Near infrared spectroscopy evaluated cerebral oxygenation during anesthesia

Henrik Sørensen

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Official opponents: Matthias Heringlake, Thomas W.L. Scheeren and Hanne Berg Ravn (chairman)

Correspondence: Copenhagen Muscle Research Center, Department of Anesthesia, Rigshospitalet. Blegdamsvej 9, DK-2100 Copenhagen Ø, Denmark

E-mail: hs770@hotmail.com

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THIS THESIS IS BASED ON THE FOLLOWING PAPERS:

1. Sørensen H, Secher NH, Siebenmann C, Nielsen HB, Kohl-Bareis M, Lundby C, Rasmussen P. Cutaneous vasoconstriction affects near-infrared spectroscopy determined cerebral oxygen saturation during administration of norepinephrine. Anesthesiology (2012); 117:263-270
2. Sørensen H, Siebenmann C, Jacobs RA, Haider T, Rasmussen P, Lundby C. Hypocapnia during hypoxic exercise and its impact on cerebral oxygenation, ventilation and maximal whole body O(2) uptake. Respir Physiol Neurobiol (2012); 185: 461-467
3. Sørensen H, Secher NH, Rasmussen P. A note on arterial to venous oxygen saturation as reference for NIRS-determined frontal lobe oxygen saturation in healthy humans Front Physiol (2014); 4: Article 403
4. Sørensen H, Grocott HP, Niemann M, Rasmussen A, Hillingsø JG, Frederiksen HJ, Secher NH. Ventilatory strategy during liver transplantation: implications for near-infrared spectroscopy-determined frontal lobe oxygenation. Front Physiol (2014); 5: Article 321
5. Sørensen H, Rasmussen P, Sato K, Persson S, Olesen ND, Nielsen HB, Olsen NV, Ogoh S, Secher NH. External carotid artery flow maintains NIRS-determined frontal lobe oxygenation during ephedrine administration. Br J Anaesth (2014); 113: 452-458
6. Sørensen H, Rasmussen P, Siebenmann C, Zaar M, Hvidtfeldt M, Ogoh S, Sato K, Kohl-Bareis M, Secher NH, Lundby C. Extra-cerebral oxygenation influence on near infrared spectroscopy determined frontal lobe oxygenation in healthy volunteers: A comparison between INVOS-4100 and NIRO-200NX. Clin Physiol Funct Imag (2015); 35: 177-184
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8. Sørensen H, Nielsen HB, Secher NH. Near-infrared spectroscopy-assessed cerebral oxygenation during open abdominal aortic aneurysm repair: relation to end-tidal CO2 tension. J Clin Monit Comput (2016); 4:409-15
9. Lund A, Secher NH, Hirasawa A, Ogoh S, Hashimoto T, Schytz HW, Ashina M, Sørensen H. Ultrasound tagged near infrared spectroscopy does not detect hyperventilation induced reduction in cerebral blood flow. Scand J Clin Lab Invest (2016); 76: 82-87

ABSTRACT

Likely, maintained organ and notably cerebral perfusion, secures rapid recovery following anesthesia. To secure cerebral blood flow (CBF) at least mean arterial pressure (MAP) and the arterial carbon dioxide tension (PaCO2) need to be considered. CBF is "autoregulated", i.e. stays more or less stable within a MAP of 50 – 150 mmHg, but the lower limit appears to depend on the central blood volume and/or cardiac output, illustrated by a decrease in CBF at a MAP of 80 mmHg with a compromised central blood volume, while CBF remains constant with a MAP <40 mmHg, if the central blood volume is maintained. During anesthesia, MAP is often around 50 mmHg meaning that it remains unknown whether CBF is maintained, why an evaluation of CBF, e.g. by near-infrared spectroscopy (NIRS) seems desirable. NIRS is sensitive to changes in PaCO2, detects hypoxemia, identifies cerebral autoregulation as well as regional distribution of CBF. As summarized, especially elderly patients and patients undergoing complex surgery and notably heart and liver surgery, seem to benefit from a strategy focusing on maintaining NIRS-determined cerebral oxygenation during anesthesia. Similarly, NIRS may be applied to guide the ventilatory strategy during anesthesia when there are large deviations in metabolism, seen when clamping of the aorta and with reperfusion of the lower body during open aortic surgery, as with hepatectomy and following reperfusion of the donated liver during liver transplantation surgery. Finally it is illustrated how NIRS can be applied to select sympathomimetic agents, used to correct anesthesia-induced hypotension in order to preserve CBF and skin oxygenation.

INTRODUCTION

In contrast to skeletal muscles, the brain has no store of oxygen and depends on tight control of cerebral blood flow (CBF). Elaborated mechanisms maintain CBF to ensure a favorable balance between oxygen supply and demand and also, in contrast to skeletal muscles, cerebral "activation" is associated with surplus flow [1]. Consequently, regional cerebral oxygenation increases upon activation of the brain as detected by the blood-oxygen-level dependent (BOLD) signal by magnetic resonance imaging or by near infrared spectroscopy (NIRS) [2,3]. Such adaptation of CBF takes place through vasomotor, neurogenic, metabolic and chemical mechanisms and likely because of the multiple influences involved, coupling between increase in (regional) CBF and activity is not understood [4]. What is established is that CBF is "autoregulated", i.e. stays more or less stable within wide variations in blood pressure as described for humans by Lassen [5]. Also, the arterial carbon dioxide tension (PaCO2) has a marked influence on CBF with a "reactivity" of about 3% $mmHg^{-1}$ [6].

In humans, assessment of CBF was introduced by Kety & Schmidt (1945) with the determination of the brain's uptake of nitrous oxide over time and for the regional distribution of flow, clearance of ^{133}Xenon was often used [7,8]. Today positron emission tomography [9] and magnetic resonance imaging [10] dominate in evaluating CBF. As a consequence of the large apparatus needed for such evaluation, there is an apparent need for ambulatory evaluation of CBF. Aaslid et al. [11] introduced transcranial Doppler determination of flow velocity in basal cerebral arteries. Duplex ultrasound was introduced, making it possible to measure flow in the internal and vertebral arteries and thereby CBF even during intense exercise (e.g. Sato et al.[12]). Both methods have the advantage that the evaluation is on a beat to beat basis, e.g. allowing for determination of so-called "dynamic" cerebral autoregulation [13]. Another and more readily available option is to record, e.g. frontal lobe oxygenation (ScO2) with NIRS that seems to reflect both cerebral autoregulation and the brain's CO2 reactivity [14], while also allowing evaluation of the regional distribution of flow [15].

This review addresses how NIRS has been applied to monitor cerebral oxygenation during anesthesia and reflects on which patients would benefit from such monitoring. Furthermore, it addresses the influence from the oxygenation of the scalp and possibly the scull, to the NIRS signal. Finally, it is considered whether it is possible to obtain a NIRS signal that is not "contaminated" by scalp and scull oxygenation. Monitoring cerebral oxygenation by NIRS during neurocritical care [16], resuscitation after cardiac arrest [17], interventional radiology [18], orthopedic surgery [19,20] and for infants [21] is not addressed here, but such patients may, as it seems, benefit from such an intervention.

