GHENT UNIVERSITY

FACULTY OF MEDICINE AND HEALTH SCIENCES

EXPLORING THE POTENTIAL OF NEAR-INFRARED SPECTROSCOPY FOR SPINAL CORD PERFUSION MONITORING

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Onderzoek naar het potentieel van nabij-infrarood spectroscopie als monitor voor de ruggenmergdoorbloeding

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List of Contents

List of Abbreviations

ASA: anterior spinal artery

CN: collateral network

CO: cardiac output

CO_2: carbon dioxide

L: lumbar vertebrae

MAP: mean arterial pressure

MEPs: motor evoked potentials

NIRS: Near-infrared spectroscopy

O_2: oxygen

P_aCO_2: partial pressure of carbon dioxide in the arterial blood

rS_cO_2: regional cerebral tissue oxygen saturation

$rS_{ps}O_2$: regional paraspinal tissue oxygen saturation

$rS_{pv}O_2$: regional paravertebral tissue oxygen saturation

rS_tO_2: regional tissue oxygen saturation

SCI: spinal cord ischaemia

SSEPs: somatosensory evoked potentials

T: thoracic vertebrae

T(A)AA: thoraco(abdominal) aortic aneurysms

TcMEPs: transcranial motor evoked potentials

TEVAR: thoracic endovascular aortic repair

1

Background and Objectives

The world is full of obvious things,

Which nobody by any chance ever observes.

Sherlock Holmes

1

Background and Objectives

Paraplegia or paraparesis after perioperative ischaemia of the spinal cord is one of the most feared complications following aortic repair. Haemodynamic management of these patients is thus especially challenging because of the need to also maintain adequate oxygen delivery to the spinal cord.

In daily practice, near-infrared spectroscopy (NIRS) serves as a tool for monitoring the oxygen saturation of underlying tissues. While it is routinely applied to monitor regional cerebral tissue oxygen saturation (rS_cO_2) during carotid and cardiac surgery, it is also increasingly implemented in the perioperative anaesthesia management of aortic surgery, where it is expected to help detecting spinal cord ischaemia (SCI).

Previous research has shown that haemodynamic alterations affect rS_cO_2 with impaired tissue oxygenation in case of hypotension.[1] Furthermore, it has also been observed that vasoconstrictive drugs differently affect rS_cO_2 despite having a similar effect on systemic blood pressure.[2,3]

Current guidelines advocate for pharmacologically maintaining adequate systemic blood pressure in order to prevent spinal ischaemic complications during aortic repair surgery. However, the effects of such interventions on spinal tissue perfusion and oxygenation remain ill-defined.

The aim of the research project presented in the current thesis was exactly to get a better insight in the effects of vasoconstrictive medication on spinal and paraspinal tissue oxygenation. In order to have a comparative standard, we examined whether an endogenous blood pressure increase, elicited by a laryngoscopy-induced sympathetic-mediated stress reaction affects regional paravertebral tissue oxygen saturation ($rS_{pv}O_2$) (Chapter 3). Then the effect of a bolus (Chapter 4) and a continuous (Chapter 5) administration of two differently acting vasoactive agents on $rS_{pv}O_2$ were examined.

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2

General Introduction

2

General Introduction

The incidence of thoraco(abdominal) aortic aneurysms (T(A)AA) is rare, affecting approximately 5.9 per 100,000 individuals.[1] Surgical repair is indicated when the aneurysm has exceeded a diameter of 5.5 cm for both ascending and descending aneurysms,[2] when the aneurysmal diameter is rapidly increasing, or when the patient develops symptoms such as pain. This may be accomplished by open surgery or by an endovascular approach.

Geishbusch et al. analysed data of 2607 patients with either ruptured (406) and non-ruptured (2201) T(A)AA over a period of 10 years.[3] In hospital mortality depended on its presentation: 46.1% for ruptured and 15.9% for unruptured T(A)AA. Open surgical repair was performed in 54.5% of the cases, but during this time period the choice of surgical treatment modality changed in favour of the endovascular approach (either fenestrated or branched), which was related with a lower in hospital mortality (RR= 0.35).

One of the most devastating complications following repair is the occurrence of spinal cord ischaemia (SCI), resulting in paraparesis (temporarily or permanent) or paraplegia. This complication is estimated to occur in 2 to 10% of the patients in both endovascular and open T(A)AA repair.[4]

In addition to the personal disability and medical implications, such as incontinence, infections, thrombosis, etc..,[5] the occurrence of SCI also results in substantial personal, medical and healthcare-related expenses.[6] Moreover, SCI itself has been identified as an independent risk factor for increased mortality following T(A)AA -repair in both open and endovascular repair.

Scali et al. have retrospectively analyzed prospective collected data of the Vascular Quality Initiative Registration in patients with thoracic endovascular aortic repair (TEVAR).[7] Analysis was conducted on a cohort of 11473 patients, revealing an overall incidence of SCI of 3.7%. They also observed a significant lower in-hospital mortality and mortality at 1 year following surgery in patients without

SCI (5 vs. 19% and 13 vs. 35%, respectively). Moreover, 1 year mortality was significantly higher in patients with permanent symptoms of SCI at the time of discharge, compared to patients in whom symptoms were transient (46% vs. 20%). Other complications, such as cardiopulmonary events, kidney replacement therapy, infections, and embolisms were more present in patients who developed SCI.

