-sided rS_cO_2, ranging from a decrease to an increase in rS_cO_2, independent of the treatment group. Therefore, we conclude that the decrease in left-sided rS_cO_2 is not the result of an agent specific effect, but most probably reflects a deficient circle of Willis. In this study, we also observed impairment of cerebral autoregulation with sodium nitroprusside and sevoflurane, whereas autoregulatory capacity was maintained with nitroglycerin.

With the exception of the patient with moyamoya disease (chapter 3.4), who suffered from prolonged somnolence and a transient paresis of the left arm, none of our patients developed gross neurological or cognitive dysfunction postoperatively. In this regard, it is important to note that it is a time-dependent exposure to a certain degree of cerebral desaturation (a viability-time threshold) that eventually leads to irreversible tissue damage and subsequent functional impairment [4,5]. Therefore, the term 'desaturation score' was introduced

[5], which represents an integrated oxygen saturation, or an area under the curve (AUC). This value is calculated by the product of length of time and depth of rS_cO_2 below a specific threshold, and is expressed in %.sec. To account for both depth and duration of change in tissue oxygen saturation, we used the AUC value in many of the studies presented in this thesis.

For the applicability of NIRS for assessment of perioperative cerebral perfusion deficit, we conclude that monitoring of cerebral oxygen saturation with NIRS allows to identify global and regional cerebral hypoperfusion, enabling real-time assessment of the effects of critical events and therapeutic actions. We demonstrated that changes in cerebral oxygenation are related to blood pressure and pulsatility, and to changes in CO_2, and that cerebral autoregulation might be impaired by the use of vasodilating drugs.

Applicability of NIRS to assess perioperative tissue perfusion

Initial research focused on the use of NIRS as a monitor of cerebral oxygen saturation, however interest extended soon to applications in tissues other than the brain. For a number of applications there is little evidence yet that the device truly interrogates the organ of interest, nor that changes in the oxygen status of non-vital organs have to be intervened upon. Future work is needed to identify which applications, and which changes in oxygen status in these applications, are of benefit in clinical practice.

In **chapter 4.3**, we evaluate the effect of different blood pressure regulating agents on renal and muscle oxygen saturation in children undergoing aortic coarctation repair. As expected, renal and muscle oxygen saturations showed a rapid and significant drop after aortic cross-clamping, which recovered promptly after release of the aortic

cross-clamp. Interestingly, in this clinical study, we demonstrated that decreases in renal and muscle oxygen saturation were larger and had a faster rate of decay in patients treated with sodium nitroprusside (SNP) compared to nitroglycerin (NTG), which confirms the results of a previous animal study. Our data suggest that NTG might be preferable for blood pressure control during surgical procedures involving aortic cross-clamping.

During thoracoabdominal aortic aneurysm repair, spinal cord perfusion is severly jeopardized. Close monitoring is mandatory to detect spinal cord ischemia in time to treat it. However, due to technical difficulties and inherent limitations, central nervous system monitoring is not widely used in these cases. In **chapter 4.4**, we present preliminary data suggesting that NIRS monitoring at the level of the spinal cord may identify spinal cord ischemia, and may function as a valuable perioperative non-invasive guide to the management of blood pressure in patients undergoing thoracoabdominal aneurysm repair.

Investigation of the effect of aortic cross-clamping on renal, muscle, and spinal oxygen saturation, demonstrated that NIRS provides real-time assessment of regional tissue perfusion. Its use might optimize perioperative blood pressure management in surgical procedures involving aortic cross-clamping.

Applicability of NIRS to assess the physiological determinants of tissue oxygen saturation

A growing understanding of the physiological principles of NIRS led to an appreciation of its applicability as a monitor of global oxygen balance, providing a non-invasive estimate of systemic oxygen balance.

In **chapter 5**, we examine the equivalence and interchangeability of mixed venous and cerebral oxygen saturation. The study demonstrates that mixed venous oxygen saturation has a substantial time delay between changes in blood pressure and concomitant oxygen saturation changes, whereas cerebral oxygen saturation reacts promptly, without time delay, indicating that cerebral oxygen saturation might represent a prompter more reliable variable than mixed venous oxygen saturation to assess the effects of changes in blood pressure on tissue perfusion.

Considering the important time delay between $S_{mv}O_2$ and rS_cO_2, correlation analysis is probably not the right test to evaluate the equivalence of these 2 parameters. Though correlation is the simplest way to compute the relation between two signals, delayed dynamics between the signals generate smaller correlation coefficients, as demonstrated in our study. Coherence, as correlation, is a measure of strength of a linear relation, but was developed for the analysis of time-invariant systems [6]. In future studies comparing $S_{mv}O_2$ and rS_cO_2, this time delay has to be accounted for when choosing the statistical method.

The data in this thesis demonstrate that tissue oxygen saturation measured with NIRS provides a prompt responsive monitor of changes in perfusion. However, in vivo changes in pressure are accompanied by changes in flow, and therefore it remained undetermined if maintaining pressure and/or flow was the best strategy for prevention of perfusion deficit and the resulting end organ failure. We therefore explored the impact of flow and pressure on cerebral and whole body oxygen saturation during cardiopulmonary bypass, where flow and pressure can be modified independently and in a controlled manner (**chapter 6**). In the elective cardiac surgery population used in that study, maintaining flow seemed to be more important than maintaining pressure. Moreover, increasing blood pressure with phenylephrine elicited reduced cerebral and systemic oxygen saturation. It is important to note that, throughout all our studies, our lowest mean

blood pressure values were consistently higher than the reported critical value of 50 mmHg, and therefore, the obtained results do not exclude perfusion pressure as an important variable. Nevertheless, our results are in accordance with data demonstrating that organ injury can be prevented by targeting oxygen delivery levels above a critical threshold.