APPLICATION OF NIRS TO ANESTHESIA

In the operating room, the brain has to be considered somewhat a black box as there is little possibility of monitoring CBF. Largely, CBF is taken to be adequate when mean arterial pressure (MAP) is above what is considered the lower limit for cerebral autoregulation, i.e. about 50 mmHg as reviewed by Paulson et al. [22]. Yet, in clinical practice, a MAP around 50 mmHg is frequently seen, e.g. during propofol based anesthesia. Lower values may manifest, especially while inducing anesthesia [23] and during so-called hypotensive anesthesia, established in order to reduce bleeding during some surgical procedures [24]. In other words, it could be suspected that sufficient CBF is left in jeopardy during at least some anesthetic procedures and it has to be accepted that not all patients find themselves mentally alert after anesthesia as supported by psychological tests [25].

Obviously, it is an exception rather than the rule that patients experience mental problems after anesthesia. An explanation might be that the so-called lower limit of cerebral autoregulation seems to vary between patients and or related to events taking place, when the central blood volume and in turn cardiac output (CO) is reduced [26]. Experimental identification of the lower level of cerebral autoregulation typically involves a procedure that reduces the central blood volume [27], e.g. exposing people to lower body negative pressure [28] or head-up tilt and often with a decrease in the estimated CBF including ScO2 at a MAP of 80 mmHg [29]. In contrast, Nissen et al. [30] report no decrease in ScO2 when MAP is reduced to 40 mmHg when the central blood volume is controlled strictly and the cerebral metabolic rate for oxygen is independent of blood pressure when CO is controlled rigorously [31]. On the contrary, patients with apparent lack of cerebral autoregulation, experience a decrease in cerebral oxygenation in response to a low blood pressure [30]. In summary, a blood pressure of 60 mmHg or lower may be acceptable if it represents a response to anesthesia with preserved CO and or central blood volume, but will affect CBF if the pressure represents a reduction in CO, e.g. by hemorrhage or head-up tilt (e.g. for upper abdominal minimal invasive procedures or the beach chair position as for shoulder surgery with eventual catastrophic neurological injury in otherwise healthy patients despite a MAP of 60-80 mmHg [32,33]).

Such considerations and observations seem to explain why a strategy that focuses on maintaining CO during surgery, e.g. by so-called individualized goal-directed fluid therapy enhances outcome [34]. Similarly, it seems an advantage to monitor cerebral oxygenation, e.g. by NIRS to allow for early detection of a scenario where the brain is subjected to otherwise covert ischemia and thereby at least potentially improve outcome. It is considered that a growing elderly population is presented to surgery and that, these patients, due to their limited physiological reserve, inherent with the aging process will need comprehensive monitoring. Thus, several cardiovascular and brain diseases [22] as inhalation anesthesia [35] impair or abolish CBF autoregulation but whether cerebral autoregulation is intact remains unknown without some monitor of CBF.

Cardiac Surgery

Evaluation of NIRS during anesthesia has been carried out mainly during cardiac surgery to avoid postoperative cognitive dysfunction [36], stroke [37], or delirium [38]. Since open heart surgery was introduced (1953), improvement in perfusion technology, surgery and anesthesia has taken place [39], but the devastating neurological complication remains a concern, especially for elderly patients [40], may be related to decrements in ScO2 although results are not consistent [41,42].

For example, monitoring ScO2 is attractive during hypothermic aortic arch surgery with circulatory arrest during which the brain is perfused selectively [43]. A significant interrupted circle of Willis appears in approximately 40% of cardiac patients [44] and therefore monitoring of ScO2 supports the decision to switch from unilateral to bilateral brain perfusion [45]. Also, ScO2 identifies aortic cannula malposition [46] and allows for early detection of air embolism [47,48] or aortic dissection [49]. Furthermore, a low ScO2 predicts neurological events (confusion, seizures, pupil or motor deficit) [50], stroke [51-53] and major organ dysfunction [54-57]. Similarly, a link between reduced cognitive function (assessed by, e.g. minimal mental state examination; MMSE) and a low ScO2 is described [58-62], but again not without exceptions [63-65]. It has to be acknowledged that multiple factors impact neurological function after cardiac surgery, but a low pre- and perioperative ScO2 is independently associated with delirium, time to extubation and even mortality [66-68].

Liver transplantation

As for heart surgery the use of NIRS has been addressed on other patient groups. Patients undergoing liver transplantation (LTx) are of interest due to potential significant reduction of the central blood volume due to bleeding during the dissection phase of the operation, by limited or clamped inferior caval flow in the anhepatic phase and blood pressure may become low during reperfusion of the grafted liver [69]. Even before patients are presented for surgery, liver disease may impair cerebral autoregulation and the blood brain barrier and thereby dispose to ischemic or hyperemic brain injury [70], eventually leading to

death [71]. Besides the neurotoxic effect of ammonia, CBF and intracranial pressure may double, allegedly due to concomitant activation of cyclooxygenase [72,73], but not nitric oxide synthase [74]. Remarkably, such cerebral hyperperfusion is eliminated immediately by hepatectomy [75] or by plasmapheresis [76].

In the anhepatic phase of LTx, inadequate venous return to the heart with clamping of the inferior caval vein reduces CO by as much as 50% and can result in compromised perfusion to vital organs including the brain [77]. To facilitate hemodynamic stability and to optimize organ perfusion, a veno-venous bypass may be established [78]. Alternatively, venous return to the heart is assisted by only partially clamping the inferior caval vein (so-called piggyback technique). However, even with the piggyback technique, ScO2 is likely to decrease by about 15% [79]. Moreover, unintended hyperventilation affects ScO2 as the metabolic rate is about 30% reduced by hepatectomy. Thus, in order to preserve CBF as expressed by ScO2, ventilation needs to be lowered [80] and thereby, hopefully, reduce the risk of cerebral ischemia and an increase in postoperative biomarkers of brain tissue damage, including neuron-specific enolase and S-100β that may increase threefold when cerebral deoxygenation manifests [81].

Conversely, with reperfusion of the grafted liver, metabolism is restored and despite a low blood pressure, the brain may be subjected to hyperperfusion as expressed by ScO2 because CO2 is released from the grafted liver and the lower extremities. Cerebral hyperperfusion could lead to brain edema, but may be attenuated if ventilation is increased to eliminate CO2 [82].

CBF and PaCO2 demonstrate an only moderately s-shaped relationship between 2 and 10 kPa [83] while a PaCO2 above 10 kPa mitigates the CO2-reactivity because of near-maximal cerebral vasodilatation, but PaCO2 seldom exceeds such a value during LTx. During reperfusion of the graft, however, the increase in CBF seems beyond what can be explained by the increase in PaCO2 and, therefore attributable to some yet unknown vasodilating substance(s) [84]. Thus, with reperfusion of the grafted liver, patients demonstrate more than doubled CO2-reactivity [85].

Such considerations are important since ScO2 relates to neurological deficit [86] and during LTx cerebral de- or hyperoxygenation manifest with an incidence of about 35% and 15%, respectively (Table 1; [87]). Thus, ScO2 may guide ventilatory control not only in the anhepatic phase of LTx, but also upon reperfusion of the grafted liver, i.e. by increasing ventilation to attenuate an increase in (end-tidal) CO2 (Table 2;[80].

Table 1. Incidence of cerebral deoxygenation (↓ScO2), hyperoxygenation (↑ScO2) and impaired cerebral autoregulation (%CA) during major abdominal surgery and liver transplantation [87].

	n	↓ScO2	↑ScO2	%CA
Open abdominal surgery	240	24%	0%	-
Laparoscopy surgery (supine)	328	0%	0%	-
Laparoscopy surgery (reverse-Trendelenburg's position)	142	31%	0%	-
Liver transplantation	191	36%	14%	25%

Open abdominal aneurysm repair

The implication of monitoring NIRS during vascular surgery has been reviewed [88]. Somewhat similar to patients undergoing LTx, patients undergoing open abdominal aortic aneurysm repair are also exposed to significant changes in the circulation. There is a likely reduction in CO during cross-clamping of the aorta below the renal vessels and end-tidal CO2 decreases if ventilation is not lowered to compensate for attenuated need of CO2 elimination.