To gain deeper insights into the pathogenesis of SCI in both TEVAR and open T(A)AA -repair, this chapter will provide a brief overview of the spinal cord blood supply and its physiology.

2.1 Anatomy of the spinal cord blood supply

The blood supply to the spinal cord is provided by three arteries: two posterior spinal arteries and one anterior spinal artery (ASA). (Fig. 1)

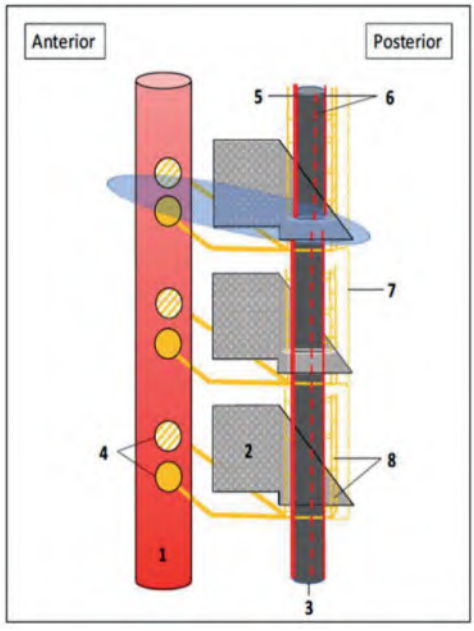

Figure 1: Schematic presentation of the longitudinal view of the spinal cord blood supply.

Blue area: collateral vascular network. 1: aorta; 2: vertebral body; 3: spinal cord; 4: segmental arteries; 5: anterior spinal artery; 6: posterior spinal arteries; 7: longitudinal connections; 8: laterolateral connections
(From: Vanpeteghem et al. Assessment of spinal cord ischemia with Near-infrared spectroscopy: Myth or reality? J Cardiothorac Vasc Anesth 2020; 34:791-6. With permission)

The posterior arteries are the primary blood supply to the posterior third of the spinal cord, responsible for supplying oxygen and nutrients to the sensory pathways. The ASA, however, is a longitudinal blood vessel that plays a pivotal role in providing blood supply to the anterior and lateral grey columns of the spinal cord, which consist of motor neurons. The ASA is nourished by multiple segmental arteries. These arteries arise from the vertebral arteries, ascending and deep cervical arteries, intercostal arteries, lumbar and iliolumbar arteries, and lateral sacral arteries.[8] The intercostal and lumbar arteries divide into a spinal and vertebral branch. The spinal branch divides into an anterior and posterior radicular artery and the former debouches into the ASA. (Fig. 2)

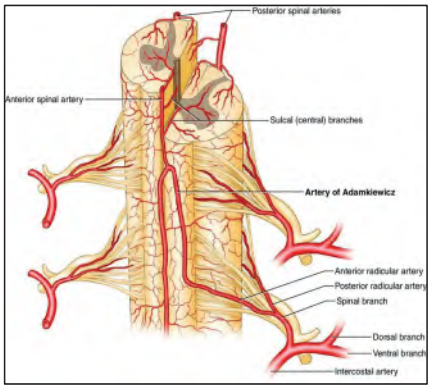

Figure 2: Spinal arterial anatomy showing the artery of Adamkiewicz.

(From: Amato, A.C.M., Stolf, N.A.G. (2019). Preoperative assessment of the spinal cord vasculature. In: Tshomba, Y., Baccellieri, D., Chiesa, R. (eds) Visceral vessels and aortic repair. With permission.)

Generally, one of the anterior radicular arteries is remarkably larger: the arteria radicularis magna or the artery of Adamkiewicz. The ASA is the major artery in the spinal canal, but its size is not constant. It appears that the diameter just cranial to the entry of a spinal artery is smaller. Due to this mechanical barrier, blood flow is forced to be directed downwards. Deprivation of blood flow to the ASA results in paraplegia or paraparesis due to spinal cord ischaemia. The classical concept that the spinal cord blood supply is highly dependent on the input of only one artery, the artery of Adamkiewicz, has been challenged by recent insights.

2.1.1. Classical theory: Artery of Adamkiewicz

The blood supply of the spinal cord was comprehensively investigated in 1881 by a Polish pathologist, named Albert Wojciech Adamkiewicz.[9] (Fig. 3)

Figure 3*:* Albert Wojciech Adamkiewicz (1850-1921)

He identified the artery of Adamkiewicz as a dominant branch of a segmental artery with a highly variable origin (from mid-thoracic to lumbar level). A meta-analysis including 5437 patients, showed that the artery of Adamkiewicz was found in only 84.6% of the population, with a slightly higher prevalence in males.[10] Interestingly, a subgroup analysis revealed geographical variations in prevalence of the artery of Adamkiewicz, with the highest prevalence in the Netherlands (pooled prevalence estimate of 99.4%). The lowest prevalence was found in the USA (pooled prevalence of 79.5%).

The authors also found that 87.4% of the patients had a single artery of Adamkiewicz, which was predominantly (76.6%) located on the left side. The remaining population presented with two (11.3%), three (0.8%) or even four (0.5%) arteries. Furthermore, they noted that the artery of Adamkiewicz originates in 89% of individuals between T_8 and L_1, with the highest frequency observed at the T_9 level, followed by T_{10} and T_{11}.