Nearly one century ago, Jarisch stated "It was fatal for the development of our understanding of circulation, that blood flow is relatively difficult to measure, whereas blood pressure is easily measured. This is the reason why the blood pressure meter has gained such a fascinating influence, although most organs do not need pressure, but blood flow." *(A. Jarisch, "Kreislauffragen" 1928).* Our results fully support this statement.

Applicability of NIRS to assess cerebral autoregulation

In **chapter 3.3**, **chapter 4.3** and **chapter 6.3**, NIRS monitoring was mentioned in the context of cerebral autoregulation.

In the current standard of care, a systemic MAP of 50-60 mmHg is widely considered to guarantee adequate cerebral perfusion, because of cerebral autoregulation maintaining a constant cerebral blood flow (CBF) in the face of changing cerebral perfusion pressure. However, this practice fails to consider that cerebral autoregulation is derived based on limited data that have been seriously questioned, has wide interindividual variation, and may be altered in specific diseases (e.g. hypertension, diabetes, stroke) and in specific conditions (e.g. changes in CO_2, pharmacologic interference) [7]. Studies identifying the lower limit of cerebral autoregulation (LLA) in healthy, normotensive, nonanesthetized adults demonstrated actual LLA values of 70 mmHg or higher [7]. Agents with cerebral vasodilating properties, including anesthetic agents, lower the effective LLA [8,9]. Although this might increase 'CBF reserve', it remains unreasonable to accept

an empirically chosen LLA for every anesthetized patient in every situation. So, if one rejects the validity of a fixed LLA to guide clinical management, do we have any alternatives?

Recently, the use of NIRS to monitor cerebral autoregulation has become an area of intense investigation. Cerebral autoregulation is measured by quantifying the consequence of changing blood pressure on CBF. It has been demonstrated in laboratory and clinical studies that NIRS signals provide an acceptable surrogate for monitoring changes in CBF for an index of autoregulation [10,11]. Real-time autoregulation monitoring can be accomplished by the continuous calculation of the correlation coefficient between MAP and rS_cO_2, generating a novel index of autoregulatory vasoreactivity, the cerebral oximetry index (COx). Blood pressure in the autoregulation range is indicated by a COx that approaches zero, while a COx approaching 1 indicates MAP below the LLA or disturbed autoregulation [12-14]. The COx has been validated and had good agreement with transcranial Doppler derived measurements of pressure autoregulation in piglets [10] and in adult patients [15-17]. However, analysis of COx requires complex signal processing and specialized software, limiting its applications mostly to research. Recently, an investigational prototype NIRS monitor was validated for automated and continuous monitoring of cerebral autoregulation [18]. The availability of such a device offers the opportunity of widespread autoregulation monitoring, providing effective means for individualizing blood pressure management.

In line with the previously mentioned studies, we evaluated the concordance between MAP and rS_cO_2 using simple correlation analysis. However, cerebral autoregulation is a complex physiological system, and correlation analysis does not cope with the complex interplay and the time-varying aspects of the different physiological mechanisms [19]. Coherence and transfer function analyses have also been used to quantify cerebral autoregulation [20,21]. Caicedo analyzed 4 different measurement models used for cerebral autoregu-

lation assessment (correlation, coherence, modified coherence, and transfer function) and proposed transfer function gain as the most robust method when used for cerebral autoregulation studies [6]. Correlation was considered as a robust method, however with some time delay-related restrictions.

Conclusion. NIRS: When and why should we measure?

In an era where clinical outcome is increasingly determined by optimizing specific target organ function, there is a constant need for accurate and specific monitoring equipment during the critical perioperative period. Based on the direct relationship between cerebral oxygenation and neurological outcome, NIRS has been used to detect deficits in cerebral perfusion during complex cardiac and cerebrovascular procedures. NIRS also demonstrated its utility for the detection of tissue hypoperfusion in other surgical areas, where specific target organ oxygenation still remains poorly monitored in clinical anesthesia. More importantly, there is growing evidence for the larger applicability of NIRS as an estimate of systemic venous saturation in correspondence with the adequacy of the circulatory status. The information provided by this technology could significantly alter our management of physiologic perturbations during anesthesia. Due to the advantage of simple, continuous and non-invasive monitoring, NIRS has the potential to become a valuable tool to optimize patient care in our daily anesthesia practice.

References

1. Lagasse RS. Anesthesia safety: model or myth? A review of the published literature and analysis of current original data. Anesthesiology 2002; 97: 1609–17

2. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, and Tomlanovich M, for the Early Goal-Directed Therapy Collaborative Group. Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock. N Engl J Med 2001; 345: 1368-77

3. Pearse R, Dawson D, Fawcett J, Rhodes A, Grounds RM, Bennett ED. Early goal-directed therapy after major surgery reduces complications and duration of hospital stay. A randomised, controlled trial. Critical Care 2005; 9: R687-R693

4. Kurth CD, McCann JC, Wu J, Miles L, Loepke AW. Cerebral oxygen saturation-time threshold for hypoxic-ischemic injury in piglets. Anesth Analg 2009; 108: 1268-77

5. Slater JP, Guarino T, Stack J, et al. Cerebral oxygen desaturation predicts cognitive decline and longer hospital stay after cardiac surgery. Ann Thorac Surg 2009; 87: 36-44

6. Caicedo A, Naulaers G, Lemmers P, van Bel F, Wolf M, Van Huffel S. Detection of cerebral autoregulation by near-infrared spectroscopy in neonates: performance analysis of measurement methods. J Biomed Opt 2012; 17: 117003 1-9

7. Drummond JC. The lower limit of autoregulation: time to revise our thinking? Anesthesiology 1997; 86: 1431-3

8. Stånge K, Lagerkranser M, Sollevi A. Nitroprusside-induced hypotension and cerebrovascular autoregulation in the anesthetized pig. Anesth Analg 1991; 73: 745-52