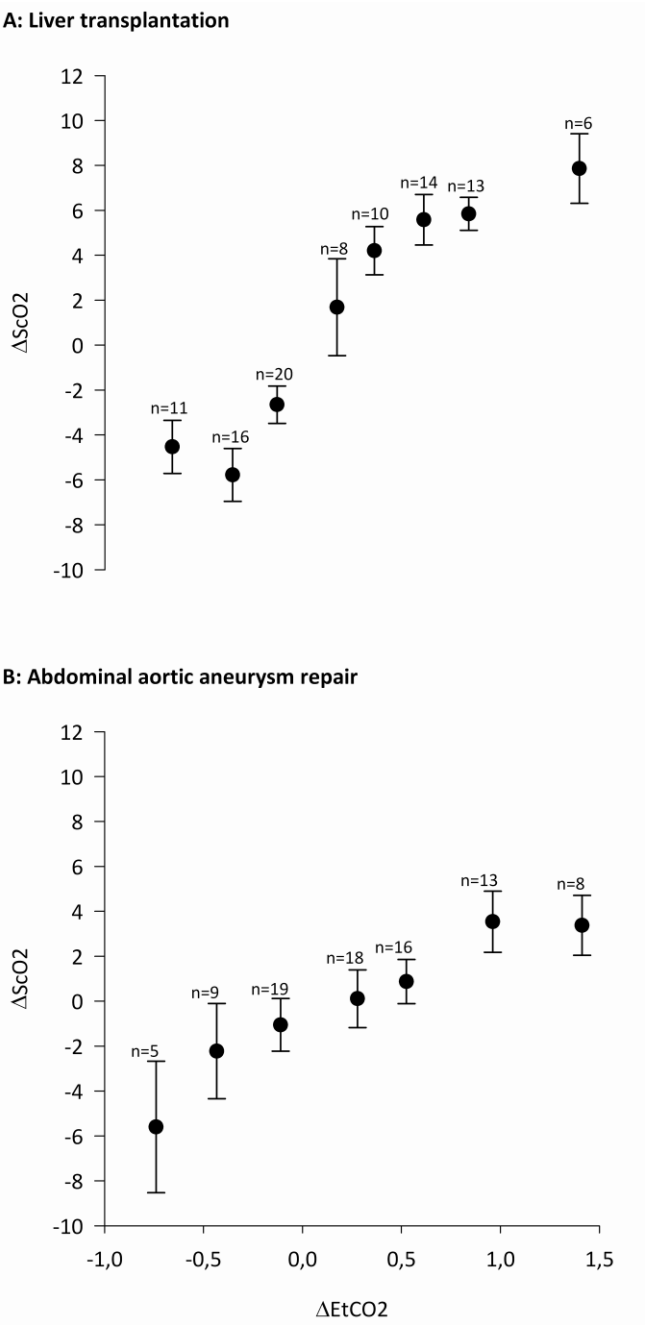

Figure 1. Near-infrared spectroscopy determined frontal lobe oxygenation (ScO2) and end-tidal CO2 tension (EtCO2) (% changes from baseline; ± SEM). (Modified from [80,85])

Accordingly, ScO2 may become affected [89]. Conversely, with reperfusion of the lower body, vasodilatory substances including CO2 are released into the circulation and provoke cerebral hyperperfusion as illustrated by a ~ 50% increase in CBF despite an often marked decrease in MAP [89,90]. Yet, by adjusting ventilation according to end-tidal CO2 during aortic aneurysm repair, ScO2 can be kept within acceptable limits, reflecting, that in contrast to LTx patients ([80]; Table 2), patients undergoing aortic surgery appear to demonstrate a normal CO2 reactivity, both when expressed by transcranial Doppler [89] and by ScO2 (Fig. 1) [85].

Table 2. Changes in end-tidal CO2 (EtCO2), frontal lobe oxygenation (ScO2) and ventilation (VE) during liver transplantation and abdominal aortic aneurysm repair. Patients demonstrating a normal ScO2 (nScO2) are shown [80,85].

Liver transplantation	EtCO2	ScO2	VE	nScO2
Clamping	-8%	-8%	-5%	78%
Reperfusion	+18%	+12%	+10%	71%
Abdominal aortic aneurysm				
Clamping	+3%	-3%	-13%	93%
Reperfusion	+11%	+3%	+31%	98%

Major abdominal surgery

Patients undergoing major abdominal surgery may also benefit from monitoring ScO2 since the incidence of cerebral deoxygenation as determined by ScO2 is reported as high as about 50%. This is typically seen in elderly patients and is related to the hospital stay, maybe as a consequence of an affected MMSE score [91-93]. As indicated, ScO2 is reduced, especially in patients exposed to manipulation of body position, but with impeded venous drainage from the brain during surgery in Trendelenburg's position, there is reported no cerebral deoxygenation [87]. To monitor ScO2, during laparoscopic surgery in either supine or Trendelenburg's positions, is currently considered only when surgery is expected to last for more than 7 hours [94,95], since prolonged steep Trendelenburg's position gradually impairs cerebral autoregulation [96].

Conversely, the orthostatic stress provoked by reverse Trendelenburg's positioning and increased intra-abdominal pressure due to CO2 insufflation, bear the potential to compromise CO and provoke cerebral deoxygenation as manifested in about one third of the patients (Table 1). The influence of orthostatic stress on ScO2 is illustrated in the beach chair position (90°) in which ScO2 is reported to decrease in 80% of patients. In support of central hypovolemia, symptoms, as postoperative nausea and vomiting, are common manifestations [97]. In a more or less upright position, sympathetic activity increases to maintain CO [98] and yet CBF and ScO2 decrease somewhat [99]. In anesthetized patients, however, the autonomic nervous system is attenuated and CBF may become pressure passive [100] and therefore, to preserve patient well-being, e.g. NIRS guided intervention seems in need [101]. Thus, patients undergoing surgery in a beach chair, during regional anesthesia, are reported to demonstrate no cerebral deoxygenation as opposed to the fact, that deoxygenation manifests in about 60% of patients who are anesthetized [102].

It remains a problem that NIRS-derived thresholds for intervention are not defined. ScO2 range from 60% to 90%, while grave hypoxia (arterial saturation <55%) is associated with a ScO2 of ~40% [103]. There is, however, no consensus on how much ScO2 should decrease before intervention is relevant. Further, it is not established whether a significant increase in ScO2 should lead to intervention but this is of interest since even brief episodes of hyperperfusion affects Starling forces within cerebral capillaries and results in endothelial damage. Thus, a >15% (relative) increase in ScO2 seems to predict cerebral hyperperfusion [104]. In regard to what decrease in ScO2 should lead to intervention, a decrease by 13% (absolute) has been suggested during clamping of the internal carotid artery for endarterectomy, with a high sensitivity (100%) and specificity (93%) for cerebral ischemia along with a relation to cerebral function [105]. Such a threshold is supported by a decrease in transcranial Doppler determined cerebral blood flow velocity, slowing of the electroencephalogram and changes in somatosensory evoked potentials [106-108]. Furthermore, healthy humans develop presyncopal symptoms with a 10%-15% reduction in ScO2 (for review see [99]). A low ScO2 before and during surgery also seems to indicate poor cognitive function and delirium [66,109,110]. For cardiac patients, an algorithm is presented, to guide intervention using both relative (20%) and absolute (<50%) changes [55,111]. The algorithm takes the following into account: MAP, CO, arterial oxygen tension, hemoglobin (Hb), body temperature, and depth of anesthesia. Yet, it remains unknown for how long ScO2 should be below or above defined thresholds to induce cerebral damage. However, estimates have been given and an extensive cerebral deoxygenation more than doubles the risk of poor cognitive outcome and a prolonged hospital stay [60].