This artery contributes significantly to the blood supply of the anterior spinal artery.[11] The artery of Adamkiewicz , with a diameter ranging from 0.8 to 1.3 mm, typically follows a hairpin-like course as it enters the ASA from its cranial side, providing blood supply in a downward direction.[10] When the artery of Adamkiewicz arises from high thoracic levels (between T_5 and T_8 in 15% of the population), it is often accompanied by an additional artery known as the Desproges-Gotteron artery. This artery is typically found between T_8 and L_4, with its main origin occurring between L_2 and L_5.[12]

Until a decade ago, the artery of Adamkiewicz was regarded as the sole significant artery involved in the blood supply of the spinal cord. Compromising the integrity of the artery of Adamkiewicz jeopardizes the anterolateral two-thirds of the spinal cord. This was formerly believed to irreversibly result in spinal cord injury. Therefore, some authors strongly recommend identifying the presence and

localization of the artery of Adamkiewicz in advance of surgery by means of imaging techniques in order to prevent ischaemic injury to the spinal cord related to transection or damage of the artery of Adamkiewicz during open or endovascular T(A)AA repair.[10]

2.1.2. Collateral network concept: a dynamic entity

Several clinical findings and experimental studies have raised doubts about the notion that the spinal cord blood supply relies solely on one artery, the artery of Adamkiewicz. Instead, recent insights have illustrated that the spinal cord blood supply is facilitated by an extensive network of interconnected arteries known as the collateral network (CN) .[11,13] The CN comprises segmental arteries, an extensive epidural arterial network, intra- and extrathecal blood vessels, and a dense tangle of small blood vessels embedded in the paraspinal musculature.(Fig. 4)

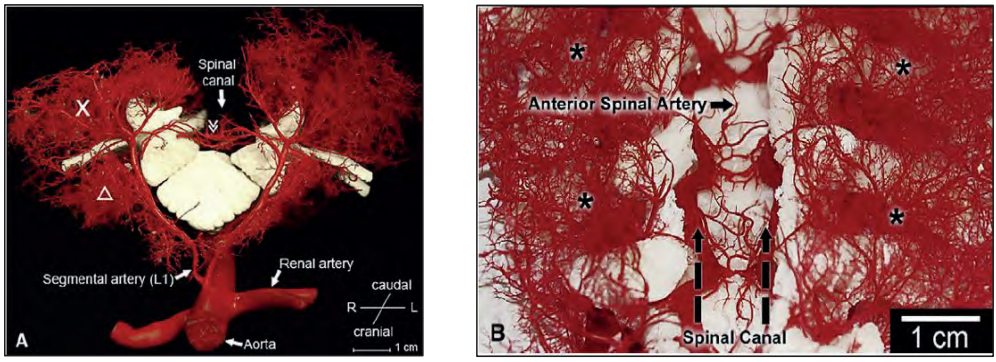

Figure 4: Anatomy of the collateral network: sagittal (A) and dorsal (B) view.

(From: Etz CD, Kari FA, Mueller CS, et al. The collateral network concept: A reassessment of the anatomy of spinal cord perfusion. J Thorac Cardiovasc Surg. 2011; 141:1020-8. With permission.)

All these blood vessels are interconnected both laterally and longitudinally. They form anastomoses with both the subclavian (cranial) and hypogastric (caudal) arteries, enabling them to supply the ASA. Consequently, they serve as a buffer, facilitating compensatory flow during hypotensive periods or during aortic surgery when spinal cord blood supply through large segmental arteries is impeded.

2.2. Physiology of the spinal cord blood supply

2.2.1. Autoregulation of the spinal cord blood flow

Autoregulation of organ perfusion is a protective mechanism against both hypoperfusion with hypoxia and hyperperfusion. When blood pressure drops, arteries will dilate to maintain adequate blood flow and oxygen supply. Conversely, in situations of high blood pressure, vasoconstriction will protect the organ from excessive perfusion. This means that, even with variations in perfusion pressure within specific boundaries, tissue blood flow will be maintained constant.

Concerning the central nervous system, until now, autoregulation of cerebral blood flow has been the most extensively studied. (Fig. 5)

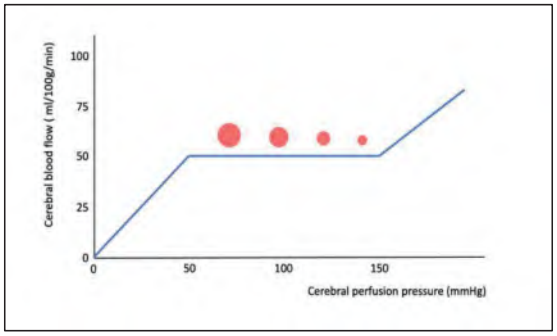

Figure 5: Cerebral autoregulation curve.

Between cerebral perfusion pressures of 50 and 150 mmHg, cerebral blood flow remains constant through vasodilation or vasoconstriction of the cerebral blood vessels.

The blood pressure limits of cerebral autoregulation can alter depending on variable conditions, such as arterial hypertension, head injury, brain tumors, cerebral vasospasms, oxygenation status, and partial pressure of carbon dioxide in arterial blood (P_aCO_2).[14]

Two theories are widely accepted to explain autoregulation in the brain:

Firstly, the myogenic theory, indicating changes of vascular muscle tone when changes in blood pressure occur.[15] In situations of high blood pressure vasoconstriction occurs, whereas during hypotension cerebral blood vessels will dilate.