9. Conti A, Iacopino DG, Fodale V, Micalizzi S, Penna O, Santamaria LB. Cerebral haemodynamic changes during propofol-remifentanil or sevoflurane anaesthesia: transcranial Doppler study under bispectral index monitoring. Br J Anaesth 2006; 97: 333-9

10. Brady KM, Lee JK, Kibler KK, Smielewski P, Czosnyka M, Easley RB, Koehler RC, Shaffner DH. Continuous time-domain analysis of cerebrovascular autoregulation using near-infrared spectroscopy. Stroke 2007; 38: 2818-25

11. Zweifel C, Castellani G, Czosnyka M, Carrera E, Brady KM, Kirkpatrick PJ, Pickard JD, Smielewski P. Continuous assessment of cerebral autoregulation with near-infrared spectroscopy in adults after subarachnoid

hemorrhage. Stroke 2010; 41: 1963-8
12. Joshi B, Ono M, Brown C, Brady K, Easley RB, Yenokyan G, Gottesman RF, Hogue CW. Predicting the limits of cerebral autoregulation during cardiopulmonary bypass. Anesth Analg 2012; 114: 503-10
13. Gilmore MM, Stone BS, Shepard JA, Czosnyka M, Easley RB, Brady KM. Relationship between cerebrovascular dysautoregulation and arterial blood pressure in the premature infant. J Perinatol 2011; 31: 722-9
14. Brady KM, Mytar JO, Lee JK, Cameron DE, Vricella LA, Thompson WR, Hogue CW, Easley RB. Monitoring cerebral blood flow pressure autoregulation in pediatric patients during cardiac surgery. Stroke 2010; 41: 1957-62
15. Steiner LA, Pfister D, Strebel SP, Radolovich D, Smielewski P, Czosnyka M. Near-infrared spectroscopy can monitor dynamic cerebral autoregulation in adults. Neurocrit Care 2009; 10: 122-8
16. Brady K, Joshi B, Zweifel C, Smielewski P, Czosnyka M, Easley RB, Hogue CW. Real-time continuous monitoring of cerebral blood flow autoregulation using near-infrared spectroscopy in patients undergoing cardiopulmonary bypass. Stroke 2010; 41: 1951-6
17. Zheng Y, Villamayor AJ, Merritt W, Pustavoitau A, Latif A, Bhambhani R, Frank S, Gurakar A, Singer A, Cameron A, Stevens RD, Hogue CW. Continuous cerebral blood flow autoregulation monitoring in patients undergoing liver transplantation. Neurocrit Care 2012; 17: 77-84
18. Ono M, Zheng Y, Joshi B, Sigl JC, Hogue CW. Technical communication: validation of a stand-alone near-infrared spectroscopy system for monitoring cerebral autoregulation during cardiac surgery. Anesth Analg 2013; 116: 198-204
19. Panerai RB. Cerebral autoregulation: from models to clinical applications. Cardiovasc Eng 2008; 8: 42-59
20. Wong FY, Leung TS, Austin T, Wilkinson M, Meek JH, Wyatt JS, Walker AM. Impaired autoregulation in preterm infants identified by using spatially resolved spectroscopy. Pediatrics 2008; 121: e604-11
21. Caicedo A, De Smet D, Naulaers G, Ameye L, Vanderhaegen J, Lemmers P, Van Bel F, Van Huffel S. Cerebral tissue oxygenation and regional oxygen saturation can be used to study cerebral autoregulation in prematurely born infants. Pediatr Res 2011; 69: 548-53

Chapter 8

Future perspectives

Near-infrared spectroscopy was introduced in our cardiac surgery department in 2006, initially for cerebral monitoring during pediatric cardiac surgery and aortic arch surgery. However, growing clinical experience, together with cases where unexpected events were detected by NIRS, soon led us to adopt NIRS as routine monitor in every cardiac surgery case. In spite of my extensive clinical experience with NIRS, and in spite of this thesis, many questions about the applicability of NIRS to optimize patient care remain.

Today, I am eager to explore two topics relating to NIRS. One topic has arisen from the research for my thesis, the other one remained in the background in favour of my thesis project. Now that my thesis has finished, I am glad that time will come available to explore these two topics in depth.

First, I would like to investigate more in detail the usefulness of NIRS to monitor spinal cord perfusion. There is a clear need for improved spinal cord monitoring during thoracoabdominal aortic surgery. Currently, evoked potential monitoring is primarily used to monitor spinal cord perfusion. However, due to its technical complexity and constraints on anesthetic management, it is not widely

used during thoracoabdominal aortic surgery. Our preliminary data with NIRS (presented in chapter 4.4) were very promising, however further investigations are required before a final conclusion can be drawn. My aim is to compare NIRS with evoked potential monitoring, and to evaluate whether measuring and intervening on the values obtained by NIRS makes a difference in the neurologic outcome of patients who underwent repair of extensive thoracoabdominal aneurysms.

Second, as endothelial dysfunction is the earliest detectable stage of atherogenesis, non-invasive endothelial function testing for the purpose of cardiovascular risk stratification is very appealing. One aspect of endothelial physiology is vasomotor function. The ability of the endothelium to vasodilate in response to pharmacological and physiological stimuli has been the most widely used clinical end point for assessment of endothelial function [1].

Near-infrared Spectroscopy (NIRS) has been introduced as a way to assess non-invasively microvascular reactivity in several disease states [2]. It enables to quantify endothelium-mediated changes in vascular tone, elicited by creating postocclusive reactive hyperemia (PORH). PORH is a reproducible transient increase in blood flow after release of an arterial occlusion. When the cuff is released, the surge of blood flow causes an endothelium-dependent Flow Mediated Dilatation (FMD) (Fig. 8.1). The speed of flow and the recovery are mostly determined by the capacity of the microvasculature to recruit arterioles and capillaries, reflecting the integrity of the microcirculation. NIRS proved to provide excellent reproducibility [3], and demonstrated a coherent directional change with simultaneously performed strain gauge plethysmography and radionuclide plethysmography [4]. Parameters of PORH measured by NIRS were able to distinguish between healthy volunteers and patients with vascular disorder [5].