In summary, for especially elderly patients, patients who go through complex surgery or who are exposed to various types of head-up tilts, it seems an advantage to secure that ScO2 is within about 15% of the resting value to maintain patient wellbeing [87,112]. Yet, it remains a concern whether NIRS in fact monitors CBF or whether it is to be considered an advanced monitor of skin and eventual scalp oxygenation, and the NIRS technique is therefore addressed briefly.

NEAR INFRARED SPECTROSCOPY

The light absorption spectra for hemoglobin (Hb) was identified by the German physiologist Immanuel EF Hoppe-Seyler [113] and the Irish physicist George G Strokes [114]. Both observed oxygenated blood to be more reddish than deoxygenated blood. This was confirmed by the German physiologist Karl von Vierordt, who described the transmission of red light through a finger [115]. These observations formed the background for development of an oximeter by the German physician Karl Matthes and the pharmacologist Franz Gross [116]. The oximeter was introduced to anesthesia at the Mayo Clinic [117]. Dentists, surgeons and anesthetists alike had until then observed skin color and chest movement to asses oxygen supply to the patient, but it seems that cyanosis was an expected rather than a feared manifestation (for review see [118]) accepting that skin color does not necessarily reflect arterial oxygen saturation [119]. Yet, it was realized that if a patient turned blue, recovery would be prolonged and with introduction of neuromuscular blockade by Griffith & Johnson [120], to relax the musculature during tracheal intubation and surgery, it became critical to ensure adequate ventilation. This concern became apparent when Beecher & Todd [121] argued that anesthesia, at that time, killed 1/6 of the 600.000 anesthetized patients in the US, or as many patients as there were victims of poliomyelitis. This implied the need for better handling of ventilation and likely also for monitoring whether the chosen ventilation strategy was adequate.

The need of monitoring whether ventilation was adequate became apparent during the polio epidemic in Denmark (1952-1953) and the Radiometer Company developed an apparatus to determine pH in blood and gradually also arterial tension for oxygen and carbon dioxide. By 1973 this became what is now called the ABL apparatus (automatic blood laboratory) [122]. Yet, such evaluation of ventilation requires blood sampling, later continuous non-invasive monitoring of arterial oxygen saturation became available when the Japanese engineer Aoyagi developed pulse oximetry [123]. Although it has not been "proven" that pulse oximetry improves patient outcome [124], few patients probably go through anesthesia without continuous registration of a pulse oximetry estimate of arterial oxygen saturation. Interestingly, a more than tenfold reduction in mortality attributed to

anesthesia coincided with the combined use of pulse oximetry and monitoring the end-tidal carbon dioxide by capnography [125].

Accordingly, complications to anesthesia may no longer manifest in mortality, but as mentioned, it has to be accepted that not all patients feel well after surgery. Besides pain, postoperative nausea and vomiting and surgical complications, mental capacity may be affected [25,126]. Monitoring whether cerebral oxygenation is maintained became a possibility when Jöbsis [127] introduced NIRS to detect cerebral oxygenation in cats. NIRS uses the same principle as pulse oximetry, but NIRS does not take the pulsatile flow into account and therefore monitors a balance between arterial, capillary, and venous blood.

Technology

According to the Beer-Lambert law, light absorbance depends on the concentration of a light attenuating object in a material sample [128-130]. For NIRS, the emitted light is captured by one or several detectors placed some distance from where light is emitted, meaning that NIRS measures the intensity of the returning photons. Photons are lost due to absorption by chromophores and scattering and ideally, i.e. in an experimental model, the absorption of light can solve the Beer-Lambert equation. *In vivo* light has to pass the scalp and the scull before it reaches the brain and none of these structures are homogenous. It remains unknown what length the light has travelled before it returns to be sampled and, therefore, the requirement of the Beer-Lambert equation to provide absolute values for Hb, cannot be fulfilled.

To compensate for that limitation, a modified Beer-Lambert equation is applied that assumes scattering and optical path length to be constant and, therefore, light attenuation to be by absorption that allows for trend monitoring of Hb [131]. More advanced NIRS technology is introduced, e.g. spatially resolved NIRS (SR-NIRS), phase modulation and time resolved spectroscopy quantify tissue optical properties, i.e. scattering, absorption and optical path length from which an estimate of chromophore concentration is derived or an oxygenation index (HbO2/Hb or HbO2/(Hb+ HbO2)) is calculated [132-134].

Of these technologies SR-NIRS is the most frequently applied, in both clinical practice and in human research. By use of multiple detectors, light intensity is determined as a function of the emitter-detector distance and in combination with an often undisclosed algorithm it is, at least in principle, possible to retrieve absolute values [135]. Yet, the algorithms applied to estimate tissue oxygenation varies between different apparatus and is known only for the NIRO apparatus [135]. In fact, different algorithms yield divergent chromophore concentrations with application of the same optical data [136], which complicates determination of the "true" ScO2 [137,138].

As technology develops, an attempt is to provide direct assessment of CBF by so-called ultrasound-tagged NIRS, where ultrasound is used to modulate light via the acousto-optic effect and thereby estimate flow as validated against single photon emission computer tomography determined CBF as approved for perioperative monitoring of CBF [139-143]. In support for this report of CBF, ultrasound-tagged NIRS reflects both cerebral autoregulation and CO2 reactivity identical to a laser Doppler signal from brain parenchyma of a pig [144]. Yet, when applied to the forehead of humans, the ability of ultrasound-tagged CBF to show CO2-reactivity is apparently lost [145], likely because the signal becomes dominated by skin blood flow or due to interference with the transcranial Doppler signal.