Secondly, the metabolic theory, indicating that variations in periarterial concentrations of metabolites, such as carbon dioxide and lactate, are responsible for restoration of blood flow.[16]

Interestingly, it has been observed that acute or chronic alterations in cardiac output (CO) affect cerebral blood flow, independently of changes in MAP or P_aCO_2.[17,18] This is an important

consideration, because, although haemodynamically well-related, both CO and MAP may affect cerebral perfusion in a distinct way.

Some clinical conditions, such as carotid artery disease,[19] brain trauma,[20] sepsis[21] and ischemia-reperfusion injury[22] are related with an impaired cerebral autoregulation. In these circumstances, the cerebral protection mechanism is disrupted, rendering patients susceptible to hypo-or hyperperfusion of the brain.

In contrast to cerebral autoregulation, there is limited knowledge regarding the autoregulation of the spinal cord. This is mostly due to constraints in study designs that hinder the measurement of spinal cord blood flow.

However, in rats, where regional blood flow was measured with radioactive microspheres, a similar autoregulation pattern has been observed in the spinal cord as in the brain when the mean arterial pressure (MAP) ranged between 60 and 120 mmHg.[14] (Fig. 6A)

Furthermore, varying regional blood flow patterns have been observed within the spinal cord itself, with a preference for the lumbar region and less perfusion to the thoracic region, compared to the lumbar and cervical areas. (Fig. 6B)

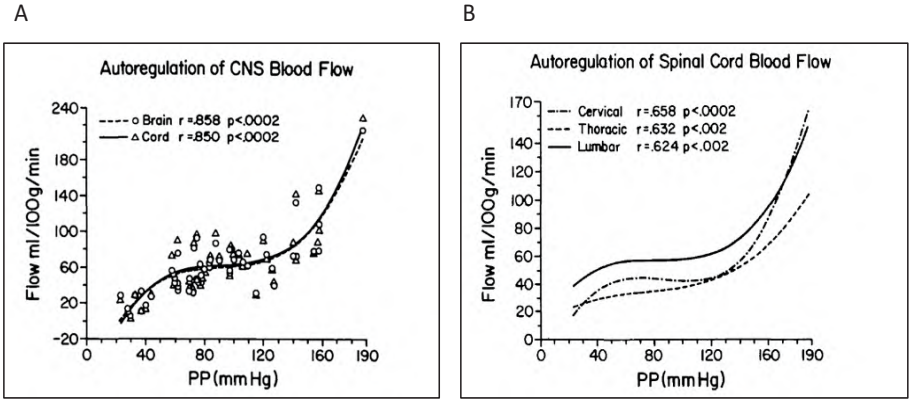

Figure 6: Autoregulation of the Central Nervous System blood flow.

A. *Autoregulation of the spinal cord mimics the brain, within an autoregulatory range of 60 to 120 mmHg perfusion pressure.*
B. *Autoregulatory curves of the cervical, thoracic and lumbar spinal cord.*

CNS: Central Nervous System; PP: perfusion pressure
(From: Hickey R, Albin MS, Bunegin L, et al. Autoregulation of spinal cord blood flow: Is the cor a microcosm of the brain? Stroke 1986; 17:1183-9. With permission.)

In contrast, no autoregulation of the spinal cord was observed by Kise and colleagues.[23] In their interventional study conducted in dogs, segmental arteries were sacrificed and distal aortic perfusion was performed. Spinal cord blood flow was measured by means of laser Doppler flowmetry, attached to the dura mater at L_5. After exclusion of the segmental arteries, a positive correlation between MAP and spinal cord blood flow was noted, both with and without distal aortic perfusion. This reflects the importance of the CN as a buffering system to maintain blood supply to the spinal cord, achieved either through distal aortic perfusion or by increasing MAP via vasoactive medication administration.

It also has to be acknowledged that SCI is not a common complication during low flow conditions such as circulatory failure or cardiac arrest. Nevertheless, conditions of low flow may substantially contribute to SCI when superposed on a disrupted vascular anatomy.

2.2.2. Adaptation of the vascular anatomy to spinal cord ischaemia

It is important to mention that most anatomical studies on spinal cord vasculature are performed in pigs. Nevertheless, a strong resemblance between the anatomy of the spinal cord vasculature of humans and pigs has been described.[11,24] Despite its similarities, it remains unclear whether the structural adaptations of the CN in patients with an aneurysm resemble the anatomical changes observed in the CN of healthy pigs.

In an experimental study with pigs, Strauch et al. could demonstrate the impact of excluding collateral blood flow to the CN by clamping the subclavian and median sacral arteries.[25] The median sacral arteries in pigs are analogous to the hypogastric arteries in humans. If there is a hindrance to the input of the subclavian arteries or the median sacral artery to the CN , fewer segmental arteries can be sacrificed to maintain an adequate blood flow to the spinal cord, as was objectified with MEP monitoring.[26,27]

Under steady-state conditions, the pressure within the CN ranges from 60 to 80% of patient's baseline MAP.[28] After discontinuation of the segmental artery blood flow to the CN, the pressure in the CN is decreasing and reaches its lowest value within 5 hours. (Fig. 7)

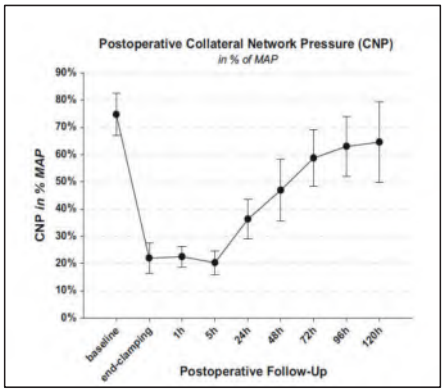

Figure 7: Collateral Network pressure, measured in distal end of 1st lumbar segmental artery in 10 pigs after ligation of all segmental vessels.