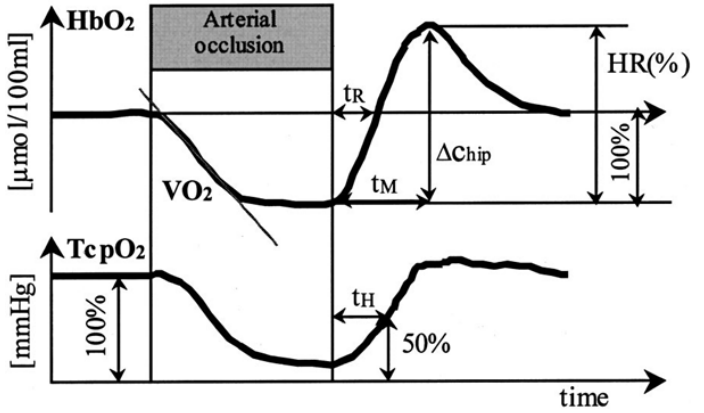

Figure 8.1: Parameters of postocclusive reactive hyperemia evaluated from NIRS and $TcpO_2$ signals. HbO_2: oxyhemoglobin, $TcpO_2$: transcutaneous oxygen partial pressure, VO_2: oxygen consumption, t_R: time of recovery, t_M: time to peak value, ΔC_{hip}: maximal change of the NIRS signal, HR: maximal hyperemic response, t_H: half time of the response. Ann Biomed Eng 2001; 29: 311-20

We hypothesize that by means of NIRS we could introduce an easy-to-use, user-independent method to estimate the cardiovascular risk profile of patients and, consequently, that we might predict which patients have a higher risk for compromized perfusion during the critical perioperative period.

The purpose of future studies is to determine the applicability of NIRS for quantification of PORH. In order to fulfill this task we aim to: (1) determine the parameters of PORH measured by NIRS and examine the reproducibility; (2) compare these results with the digital pulse amplitude responses measured with the EndoPAT 2000 device (Itamar Medical, Caesarea, Israel), which is widely recognized as the standard method for non-invasive endothelial function assessment.

References

1. Deanfield JE, Halcox JP, Rabelink TJ. Endothelial function and dysfunction: testing and clinical relevance. Circulation 2007; 115: 1285-95

2. Nanas S, Gerovasili V, Renieris P. Non-invasive assessment of the microcirculation in critically ill patients. Anaesth Intensive Care 2009; 37: 733-9

3. Lacroix S, Gayda M, Gremeaux V, Juneau M, Tardif JC, Nigam A. Reproducibility of near-infrared spectroscopy parameters measured during brachial artery occlusion and reactive hyperemia in healthy men. J Biomed Opt 2012 Jul; 17(7). doi:10.1117/1.JBO.17.7.077010

4.Harel F, Denault A, Ngo Q, Dupuis J, Khairy P. Near-infrared spectroscopy to monitor peripheral blood flow perfusion. J Clin Monit Comput 2008; 22: 37-43

5.Kragelj R, Jarm T, Erjavec T, Presern-Strukelj M, Miklavcic D. Parameters of postocclusive reactive hyperemia measured by near infrared spectroscopy in patients with peripheral vascular disease and in healthy volunteers. Ann Biomed Eng 2001; 29: 311-20

Summary

The primary goal in the hemodynamic management of patients undergoing surgery is to preserve oxygen delivery at a level sufficient to cover all metabolic needs. Although it has been increasingly demonstrated that clinical outcome is determined by optimizing tissue oxygenation, specific target organ oxygen saturation still remains poorly monitored in clinical anesthesia.

Within the last decades, near-infrared spectroscopy (NIRS) is introduced with the potential to continuously assess tissue oxygenation. NIRS is a noninvasive device that measures the absorption of near-infrared light by tissue chromophores, a technique similar to pulse oximetry. Specific wavelengths of near-infrared light are emitted through the tissues lying below a sensor. Depending on the amount of light reflected back to light detectors built into the same sensor, regional oxygen saturation of the underlying tissue can be determined.

In the present work, NIRS was used to detect perioperative compromised perfusion, in order to explore the physiological determinants of cerebral and peripheral tissue oxygen saturation in different patient populations. The ultimate goal is the optimization of patient management in daily anesthesia practice.

The brain, arguably our most important of organs and despite being an obvious site of anesthetic action, ironically is inconsistently the focus of targeted monitoring during anesthesia. Moreover,

several clinical conditions routinely encountered in our daily medical practice have the potential to disrupt the brain oxygen balance exposing patients to the risk of intraoperative cerebral ischemia. In this thesis, we demonstrated that monitoring of cerebral oxygen saturation with NIRS allowed to identify global and regional cerebral hypoperfusion, enabling real-time assessment of the effects of critical events and therapeutic actions. Changes in cerebral oxygenation were demonstrated to be related to blood pressure and pulsatility, and to changes in CO_2. We also indicated that the use of vasodilating drugs might impair cerebral autoregulation.

The use of NIRS for monitoring regional oxygen saturation at somatic sites has been advocated as an early warning system for regional hypoperfusion. However, it remains to be identified which changes in oxygen status of non-vital organs have to be intervened upon. The present work demonstrated that NIRS provided real-time assessment of renal, muscle, and spinal oxygen saturation during aortic cross-clamping. Changes in tissue oxygen saturation were pressure dependent, and seemed to be negatively affected by the concomitant use of sodium nitroprusside.