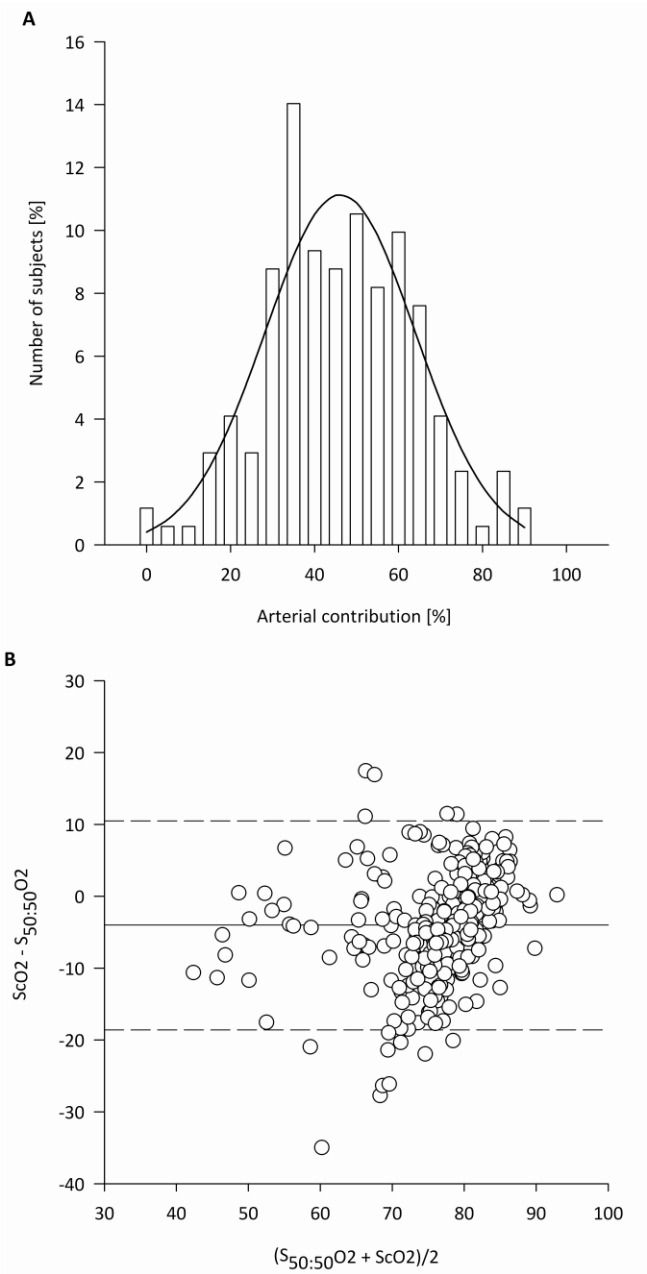

Figure 2. A: Number of subjects (%) for whom the difference between Invos-determined frontal lobe oxygenation (ScO2) and the arterial fraction of the calculated reference saturation is zero. Solid line represents the distribution. B: Bland-Altman plot of ScO2 and a calibration ratio of 50% arterial and jugular bulb oxygenation [149] with permission from Frontiers in Physiology.

Calibration

Determination of ScO2 by NIRS, most often assumes a fixed ratio of 70:30 or 75:25 for the venous and arterial blood volume, based on anatomical evidence, not taking the capillary blood volume (approximately 5%) into account. In support, no negligible mismatch between ScO2 values and the calibration ratio is observed with the use of five different NIRS devices in healthy subjects exposed to isocapnic hypoxemia [146], but using a fixed ratio between venous and arterial blood volume for calibration of the NIRS signal is not robust. Hypercapnia and isocapnic hypoxemia induce cerebral vasodilation and alters the cerebral blood volume, mainly by an increase in the arterial fraction [147]. Thus, it is likely that the illuminated area of the brain then encompasses

more arterial blood and explains the aggravated mismatch between ScO2 and the calibration ratio during hypoxia [146].

Alternatively, ScO2 is compared to a balance ratio of 50% jugular bulb and 50% arterial oxygen saturation as the estimate of cerebral capillary oxygenation as this ratio seems more accurate [148-150] (Fig. 2). However, the arterial to venous balance within the brain may differ between individuals and explain part of the inter-individual variation in absolute ScO2 readings [146]. Heterogeneity of blood vessels in the illuminated area of the brain seems to affect light absorption because photons are "lost" in major blood vessel, e.g. the sagittal sinuses [151]. Other factors affecting light absorption and thereby the ScO2 readings include variation in skull thickness and amount of cerebrospinal fluid [152], skin pigmentation [146] and degradation products of heme because of its competitive absorption of light [153]. An alternative approach is to base the evaluation of ScO2 on more than one optode and thereby obtain a more stable value [154].

Optode configuration

To determine the balance between two chromophores (HbO2/Hb) two wavelengths are required. Many devices employ more wavelengths to improve accuracy and to include an account for cytochrome C oxidase [136] (Table 3), e.g. to demonstrate a small decrease when pre-syncopal symptoms develop during head-up tilt [155].

An optode often includes one or two emitters and two to four detectors and the penetration depth of light is taken to be approximately 1/3 to 1/2 of the emitter-detector distance [156]. Thus, the longer the emitter-detector distance is, the deeper tissue can be interrogated, but then at the expense of the signal to noise ratio [157]. With an emitter-detector distance between 15 and 30 mm, "cerebral" O2Hb is influenced by skin oxygenation as the evaluation is equally reduced by scalp ischemia [158], but it has to be noted that the evaluation did not include procedures that would be expected to affect CBF.

In an attempt to minimize influence of skin and scalp oxygenation to the NIRS signal, some devices, e.g. Invos, use a subtraction-based algorithm with the assumption that light returning to the proximal detector (e.g. 30 mm from the emitter) has passed mainly through superficial tissues, while light captured by the distal detector (e.g. 40 mm) is more representative for "deep" tissue, i.e. for the brain. Alternatively, the distance from the emitter to the distal detector may be 43 and 50 mm (Niro and Foresight, respectively) (Table 3) and it is argued that a distance of at least 48 mm is preferred [157]. Whether such an optode distance allows for a "selective" report of cerebral oxygenation is questioned. When Davie and Grocott [159] applied a cuff around the head to eliminate skin blood flow, all apparatus (Invos, Foresight, Equanox), even with a emitter-detector distance of 50 mm (Foresight), demonstrated a decrease in ScO2, suggesting that scalp oxygenation cannot be ignored. This is also evident during heating of the skin [160,161] or carotid cross-clamping [162].

It appears that the present NIRS technology requires an individual correction factor derived by creating scalp and scull ischemia, e.g. by applying pressure to the temporal artery for unbiased estimate of cerebral O2Hb during interventions [158].

CO2-reactivity and hypoxia

When accepting that there is a significant influence of skin and scalp oxygenation to the NIRS signal, it remains fundamental whether NIRS responds to changes in the arterial CO2 tension

Table 3. Characteristics for five NIRS devices

	WL (nm)	E;D (n)	E-D (mm)	CO2 (% kPa^{-1})	Measurements
Invos-5100 (SR)	730, 808	1;2	30, 40	1.7	ScO2
Foresight (SR)	690, 780, 808, 850	1;2	15, 50	1.6	ScO2
Niro-200 (SR)	735, 810, 850	1;2	37, 43	2.1	ScO2, THI, O2Hb, Hb
Equanox 7600 (SR)	Unknown	2;2	20, 40	Unknown	ScO2
CerOx (UT)	Unknown	1;2	12	0.4	ScO2, CFI

CO2: CO2 reactivity. CFI: cerebral flow index. D: detector. E: emitter. Hb: hemoglobin. ScO2: cerebral oxygenation index. SR: spatially resolved. THI: total hemoglobin index. UT: ultrasound tagged. WL: wavelength