CNP: Collateral Network pressure; MAP: Mean arterial pressure.
(From: Etz CD, Zoli S, Bischoff MS, et al. Measuring the collateral network pressure to minimizeparaplegia risk in thoracoabdominal aneurysm resection. J Thorac Cardiovasc Surg 2010; 140: S125-30; discussion S142-S146. With permission.)

This was also seen in humans, where the pressure within the CN remained low until pulsatile flow was restored following the construction of a bypass.[29] In a clinical setting, the time when the pressure in the CN is at its lowest typically coincides with rewarming and awakening from anaesthesia. The pressure in the CN usually returns to normal within 72 hours to 5 days, which means that during this period, the spinal cord remains vulnerable and susceptible to ischaemia.

Injecting juvenile pigs with a barium/latex mixture offers a clear demonstration of the reorganization of the CN vasculature after ligating all the segmental arteries.[30] Due to a progressive increase in the number of blood vessels, resulting in a larger capacity of the CN, it seems reasonable that the CN pressure reaches its normal pressures within 5 days. Also, an enlargement of the ASA was observed within 24 hours following an extensive sacrifice of segmental arteries. Beside an increase in capacity, a reorientation of proliferating blood vessels could be demonstrated following an extensive sacrifice of segmental arteries.[11] The initially random arrangement of blood vessels in the CN transforms into a well-structured matrix, aligned parallel to the spinal cord, after blocking the inflow through the segmental arteries. The physiologic meaning behind this craniocaudal reorientation of the CN is still unclear. Because of its vertical orientation, this configuration could potentially enhance a more effective blood flow from the cranial and caudal feeding vessels to the CN section situated in the mid-thoracic region, which is the most vulnerable region to developing ischaemia after the segmental arteries are sacrified.[13]

The mechanisms that trigger the progressive and structural changes in the anatomy of the CN vasculature are still not fully understood. On the one hand, the enlargement of the ASA may result from ischaemia-related vasodilation. On the other hand, the proliferation of the CN is caused by both angiogenesis (the formation of new blood vessels) and arteriogenesis (the transformation of small-sized arteries into larger-sized arteries).[13] These adaptations facilitate flow from the subclavian and hypogastric arteries – i.e. flow in both cranial and caudal direction- to the region of the spinal cord that has been deprived of blood supply through the segmental arteries.

In specific situations, blood flow to the spinal cord can be redirected. This phenomenon, known as the "steal" phenomenon, can occur during open surgery when large segmental arteries are bleeding, causing a reversal of blood flow away from the CN. Additionally, rewarming of the patient at the end of surgery and increased muscle activity due to shivering can also negatively affect the spinal cord perfusion.[11]

2.3. Pathophysiology of spinal cord ischaemia in aortic surgery

2.3.1. Spinal cord ischaemia following open T(A)AA repair

Aortic cross clamping during open T(A)AA repair not only results in proximal hypertension, an increase in central venous pressure and intracranial hypertension, but also leads to hypotension distal to the aortic clamp.[31] Distal hypotension directly impacts the blood supply to the spinal cord, leading to SCI. Additionally, permanent occlusion by ligating or oversewing many SAs may also substantially contribute to the development of SCI. Moreover, SCI can be further exacerbated by the inflammatory response that occurs during reperfusion following aortic unclamping.[32]

To reduce the risk of SCI, it appears evident that the segmental arteries should be reimplanted. However, this subject is still a matter of debate. Some authors recommend reimplanting all excluded segmental arteries, while others propose reimplanting only the critical segmental arteries or even none of them.[33] In all cases of planned extensive segmental artery sacrifice, it is of outmost importance to maintain the integrity of the subclavian and hypogastric arteries. Additionally, the surgeon has to pay attention to the potential occurrence of back-bleeding through the open segmental arteries. Furthermore, it is essential to uphold perfusion pressure during surgery, both in the proximal aorta and distal to the resected segment. Also, postoperatively perfusion pressure should be maintained by treating hypotension and sustaining low central venous pressures and cerebrospinal fluid pressures.

In open T(A)AA repair, SCI primarily occurs immediately, either due to aortic cross clamping, ligation of SA, or following reperfusion. Haemodynamic instability must be prevented during the first 72 to 120 hours postoperatively because the CN may not have fully reorganized by that point in time.[28]

2.3.2. Spinal cord ischaemia following TEVAR

In the past, it was commonly thought that TEVAR procedures were less likely to result in SCI due to the absence of both aortic cross clamping, leading to distal hypotension, and reperfusion injury. Surprisingly, this is not the case, as the incidence of paraplegia and paraparesis remains unaffected by the surgical approach.

However, in TEVAR procedures, the segmental arteries are permanently excluded, leading to long-lasting effects compared to the relatively brief periods of aortic cross-clamping during open repair.[4]

Following TEVAR, SCI can manifest shortly after the emergence from anaesthesia, but it typically occurs with a delay, seen in over 60% of cases. In a retrospective study of a prospectively collected database, data of 424 patients following TEVAR over a period of 8 years were analysed.[34] Twelve patients (2.8%) suffered from SCI. The onset of SCI occurred at a median time of 10.6 hours following surgery, ranging from 0 to 299 hours. Only 2 patients suffered from SCI immediately following awakening of anaesthesia.