The data in the present thesis demonstrate that tissue oxygen saturation measured with NIRS provides a prompt responsive monitor of changes in perfusion. However, in vivo changes in pressure are accompanied by changes in flow, and therefore it remained undetermined if maintaining pressure and/or flow was the best strategy for prevention of perfusion deficit. We therefore explored the impact of flow and pressure on cerebral and whole body oxygen saturation during cardiopulmonary bypass, where flow and pressure can be modified independently and in a controlled manner. In this elective study population, maintaining flow seemed to be more important than maintaining pressure. It is important to note that, throughout all our studies, the lowest mean blood pressure values were consistently higher than the reported critical value of 50 mmHg, and therefore, the obtained results do not exclude perfusion pressure

as an important variable. Nevertheless, our results are in accordance with data demonstrating that organ injury can be prevented by targeting oxygen delivery levels above a critical threshold.

Conclusion. In this thesis, NIRS has demonstrated its utility for assessing specific target organ perfusion. The information provided by this technology could significantly alter our management of physiologic perturbations during anesthesia. Due to the advantage of simple, continuous and non-invasive monitoring, NIRS has the potential to become a valuable tool to optimize patient care in our daily anesthesia practice.

Samenvatting

Het doel van het hemodynamisch beleid tijdens anesthesie is om de weefsels van voldoende zuurstof te voorzien. Het is bewezen dat de klinische uitkomst beter is wanneer de weefseloxygenatie geoptimaliseerd wordt, maar omwille van een aantal praktische problemen, wordt de zuurstofverzadiging van specifieke organen tot op heden niet routinematig gemonitord tijdens anesthesie.

Nabije-infrarood spectroscopie (NIRS) is een niet-invasieve techniek die de mogelijkheid biedt om continu de weefseloxygenatie te meten. Specifieke golflengtes van nabije-infrarood licht worden door weefsel gezonden. Afhankelijk van de mate waarin de straling geabsorbeerd wordt, kan de zuurstofsaturatie in het weefsel bepaald worden.

De doelstelling van deze thesis was om door middel van NIRS oxygenatieproblemen ter hoogte van de hersenen en de perifere weefsels te detecteren, en de fysiologische determinanten van de weefselsaturatie te bepalen. Het uiteindelijk doel is de optimalisatie van het hemodynamisch beleid in de dagelijkse anesthesie praktijk.

Meerdere factoren tijdens anesthesie kunnen de zuurstofbalans in de hersenen verstoren, met mogelijks cerebrale letsels tot gevolg. Desondanks worden de hersenen momenteel niet routinematig gemonitord. In deze thesis toonden we aan dat NIRS monitoring zowel globale als regionale cerebrale hypoperfusie kan detecteren. Veranderingen in cerebrale oxygenatie waren gerelateerd aan bloed-

druk en pulsatiliteit, en aan CO_2 veranderingen. We toonden ook aan dat bloedvatverwijdende medicatie de cerebrale autoregulatie kan verstoren.

Tijdens operaties waarbij een aortaklem geplaatst werd, toonden we aan dat NIRS onmiddellijk veranderingen in de nier-, spier-, en ruggenmergsaturatie detecteerde. De veranderingen in de weefselsaturaties waren drukafhankelijk, en werden negatief beïnvloed door het gebruik van sodium nitroprusside.

De gegevens in dit proefschrift toonden aan dat de met NIRS gemeten weefseloxygenatie een snelle weergave geeft van doorbloedingsveranderingen. Echter in vivo gaan bloeddrukveranderingen steeds gepaard met flowveranderingen, en daarom blijft de vraag of druk dan wel flow de beste strategie is om perfusietekort te voorkomen. Daarom onderzochten we het effect van druk en flow op de cerebrale en globale zuurstofsaturatie tijdens cardiopulmonale bypass, waarbij flow en druk gecontroleerd en onafhankelijk van elkaar kunnen veranderd worden. Uit deze studie bleek dat flow belangrijker is dan druk voor het behoud van cerebrale en systeem oxygenatie. Het is evenwel belangrijk op te merken dat, in al onze studies, de laagste gemiddelde bloeddrukwaarden steeds hoger waren dan de algemeen aanvaarde kritische waarde van 50 mmHg, en dat derhalve de verkregen resultaten perfusiedruk niet uitsluiten als een belangrijke variabele. Desalniettemin zijn onze resultaten in overeenstemming met gegevens die aantonen dat orgaanschade kan voorkomen worden door de zuurstofaanvoer boven een bepaalde kritische drempel te houden.

Besluit. In dit proefschrift toonden we aan dat NIRS snel en betrouwbaar weefseloxygenatieproblemen detecteerde. Door een beter begrip van de fysiologische veranderingen tijdens anesthesie kan deze techniek het anesthetisch beleid optimaliseren.