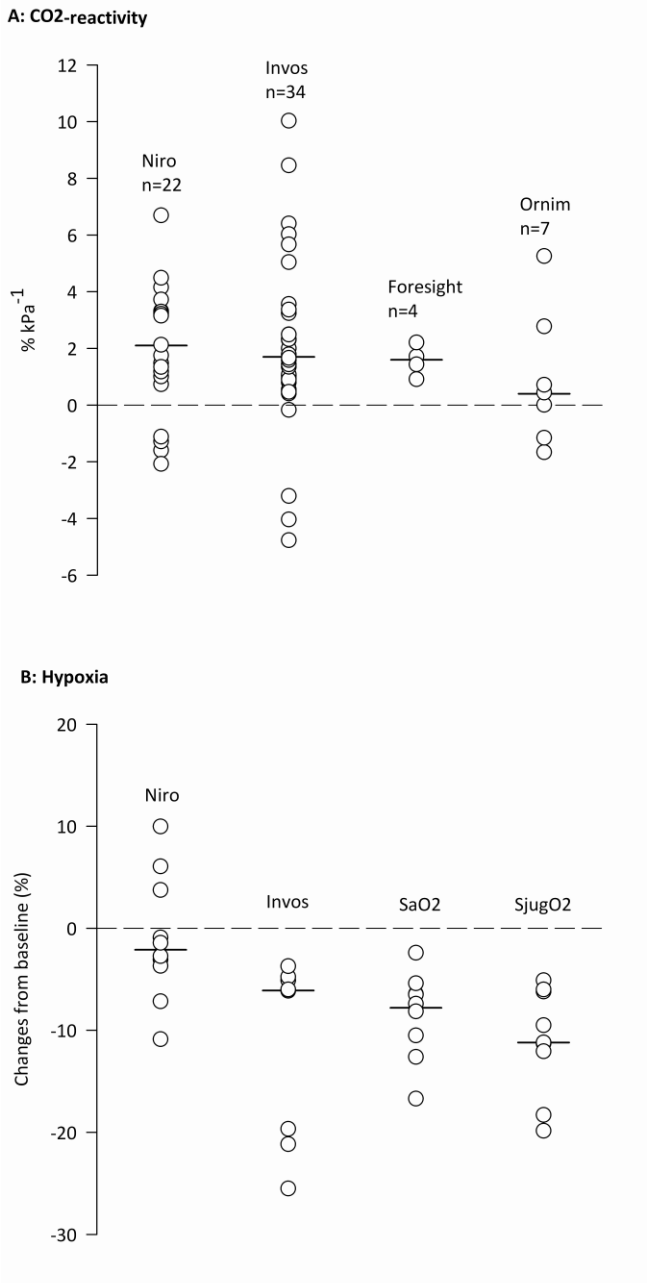

Figure 3. Data from healthy subjects (solid line indicates median) A: CO2-reactvity for each device during hyperventilation [145, 149, 202]. B: Frontal lobe oxygenation determined by Invos and Niro during hypoxia (FiO2=0.12). SaO2: arterial oxygenation. SjugO2: internal jugular bulb oxygenation [169].

because extra-cerebral blood flow is only vaguely affected by CO2 [163]. When PaCO2 is manipulated by inhaling, e.g. 5% CO2 vs. hyperventilation induced reduction in PaCO2, NIRS does demonstrate an adequate response independent of extra cranial blood flow [150,164,165]. The exception is the previously mentioned ultrasound-tagged NIRS [145] (Table 3). In healthy humans the CO2-reactivity is about 2 % kPa^{-1} (Fig. 3) similar to that in patients undergoing open abdominal aneurysm repair (1.8% kPa^{-1}), but in patients undergoing LTx the CO2-reactivity is more than doubled (7.3% kPa^{-1}) (Fig. 1). The inter-device difference for the determination of CO2-reactivity may both reflect disparate optode configuration and algorithm applied [136].

In regard to the ability of NIRS to detect hypoxia, systemic hypoxemia below 7 kPa PaO2 induces cerebral vasodilation that gradually doubles CBF until CBF is counterbalanced by hypocapnia secondary to hypoxia, NIRS detects changes in cerebral O2Hb and cytocrome C oxidase that correlates to jugular bulb oxygenation [103,166] Also, evaluation of NIRS by isocapnic hypoxia reveals a relation to jugular bulb oxygenation but, unfortunately, does not allow for separate evaluation of influence from the brain, respectively, the scalp [146,167,168]. Furthermore, compared to the Invos apparatus, Niro-200NX seems to demonstrate a limited sensitivity to hypoxia, while CBF CO2-reactivity is presented (Fig. 3).

Problems with the recording of cerebral oxygenation do not only relate to the apparatus used, but also depend on the optode applied. We have been confronted with two (Niro) optodes of which one did report a decrease in cerebral oxygenation in response to hyperventilation, but was unaffected by hypoxia while the second optode demonstrated the opposite [169].

Exercise

Besides being able to report responses to hypoxia and demonstrate the brain's CO2 reactivity, NIRS should be able to report the increase in cerebral oxygenation associated with activation of the brain, as established in "neurological orientated" studies, e.g. by exposure to cognitive, visual tests or exercise [3,15]. The CBF response to whole-body exercise is, however, complex with an increase during light to moderate work intensities and a decrease in flow at high workloads, as the exponential increase in ventilation lowers PaCO2 [170]. In support of NIRS' ability to report a value relevant to CBF, ScO2 increases at work intensities up to 60%–80% of the subject's capacity after which it plateaus or decreases towards or below resting values, attributed to hypocapnia secondary to hyperventilation [171]. Thus, with increasing exercise intensity, ScO2 follows changes in CBF as determined by jugular bulb oxygenation [172]. In regard to NIRS' ability to report CBF rather than scalp and skull blood flow, it is important that the decrease in ScO2 at high workloads takes place despite an increase in skin blood flow due to heat exchange [169].

When evaluating which decreases in ScO2 that are clinically relevant, i.e. lead to intervention, it is of interest that the decrease in ScO2 at high workloads, is so marked that a low ScO2 has been suggested to limit work capacity, so-called central fatigue [150,173]. Although this hypothesis is attractive, the argument is not easy. By clamping CO2 and thereby maintaining CBF and ScO2, performance is not enhanced in neither normoxia nor mild to severe hypoxia [174-177]. On the other hand, it has to be accepted that CO2 also influences muscle metabolism and that an eventual positive effect on the brain of supplementing CO2 and thereby CBF, could be offset by "peripheral" fatigue by acidosis [178] and sympathetic activation [179].

EFFECT OF SYMPATHOMIMETIC AGENTS ON SCO2

Awake subjects

Besides applying a cuff around the head [159] or pressure over the temporal artery [158], skin blood flow may be influenced by administration of sympathomimetic agents used to correct anesthesia-induced hypotension. α-adrenergic activation increases total peripheral resistance and thereby MAP with phenylephrine (e.g. by 35%) and norepinephrine (e.g. by 30%), while ephedrine increases CO, leaving peripheral resistance unaffected. A small dose of epinephrine has little effect on MAP but CO increases [180].

Norepinephrine

In a pioneering evaluation of sympathomimetic agents' influence on CBF (by ^{133}Xenon clearance), norepinephrine had no effect on CBF [181]. This observation has be challenged by recording transcranial Doppler determined middle cerebral artery mean flow velocity (MCA Vmean), ScO2 or jugular bulb oxygenation for continuous evaluation of CBF. For example, MCA Vmean is reported to decrease with increasing MAP following administration of norepinephrine together with a decrease in ScO2 and jugular bulb oxygenation and therefore points to a reduced CBF [182].

In animals, stimulation of the superior cervical ganglion [183], activation of the central sympathetic pathway from locus coeruleus [184] and administration of norepinephrine reduces CBF (for review; [185]) and is therefore attributed to the stimulation of α-adrenergic receptors [186]. Yet, the role of sympathetic activity for regulation of CBF in humans remains debated [187-190]. When arterial administration of norepinephrine does not influence CBF [181] it has been attributed to norepinephrines' poor ability passing the blood brain barrier [191,192].

Norepinephrine may also exert an indirect cerebral vasoconstriction through the so-called Bayliss effect (1902) (vasoconstriction in response to an increase in blood pressure). Likewise, sympathetic activity increases even with transient hypertension as measured in the superior cervical ganglion in lambs [194]. In chronic hypertension, the lower as well as the upper limit of the autoregulation, shifts to the right probably due to hypertrophy of the arteries, but as demonstrated both in humans and rats, the limits of the cerebral autoregulation is normalized with administration of renin-angiotensin system inhibitors, allegedly due to endothelium dependent relaxation [195-198].