The exact reason behind this characteristic delay is not completely understood. It is possible that this phenomenon is related to a temporary preservation of blood flow through segmental arteries which may still receive blood from the aneurysm sac.[35]

Additionally, it is believed that the CN undergoes remodeling after stent deployment in TEVAR.

According to Colman et al., the non-occluded segmental arteries, which remain perfused and are located both distal and proximal to the covering stent, are thought to reverse the direction of blood flow within the ASA. This reversal helps in preserving blood flow to the segment of the spinal cord that is at risk of ischaemia.[36]

Nevertheless, in both open and endovascular aortic surgery, SCI may still occur when the compensation mechanisms are deficient or fail because of either thrombus formation in the CN or embolisms. During endovascular repair, SCI may also develop following manipulation of plaques due to endovascular tools or cessation of the endoleak.[4] In these situations, blood supply to the watershed area of the grey zone in the spinal cord may be insufficient, resulting in SCI.

2.4. Receptors of the collateral network vasculature

This thesis aims to investigate the impact of various vasoactive agents on $rS_{pv}O_2$.

In literature, numerous studies have already examined the effects of vasoactive agents with diverse mechanisms of action on rS_cO_2. A more comprehensive discussion of these findings will be provided in Chapter 4. One theory explaining the differences in the effects on rS_cO_2 focuses on the working mechanism of vasoactive agents on adrenergic receptors located on blood vessels. However, it is

important to note that the distribution of adrenergic receptors in the collateral network has not been described yet. Therefore, basing our study's conclusions solely on this theory would be purely speculative.

2.5. Monitoring the spinal cord function

Due to the profound disabling nature of paraplegia and the detrimental impact of SCI on patient survival,[37] it is of utmost importance to vigilantly monitor spinal cord function. Such monitoring enables the adaptation of haemodynamic management to optimize oxygen delivery to the spinal cord. This may involve raising blood pressure, increasing distal aortic perfusion, or administering red blood cells transfusions (target haemoglobin >10g/dl).[38] Additionally, it provides guidance to the surgeon for adjusting their surgical strategies, including the detection and potential reimplantation of critical segmental arteries.

Intraoperative monitoring of spinal cord function can be accomplished through somatosensory evoked potentials (SSEPs), motor evoked potentials (MEPs), or, more recently, NIRS.

2.5.1. Evoked potentials

Evoked potentials refer to the electrophysiological responses of neurons that occur following motor or sensory stimulation. This stimulation initiates a signal transmission, which is recorded as evoked potential along the stimulated pathway.[39]

The feasibility of using evoked potentials to monitor impending spinal cord ischaemia depends on their ability to detect the *penumbra*.[40] The penumbra represents a pathophysiological condition induced by acute ischaemia, where neurons become dysfunctional. Hence, following restoration of blood flow, the neuronal function is able to recover. In other words, within the penumbra, the ischaemic insult may still be reversible.

The neuronal sensitivity to ischaemia depends on two factors.

Firstly, it is influenced by the speed of metabolism, with higher metabolism making neurons more sensitive. This renders grey matter more susceptible to ischaemia than white matter, both in the brain and the spinal cord. Secondly, it is determined by the integrity of watershed areas, where there is overlapping blood supply from the most distal ends of large arteries, such as the ASA and the iliolumbar arteries in the case of the spinal cord.

2.5.1.1. Somatosensory evoked potentials (SSEPs)

In case of SSEP-monitoring, a peripheral nerve (median nerve, posterior tibial nerve, or common peroneal nerve) is stimulated, using surface or needle electrodes. This signal is transmitted through the dorsal root of the spinal cord to the sensory cortex.[39]

SSEPs are able to identify ischaemia at the white matter tracts located in the dorsal columns and at the peripheral nerves.[41]

Some conditions may interfere with the SSEP signal, such as ischaemia, surgery and anaesthetics. Therefore, it is mandatory to adapt anaesthetic management during SSEP monitoring by avoiding high doses of anaesthetics.[39] On the other hand, opiates and neuromuscular blocking agents do not interfere with SSEP signals. SSEP monitoring is associated with a high rate of false positives (40-67%) and a 13% rate of false negatives, along with slow response times (7-30 minutes).[41] Technical errors in recording and delivering the stimulus, accounting for false positive results, are not uncommon. False negative results – no transmission of a warning signal in case of ischaemia –are even more concerning when SSEP monitoring is used. This underlines the need for specialized personnel, being able to interpret the signal correctly.

2.5.1.2. Transcranial motor evoked potentials (TcMEPs)

Transcranial motor evoked potentials (TcMEPs) are muscle action potentials, induced by high voltage transcranial brain stimulation. This signal propagates through the corticospinal tract to the anterior side of the spinal cord. MEPs can be recorded either at the level of the spinal cord, or in muscles with adequate corticospinal innervation, such as the tibialis anterior or abductor pollicis brevis.[42]

In contrast to SSEP monitoring, MEPs are able to reliably detect ischaemia at the anterolateral white matter tract, the spinal grey matter and the peripheral nerves.[41] This finding is particularly interesting because dog studies have shown that the spinal cord ischaemia predominantly involves the gray matter following aortic cross clamping.[43] Thereby, MEPs are preferred to monitor the functional motor integrity of the spinal cord.[44] Similar to the use of SSEPs, intraoperative monitoring with MEPs requires adjustments to the anaesthetic management.[45] The use of intravenous anaesthetics and opioids do not interfere with MEP signals and can be administered safely. On the other hand, one should be cautious with the administration of inhalation anaesthetics (dose adaptation < 0.5 MAC is required) and neuromuscular blocking agents (train of four-guided).