List of abbreviations

AUC area under the curve

BIS bispectral index

CBF cerebral blood flow

CEA carotid endarterectomy

CO_2 carbon dioxide

CPB cardiopulmonary bypass

CPP cerebral perfusion pressure

CVP central venous pressure

CX aortic cross-clamping

DO_2 systemic oxygen delivery

$EtCO_2$ end-tidal concentration of carbon dioxide

ETsevo end-tidal concentration of sevoflurane

FiO_2 fractional inspired oxygen

Hb hemoglobin

HHb deoxygenated hemoglobin

Hct hematocrit

HR heart rate

ICP intracranial pressure

LLA lower limit of autoregulation

MAP mean arterial blood pressure

MMD moyamoya disease

NTG nitroglycerin

OER oxygen extraction ratio

O2Hb oxygenated hemoglobin

OPCAB off-pump coronary artery bypass

$PaCO_2$ arterial carbon dioxide partial pressure

PaO_2 arterial oxygen partial pressure

PtO_2 tissue oxygen tension

$PvCO_2$ venous carbon dioxide partial pressure

PvO_2 venous oxygen partial pressure

Q pump flow

$rScO_2$ regional cerebral oxygen saturation

SaO_2 arterial oxygen saturation

SAP systolic arterial blood pressure

ScO_2 cerebral oxygen saturation

Sevo sevoflurane

$SjvO_2$ jugular vein oxygen saturation

SmO_2 muscle oxygen saturation

$SmvO_2$ mixed venous oxygen saturation

SNP sodium nitroprusside

SpO_2 pulse oximetry

SsO_2 spinal oxygen saturation

SR Spatial Resolution

SrO_2 renal oxygen saturation

SRS Spatially Resolved Spectroscopy

SvO_2 venous oxygen saturation

TAAA thoracoabdominal aortic aneurysm

THb total hemoglobin

Dankwoord

A closed mind is a good thing to lose... Dit proefschrift opende voor mij een stukje van de "black box" van het menselijk lichaam. Maar ik leerde niet enkel bij over de fysiologische veranderingen tijdens het perioperatieve gebeuren. Ik leerde evenzeer dat een thesis niet de verdienste is van één enkele persoon, maar een proces, een project, waarin velen zowel rechtstreeks als onrechtstreeks bijdragen. Daarom een oprecht dankwoord voor ieder die heeft bijgedragen tot de verwezenlijking van deze thesis.

Als allereerste wil ik de mensen danken waarmee alles begonnen is, mijn ouders. Zij hebben mij alle vrijheid en kansen gegeven, en daar ben ik hun zeer dankbaar voor. Zij gaven mij ook een aantal waarden mee, die ervoor gezorgd hebben dat ik hier nu sta. Voor de warme familie die ze gecreëerd hebben, en voor de manier waarop ze mij opgevoed hebben en steeds nabij zijn geweest, heb ik veel respect. Bedankt pa en ma!

Vervolgens wil ik diegene danken die mij besmet heeft met de microbe voor anesthesie, ook al is hij er zich zelf niet van bewust. Lang geleden, op mijn allereerste stage heelkunde in het ziekenhuis in Wetteren, was ik danig onder de indruk van de sereniteit en de rust die van de anesthesist uitging. Voor mij was gans het gebeuren rond anesthesie pure "magie", en daar in Wetteren is mijn interesse

in anesthesie gewekt. Dus bedankt, Dr. Donadoni!

Ik dank mijn toenmalig diensthoofd, Prof Dr. G. Rolly, die mij de mogelijkheid heeft geboden om mijn opleiding anesthesie te starten, en mij 5 jaar later steunde in mijn droom om mij verder te bekwamen in de cardio-anesthesie. Ik ben zeer veel verschuldigd aan mijn toenmalige collega's cardio-anesthesie, Yvon Deryck, Luc Foubert, Luc Herregods en Jan Poelaert, die mij als compleet groentje niet alleen de "grote" knepen van het vak geleerd hebben, maar ook hun gebetenheid en hun enthousiasme voor de nuances van de cardiovasculaire fysiologie met mij deelden. Nu nog, als het oplijnen van een neonaat probleemloos verloopt, denk ik met plezier terug aan de gouden raad van Yvon, die ik hier om redenen van censuur, jammer genoeg niet kan/durf neerschrijven.

Uiteraard zou dit proefschrift er niet gekomen zijn zonder de nodige wetenschappelijke begeleiding. Eerst en vooral wil ik mijn promotor en diensthoofd, Prof. Dr. Patrick Wouters, danken voor de praktische en professionele ondersteuning, voor de kritische reflecties en verbeteringen (de cardiovasculaire fysiologie heeft voor hem écht geen geheimen), en last but not least om mij de mogelijkheid te geven vrijgesteld te worden van het klinisch werk zodat ik ongestoord aan mijn project kon werken.
Ik dank mijn beide co-promotoren, Prof. Dr. Stefan De Hert en Prof. Dr. Chris Verborgh, voor de wetenschappelijke begeleiding. In het bijzonder wil ik Prof. De Hert bedanken om mij letterlijk op te leiden in de wetenschap. Hij heeft mij systematisch leren werken en schrijven, met een scherp afgelijnde vraagstelling, een sluitende methodiek, heldere resultaten, en (dixit) "de discussie komt dan vanzelf". Sinds zijn komst op onze dienst heeft mijn project een *boost* gekregen, niet alleen dankzij zijn ruime wetenschappelijke ervaring en zijn sterk analytische geest, maar ook omdat hij ondanks zijn eigen drukke bezigheden, er toch steeds in slaagde om mijn werk

voor te nemen, en in een minimum van tijd zijn opmerkingen en/of verbeteringen terug te sturen. Los van de wetenschap, hebben zijn vermogen om te relativeren en zijn advies om geen negatieve energie te verspillen, menigmaal bij mij de "stoom van de ketel" gehaald. Stef, bedankt, ik hoop samen met jou nog veel projecten uit te werken.
Verder gaat mijn dank uit naar de leden van de doctoraatscommissie, Prof. Dr. Daniël De Wolf, Prof. Dr. Luc Herregods, Prof. Dr. Eric Mortier, Prof. Dr. Gunnar Naulaers, Prof. Dr. Yves Van Belleghem, Prof. Dr. Johan Vande Walle en Prof. Dr. Frank Vermassen, voor hun bereidheid om mijn proefschrift te beoordelen en voor hun waardevolle bemerkingen en suggesties bij het nalezen van dit werk.

Ik dank de co-auteurs van mijn publicaties, voor hun hulp bij het recruteren van patiënten, en voor hun kritische bemerkingen bij het uitwerken van studieprotocols, het verwerken van data, en het uitschrijven van resultaten. Hun inbreng, hun interesse en onze talrijke discussies waren een verrijking en een stimulans voor mijn onderzoek. Een deel ervan gebeurde in samenwerking met assistenten anesthesie. Pieter, Wouter, Arif, jullie leverden prima werk, bedankt! Verder ben ik veel verschuldigd aan Marc De Buyzere, die mij doorheen een extreem moeilijke statistische revisie geholpen heeft, en die mij met een eindeloos geduld het verschil in "slang" en in denkpatroon tussen clinici en statistici heeft uitgelegd.