As addressed by Olesen [181], is should be considered, that norepinephrine increases ventilation and thereby reduces MCA Vmean, ScO2 and jugular bulb oxygenation in response to a lower PaCO2. In support, when CO2 is clamped during administration of norepinephrine, jugular bulb oxygenation remains stable although MCA Vmean increases, suggesting constriction of the artery [160]. In conclusion, unchanged jugular bulb oxygenation points to a stable CBF, but ScO2 together with skin blood flow, remains low following norepinephrine with CO2-clamping. Consequently, the reduction in ScO2 in response to administration of norepinephrine is likely explained by scalp and maybe also scull oxygenation, rather than by cerebral vasoconstriction, acknowledging that the diameter of MCA has not been evaluated with the administration of norepinephrine.

Phenylephrine

In contrast to norepinephrine, phenylephrine does not affect ventilation. Lucas et al. [199] used the increase in MCA Vmean with blood pressure in response to administration of phenylephrine, to calculate a slope for the otherwise often reported horizontal part of the autoregulation curve, i.e. from approximately 50 to 150 mmHg, as confirmed in figure 4.

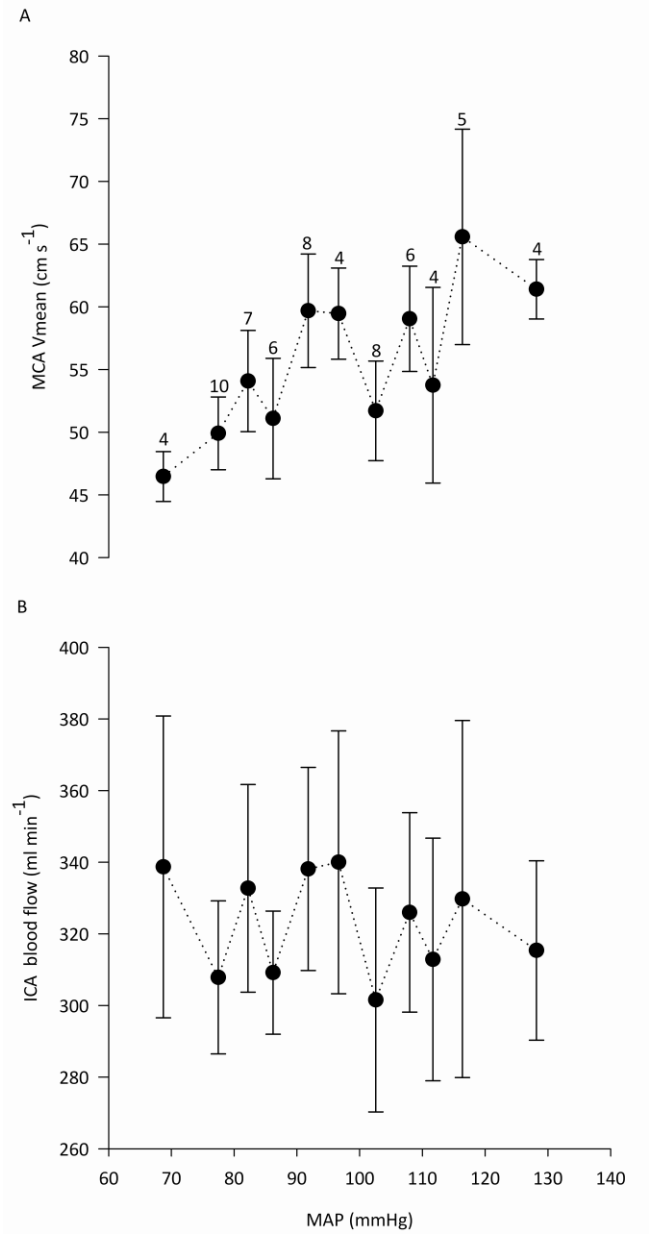

Figure 4. Changes in middle cerebral artery mean flow velocity (MCA Vmean) and internal carotid artery (ICA) blood flow during phenylephrine infusion. Mean ± SEM with number of data points indicated. Modified from [145,200-202].

A small slope on this part of the autoregulatory curve is attractive since no regulatory mechanism has an infinite gain and it has to be accepted, that when the graph describing the autoregulation is reported as horizontal, it can be considered as much a statistical as a biological phenomenon. For example, one way to calculate the lower level of cerebral autoregulation is to identify a line between an index of CBF (e.g. ScO2 [203] or jugular bulb oxygenation [197]) and MAP at low blood pressures. Then finding the point at which that line crosses a horizontal line established by taking changes in an index of CBF at high blood pressures into consideration, i.e. the lower level of cerebral autoregulation is identified by iteration to a horizontal line.

That said, it has to be accepted that MCA Vmean expresses flow velocity and not flow and MCA Vmean may be influenced by vasoconstriction of the artery in response to the administration of phenylephrine, leading to an increase in MCA Vmean for any given CBF. When recording flow in the internal carotid arteries, CBF is stable between 70 and 130 mmHg (Fig. 4B), but with focus on the response before and after phenylephrine, a marginal increase in CBF appears (Fig. 5), suggesting that the "plateau" is not quite horizontal. Conversely, as blood flow in the external carotid artery is reduced by 30% with administration of phenylephrine, blood flow to the forehead is likely to explain the decrease in ScO2 [201,202].

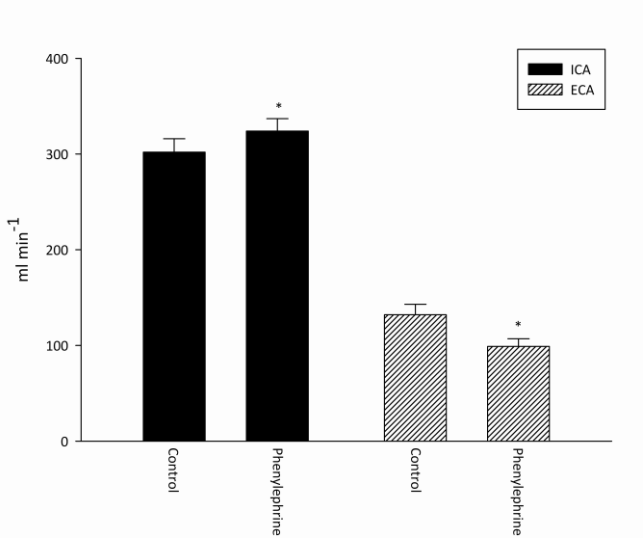

Figure 5. Blood flow in the external (ICA) and internal carotid (ICA) artery in rest and following phenylephrine administration. Mean ± SEM, n=29. Modified from [200,201,202,145].

Ephedrine

Ephedrine acts mainly as a β1-adrenergic agonist but has an indirect α-adrenergic effect by release of norepinephrine and thereby increases ventilation with a slight decrease in MCA Vmean. Yet internal carotid artery flow and ScO2 are maintained [202]. Ephedrine increases CO by about 50% and thereby possibly explains the preservation of skin oxygenation, skin blood flow and ScO2 [202].