For both SSEP and MEP, ischaemia is suspected when any of the following criteria are met: a 50% reduction in response amplitude, a 10% increase in latency time, the requirement to increase stimulation voltage, or a complete loss of signal.[42] Regarding the evoked potential monitoring techniques, MEPs have lower rates of false positives (3.2 to 45%)[46] and generally show a stronger

clinical correlation compared to SSEPs.[41] Unlike SSEPs, MEPs provide a rapid (< 5 minutes) response to ischaemia. Animal studies have demonstrated that the duration of amplitude absence correlates with clinical outcomes, with signal recovery within 10 minutes associated with normal motor function, while an absence of signal for more than one hour was related to spinal cord infarction resulting in paraplegia.[47] Moreover, MEPs are related with high sensitivity and acceptable specificity.[48] Consequently, MEPs continue to be regarded as the gold standard for intraoperative monitoring of spinal cord ischaemia. Unfortunately, MEPs come with certain inherent disadvantages, including the need for specialized personnel and the fact that it is painful in awake patients. Additionally, due to the use of high currents (up to 0.9 amperes) and high voltages (up to 900 volts), caution must be exercised to prevent tissue injury, patient movement, and tongue biting. Moreover, care should be taken to avoid electric shock hazards for the personnel involved.[49]

2.5.2. Near-infrared spectroscopy

2.5.2.1. Principles of Near-infrared spectroscopy

NIRS has been widely implemented as a continuous and noninvasive monitor of regional tissue saturation (rS_tO_2). Its operation is based on the spectroscopy of reflected near-infrared light.[50] Therefore, optodes equipped with both light emitters and detectors are strategically placed over the region of interest. The amount of transmitted light through a substance adheres to the Beer-Lambert law, which states that light absorption by the penetrated substance depends on the length of the pathway through the substance, the tissue concentration, and the absorption coefficient of the substance at a specific wavelength. Once the emitted light enters the substance, it is partly absorbed by chromophores (light-absorbing substances) and partly scattered. Scattering results in redirection or reflection of the light beam.[51] (Fig. 8A) Notably, the amount of scattering is assumed to remain constant during the measurement period. Therefore, changes in light attenuation are considered to be solely due to changes in light absorption.[52]

Haemoglobin stands out as the sole chromophore exhibiting rapid concentration fluctuations over a short duration.[51] Depending on the haemoglobin oxygenation status, changes in the near-infrared light absorption spectrum occur. (Fig 8B) The oxygenation status is quantified as the ratio of oxygenated haemoglobin to total haemoglobin, expressed as a percentage, and is represented as rS_tO_2.

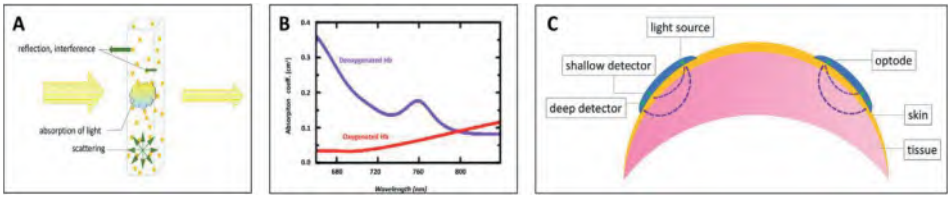

Figure 8: The principles of Near-infrared spectroscopy.

(A) Modified representation of the Lambert-Beer law. (B) Absorption spectra of oxygenated and deoxygenated haemoglobin.
(C) Mean photon pathway.
Hb, haemoglobin.
(From: Vanpeteghem et al. Assessment of spinal cord ischemia with Near-infrared spectroscopy: Myth or reality? J Cardiothorac Vasc Anesth 2020; 34:791-6. With permission.)

The light beam follows a banana-shaped pathway through the tissue. Based on the principles of spatial resolution, the depth of photon penetration is proportional to the distance between the light source and light detector. (Fig. 8C) Within the near-infrared range (700-1000 nm), light photons can penetrate up to 2.5 to 3 centimeters into the underlying tissue, including bone.[53] Nevertheless, it is crucial to acknowledge certain pitfalls associated with NIRS technology. NIRS measures differences in absorption. It does not quantify oxygen molecules but calculates the ratio of oxy- versus de-oxyhaemoglobin at predefined wavelengths. If the optodes are inappropriately taped on the skin, external light sources might influence the measurements.