Een belangrijk deel van mijn onderzoek gebeurde in samenwerking met de perfusionisten. En het mag gezegd worden, onze perfusionisten zijn gewoonweg fantastisch! Grondige vakkennis, wetenschappelijk sterk, geïnteresseerd, open-minded, consciëntieus, en ... altijd in voor een grap (Ik citeer: "ook al zijn ze daar wat te oud voor"). Filip, Dirk, Martin, Daniël, Korneel, het is een plezier om met jullie samen te werken!

Mijn collega's anesthesisten, in het bijzonder mijn cardio-collega's Stef, Isabel en Katelijne, dank ik voor hun collegiale ondersteuning en voor het compenseren van mijn afwezigheden in de kliniek. Ik wil hierbij ook mijn ex-collega Stefan Jacobs niet vergeten en bedanken voor zijn oprechte bezorgdheid dat door zijn vertrek mijn thesis tijdelijk in de diepvriezer zou terecht komen. Stef, nog eens bedankt voor je gouden raad bij je vertrek, ik probeer het nog elke dag opnieuw ...

Ann (DB), Ann (DP), Barbara, Brigitte, Frieda, Geert, Hilde, Jan, Sjoert, alias "Het secretariaat anesthesie", dank voor jullie voortdurende bereidwilligheid, ondanks het vele werk, en voor de onontbeerlijke professionele ondersteuning.

Bart, mijn "allerliefste" schoonbroer, bedankt voor je professionele hulp bij de lay-out van de kaft. Broer Koen, je hebt een extra glas wijn tegoed!

Als allerlaatste wil ik tenslotte de personen danken die als geen ander betrokken geweest zijn bij mijn proefschrift, mijn kinderen Katrien en Frederik, en mijn echtgenoot Erik. Deze thesis is net zo goed in hun vrije tijd geschreven als in de mijne, en hun begrip en betrokkenheid hebben mij gesteund in het schrijfproces. Katrien, dank je voor je immer zonnig gemoed en je warme knuffels. Het is een plezier om jou rondom mij te weten. Fredje, dank je om je computer-dummy van een moeder regelmatig uit de nood te helpen, om mijn Endnote-bibliotheek meermaals van een gewisse dood te redden, en om mij te introduceren in LaTeX. Je computerkennis is van onschatbare waarde geweest voor deze thesis. Erik, dank je om mij de ruimte te gunnen die ik mij toe-eigende voor het schrijven van dit doctoraat, bedankt om lief en leed met mij te delen. Het leukste aan elke dag is nog altijd 's avonds bij jou thuis komen.

Curriculum Vitae

Personalia
Family Name: MOERMAN
First Name: Anneliese, Thea, Agnes, Albert, Maria
Place and date of birth: Oostakker, november 9, 1963
Private Address: P. Meirestraat 11, 9030 Mariakerke
E-mail: annelies.moerman@UGent.be

Education
- Secondary education: Sint-Bavo humaniora, Gent
- Doctor in Medicine, Surgery and Obstetrics (Cum laude), University of Ghent, 1988
- Specialist in Anesthesiology, University of Ghent, 1 november 1993
- Certificate Special Studies in Anesthesiology (Magna cum laude), 1990

Professional activities
- 01.08.1988 - 31.10.1993: Assistant in training, University Hospital Ghent
- 01.11.1993 - 31.12.1994: Part time anesthesiologist in the Group Anesthesia, Intensive and Urgency Medicine and Pain Care in the Municipial Hospital of Roeselare
- 29.11.1993 - 31.12.1994: Part time consultant in the Pain Clinic of the University Hospital of Ghent
- 01.01.1995: Resident cardiac anesthesia at the Department of Anesthesiology, University Hospital Ghent
- Since 01.08.1998: Staff member cardiac anesthesia at the Department of Anesthesiology, University Hospital Ghent

Publications

Infrared thermographie evaluation of the effect of spinal cord stimulation. Devulder J, **Moerman A**, Castille F, de Thibault de Boesinghe L. Thermologie Österreich 1994, juli, pp.113-20

Awareness during anaesthesia for implantable cardioverter defibrillator implantation. **Moerman A**, Herregods L, Foubert L, Poelaert J, Jordaens L, D'Hont L, Rolly G. Anaesthesia 1995; 50: 733-5

Comparative study of limited intentional normovolaemic haemodilution in patients with left main stenosis. Herregods L, Foubert L, **Moerman A**, François K, Rolly G. Anaesthesia 1995; 50; 950-3

Relevance of Epidurography and Epidural Adhesiolysis in Chronic Failed Back Surgery Patients. Devulder J, Bogaert L, Castille F, **Moerman A**, Rolly G. Clin J Pain 1995; 11: 147-50

Limited Intentional Normovolemic Hemodilution, ST-Segment Changes and Use of Homologous Bloodproducts in Patients with Left Main Stenosis. Herregods L, **Moerman A**, Foubert L, Den Blauwen N, Mortier E, Poelaert J, Struys M. J Cardiothor Vasc Anesth 1997; 11: 18-23

Clinical usefulness of the bispectral index for titrating propofol target effect-site concentration. Struys M, Versichelen L, Byttebier G, Mortier E, **Moerman A**, Rolly G. Anaesthesia 1998; 53: 4-12

Influence of anaesthesia on defibrillation threshold. **Moerman A**, Herregods L, Tavernier R, Jordaens L, Struys M, Rolly G. Anaesthesia 1998; 53: 1156-9

Comparative efficacy and safety of remifentanil and fentanyl in fast track coronary artery bypass graft surgery: a randomized, double-blind study. Möllhoff T, Herregods L, **Moerman A**, Blake D, MacAdams C, Demeyere R, Kirnö K, Dybvik T, Shaikh S, and the Remifentanil Study Group. Br J Anaesth 2001; 87: 718-26