Epinephrine

Small doses of epinephrine increase cerebral O2Hb along with brain glucose and oxygen uptake [180,204]. A β2-receptor stimulation seems involved because combined β1/β2–blockade by propranolol in rats [205] and humans [206,207] eliminates these responses, while they are preserved during selective β1-blockade by metoprolol [208]. Thus, two modalities for measuring CBF (NIRS; jugular bulb oxygenation) point to cerebral vasodilatation following administration of epinephrine likely by β-adrenergic activation as supported by findings in piglets [209], but an evaluation of the effect of epinephrine on CBF and cerebral oxygenation by magnetic resonance imaging is lacking [2].

Anesthetized patients

Norepinephrine

In anesthetized patients the ScO2 response to norepinephrine is more ambiguous than for awake subjects (Fig. 6). Diabetes exercises an influence impairing the dynamic cerebral autoregulation [210], yet it remains unknown why diabetic patients demonstrate a more pronounced reduction in ScO2 than non-diabetic patients when undergoing cardiac surgery and when exposed to norepinephrine [211]. Impaired relaxation of the cerebral vessels, allegedly due to endothelial dysfunction and or hyper-responsiveness to norepinephrine, may contribute [212-214], as PaCO2, MAP and CO are stable [211].

One reason why the ScO2 response to norepinephrine varies more in anesthetized patients than in awake subject may be that its effect on CO appears to be preload dependent [215], i.e. norepinephrine decreases CO if the patient is "normovolemic" [216] but increases CO when the central blood volume is reduced due to norepinephrines' ability to "mobilize" blood to the central circulation [217]. Thus, ScO2 decreases when CO is reduced in response to administration of norepinephrine, but other factors influence ScO2 too. Even with maintained CO, norepinephrine decreases ScO2 [211]. In septic shock [218], norepinephrine keeps ScO2 stable, perhaps because skin vasculature is dilated, making skin blood flow insensitive to α-adrenergic activation [219]. Governed by α-receptor stimulation, norepinephrine may reduce blood flow in the cerebral capillaries to an extent that cannot be detected by ScO2, MCA Vmean or jugular bulb oxygenation, yet findings in anesthetized pigs do not supports that argument [209].

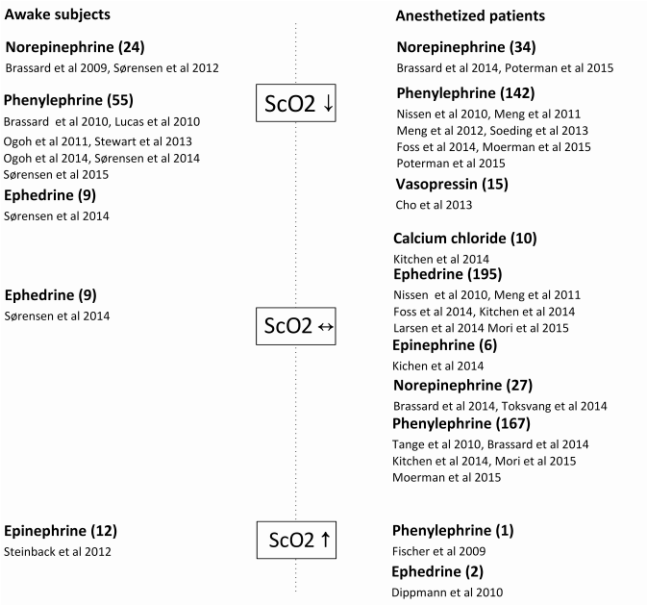

Figure 6: Responses in NIRS determined cerebral oxygenation (ScO2) upon administration of calcium chloride, epinephrine, ephedrine, norepinephrine, phenylephrine, or vasopressin to healthy subjects and anesthetized patients. (n), number of subjects investigated.

Phenylephrine

During anesthesia phenylephrine reduces ScO2 coinciding with a reduction in CO [23,220], yet, not all patients demonstrate a reduction in ScO2 upon administration of phenylephrine (Fig. 6) [221-228]. A low CO appears to influence CBF [26] and phenylephrine, like norepinephrine has a different impact on CO depending on its influence on preload to the heart, i.e. phenylephrine increases stroke volume [229] and left ventricular end-diastolic volume [230] when the heart is working on the ascending part, compared to the plateau on the Frank-Starling curve, as phenylephrine may recruit blood from, e.g. the splanchnic circulation [231]. In this context, phenylephrine has a more pronounced effect compared to norepinephrine [217]. Thus, with the reduction of the central blood volume in an upright position phenylephrine might increase CO [232], but despite an increase in cardiac filling, CO decreases due to bradycardia. This is illustrated by administration of atropine parallel to phenylephrine [229]. In an upright position, phenylephrine increases MCA Vmean, in contrast to a 10% reduction in the control group (saline infusion). The reduction in ScO2 is pronounced with phenylephrine (23%) compared to saline (14%) despite a MAP of 90 mmHg and a stable cardiac index [230].

As mentioned, NIRS identifies the limits of cerebral autoregulation, by correlation analysis to arterial pressure [203]. During cardiopulmonary bypass, individual assessment of the autoregulatory curve, reveals that about 30% of patients has a paradoxical reduced ScO2 following administration of phenylephrine, while 35% of the patients shows a pressure passive ScO2 [233]. Since CO is controlled during pulmonary bypass, these findings represent either individual adaptations to phenylephrine or that CO2-tension and administration of sevoflurane were higher in the pressure passive group [233]. Thus, insight in cerebral autoregulation and oxygenation is needed to ensure a stable CBF.

Although direct comparison of responses to phenylephrine between awake and anesthetized patients is difficult, the findings by Meng et al. [234] illustrate, that despite influence from the skin, NIRS reflects changes in CBF by altered CO2 during administration of phenylephrine. It could be argued, that CO plays a minor role for keeping CBF stable, as ScO2 is reduced to the same extent by phenylephrine, despite a decrease or controlled CO while MAP was well above the limit of the cerebral autoregulation [220,233]. However, a link between ScO2 and CO cannot be excluded since we bear in mind that the brain is probably the last organ to suffer from a reduced CO at the expense the peripheral circulation [235].

Ephedrine

Ephedrine does not affect ScO2, maybe because of little external carotid artery vasoconstriction. Moreover, CO increases upon administration of ephedrine and thereby, as least to some extent, affects CBF and in turn ScO2 [23,220]. Maybe ephedrine shows no impact on the cerebral autoregulation and thereby ScO2, in contrast to phenylephrine [233], but it seems speculative and, so far, no clinical study has taken scalp or skin blood flow into account.

PERSPECTIVE

NIRS offers an estimate of CBF that is sensitive to changes in arterial CO2 tension and hypoxemia and NIRS identifies the limits of the cerebral autoregulation. Thus, NIRS offers a possibility to evaluate whether CBF is maintained when blood pressure is low, as induced by anesthesia, or in response to reperfusion of organs. More work is needed to identify which patients would benefit by monitoring NIRS on the brain, but a focus on maintained ScO2 seems beneficial during complex surgery, in older patients and when surgery is performed in an upright position.

Yet, it must be accepted that NIRS does not solely reflect cerebral oxygenation but is influenced by oxygenation of the skin and scalp, even with use of so-called spatial resolution. An influence of skin-scalp blood flow on ScO2 is an obvious problem when the

focus is evaluation of CBF, but when monitoring patients in general, it may not be a problem. In fact, Bjørn Ibsen [236] used toe temperature (and thereby presumably skin blood flow) to target therapy of shocked patients. Yet, when selectively monitoring the cerebral oxygenation, it is suggested that there is made a separate evaluation of skin oxygenation and thereby build an algorithm that more drastically uses "spatial resolution" than provided with the current apparatus.

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