Remifentanil infusion for cardiac catheterisation in children with congenital heart disease. Foubert L, Reyntjens K, De Wolf D, Suys B, **Moerman A**, Mortier E. Acta Anaesth Scand 2002; 46: 355-60

The female coronary patient. **Moerman A**. Acta Anaesthesiologica Belgica 2002; 53: 319-20

Propofol versus Remifentanil for monitored anaesthesia care during colonoscopy. **Moerman A**, Foubert L, Herregods L, Struys M, De Wolf D, De Looze D, De Vos M, Mortier E. Eur J Anaesthesiol 2003; 20: 461-6

Ambulatory electrical external cardioversion with propofol or etomidate. Herregods L, Bossuyt G, De Baerdemaeker L, **Moerman A**, Struys M, Den Blauwen N, Tavernier R, Mortier E. J Clin Anesth 2003; 15: 91-6

Ability of the bispectral index, autoregressive modelling with exogenous input-derived auditory evoked potentials, and predicted propofol concentrations to measure patient responsiveness during anesthesia with propofol and remifentanil. Struys M, Vereecke H, **Moerman A**, Jensen EW, Verhaeghen D, De Neve N, Dumortier F, Mortier E. Anesthesiology 2003; 99: 802-12

Off-pump coronary surgery: surgical strategy for the high-risk patient. Van Belleghem Y, Caes F, Maene L, Van Overbeke H, **Moerman A**, Van Nooten G. Cardiovasc Surg 2003; 11: 75-9

Bovine glue (BioGlue) is catabolized by enzymatic reaction in the vascular dog model. Van Belleghem Y, Forsyth R, Narine K, **Moerman A**, Taeymans Y, Van Nooten G. Ann Thorac Surg 2004; 77: 2177-81; discussion 2181

Remifentanil used to supplement propofol does not improve quality of sedation during spontaneous respiration. **Moerman A**, Struys M, Vereecke H, Herregods L, De Vos M, Mortier E. J Clin Anesth 2004; 16: 237-43

Outcome analysis of major cardiac operations in low weight neonates. Bové T, François K, De Groote K, Suys B, De Wolf D, Verhaaren H, Matthys D, **Moerman A**, Poelaert J, Vanhaesebroeck P, Van Nooten G. Ann Thorac Surg 2004; 78: 181-7

Estimation of myocardial performance in CABG patients. Poelaert J, Heerman J, Schupfer G, **Moerman A**, Reyntjens K, Roosens C. Acta Anaesthesiol Scand 2004; 48: 973-9

An assessment of computer-assisted personalized sedation: a sedation delivery system to administer propofol for gastrointestinal endoscopy. Pambianco D, Whitten C, **Moerman A**, Struys MMRF, Martin J. Gastrointestinal endoscopy 2008; 68: 542-7

Manual versus Target-Controlled Infusion Remifentanil Administration in Spontaneously Breathing patients. **Moerman A**, Herregods L, De Vos M, Mortier E, Struys MMRF. Anesth Analg 2009; 108: 828-34

Near-infrared spectroscopy (NIRS) monitoring in contemporary anesthesia and critical care. **Moerman A**, Wouters P. Acta Anaesth Belg 2010; 61: 185-94

Near-infrared spectroscopy for monitoring spinal cord ischemia during hybrid thoracoabdominal aortic aneurysm repair. **Moerman A**, Van Herzeele I, Vanpeteghem C, Vermassen F, François K, Wouters P. J Endovasc Ther 2011; 18: 91-5

Are cerebral oximeters designed to measure ambient light? **Moerman A**, De Hert S. Br J Anaesth 2011; 106: 753-5

Cerebral oxygen desaturation during shoulder surgery in beach chair position. **Moerman A**, De Hert S, Jacobs T, De Wilde L, Wouters P. Eur J Anaesthesiol 2012; 29: 82-7

Critical cerebral oxygen desaturation: how should we define baseline saturation? **Moerman A**, De Hert S. Eur J Anaesthesiol 2012; 29: 352

Utility of Near-infrared Spectroscopy for Assessing Cerebral Oxygen Saturation during Beach Chair Position. **Moerman A**, De Hert S. Anesthesiology 2012; 117: 1395-6

Value of cerebral oxygen saturation monitoring during cardiopulmonary bypass in an adult patient with moyamoya disease. De Buysscher P, **Moerman A**, Bové T, De Pauw M, Wouters P, De Hert S. J Cardiothor Vasc Anesth 2013; http://dx.doi.org/10.1053/j.jvca.2011.11.002

Relation between mixed venous oxygen saturation and cerebral oxygen saturation measured by absolute and relative near-infrared spectroscopy during off-pump coronary artery bypass grafting. **Moerman A**, Vandenplas G, Bové T, Wouters P, De Hert S. Br J Anaesth 2013; 110: 258-65

The effect of blood pressure regulation during aortic coarctation repair on brain, kidney, and muscle oxygen saturation measured by near-infrared spectroscopy: a randomized, clinical trial. **Moerman A**, Bové T, François K, Deblaere I, Jacobs S, Wouters P, De Hert S. Anesth Analg 2013, 116: 760-6

Influence of variations in systemic blood flow and pressure on cerebral and systemic oxygen saturation in cardiopulmonary bypass patients. **Moerman A**, Denys W, De Somer F, Wouters P, De Hert S. Br J Anaesth 2013, in press

Implementation of a structured information transfer checklist improves postoperative data transfer after congenital cardiac surgery. Karakaya A, **Moerman A**, Peperstraete H, François K, Wouters P, De Hert S. Eur J Anaesthesiol 2013, in press

The effect of retrograde autologous priming volume on haemodilution and transfusion requirements during cardiac surgery. Vandewiele K, Bové T, De Somer F, Dujardin D, Vanackere M, De Smet D, **Moerman A**, Bouchez S, François K. Interact CardioVasc Thorac Surg 2013; doi:10.1093/icvts/ivt085