To date, NIRS is validated as a cerebral neuromonitor, measuring oxygen saturation of the vasculature in the underlying cerebral tissue. Based on correlations between NIRS and position emission tomography, the arterial and venous contribution to the cerebral blood flow is estimated to be 30% and 70%, respectively.[54]

It has to be acknowledged that multiple factors may influence changes in rS_tO_2, such as changes in blood pressure, cardiac output, oxygenation status, haemoglobin content, mechanical impairment of organ flow (e.g. embolism) and metabolism.[55] Furthermore, it has been observed that use of vasoactive agents either by their direct effect on the vascular wall or by their effect on haemodynamics may affect rS_tO_2 differently.[56–58]

Given the limited depth of light penetration, rS_tO_2 reflects regional tissue saturation which is strictly limited to the region underneath the sensor. As a consequence, a large part of the area of interest remains unmonitored. (Fig. 9)

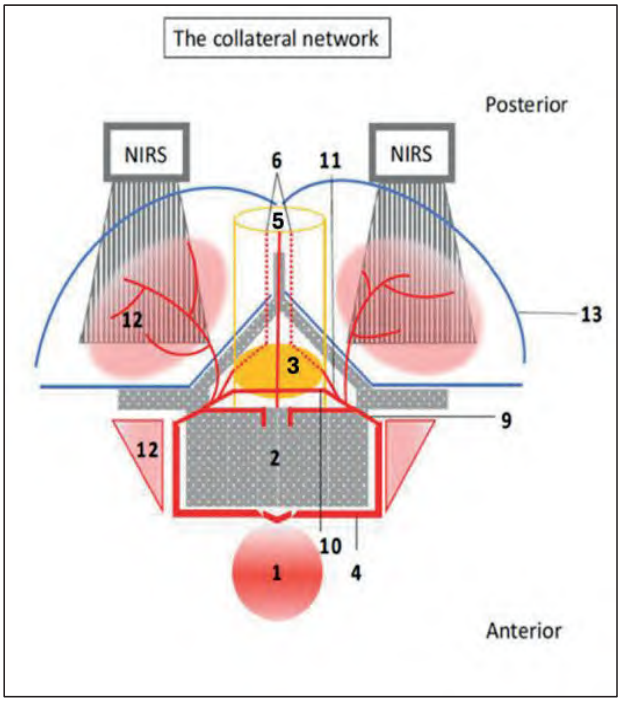

Fig. 9: The spinal cord blood supply. Cross-section at the level of the spinal cord with NIRS optodes applied in the paravertebral position.

1, aorta; 2, vertebral body; 3, spinal cord; 4, segmental arteries; 5, anterior spinal artery; 6, posterior spinal arteries; 9, spinal branch; 10, anterior medullar artery; 11, posterior radicular artery; 12, area of collateral network; 13, paraspinal musculature.
(From: Vanpeteghem et al. Assessment of spinal cord ischemia with Near-infrared spectroscopy: Myth or reality? J Cardiothorac Vasc Anesth 2020; 34:791-6.With permission.)

Due to interindividual variability in tissue composition, there is an overall variability of 10-15% in rS_tO_2 values.[53] Consequently, absolute values provide less information. Therefore, the relative changes in rS_tO_2 are of significantly greater interest for monitoring ischaemia. As such, NIRS should primarily be considered as a trend monitor.

2.5.2.2. Near-infrared spectroscopy to assess the microcirculation

NIRS technology is suggested to have the potential of evaluating the integrity of the microcirculation, a functionally independent entity, comprising arterioles, venules and capillary vessels. The microcirculation facilitates delivery of nutrients and oxygen to the tissues by adjusting its blood flow and removing metabolic byproducts.[59] While clinical practice typically focusses on macro-haemodynamic variables (such as heart rate, blood pressure and CO), ensuring sufficient oxygen delivery and maintaining tissue oxygen saturation is still regarded as the ultimate goal for optimal haemodynamic management.[60]

There is increasing evidence suggesting a dissociation between macro-haemodynamics and microcirculation in the critically ill patients.[61] In these situations, normal macro-haemodynamic parameters will mask hypoperfusion at the microcirculatory level.[62]

Results regarding the use of NIRS-technology to assess microcirculatory dysfunction in the critically ill patient are conflicting. In a study conducted by Filho et al. NIRS derived parameters were able to discriminate patients with and without circulatory shock, while other indicators for peripheral tissue perfusion (such as skin temperature and lactate) were inconclusive.[63] However, peripheral NIRS measurements in combination with a vascular occlusion test in patients following cardiac artery bypass surgery, failed to demonstrate microcirculatory dysfunction.[64]

In critically ill patients, vasoactive medication is commonly used to ameliorate the macrodynamic parameters. However, their effect on microdynamics remain a matter of debate. While increased muscle tissue oxygenation has been observed by Georger et al.[65] following restoration of MAP with norepinephrine, Jhanji et al.[66] could not find beneficial effects on the microcirculation following norepinephrine induced MAP-increase. On the other hand, administration of dobutamine[67] and levosimendan[68] was found to improve the microcirculation, independent of changes in cardiac index.

2.5.2.3. Near-infrared spectroscopy as a monitor of spinal cord ischaemia: Myth or reality? Review of the literature

This section is mostly based upon the review by Vanpeteghem et al.,[69] supplemented with findings from additional studies that had not been conducted or published yet at the time of this publication. For each topic, the animal data[70–78] (Table 1) are summarized before the human data.[79–85] (Table 2)

Table 1: Overview of literature in animal studies.

Year	Author	Number	Level	Location	Onset	Return to baseline	Monitor
2002	Macnab et al.[70]	3	T_9-T_{10}	Spinous process Lamina Spinal cord	< 1 sec	< 2 min	Niro 500 (Hamamatsu, Hamamatsu city, Japan)
2006	Lemaire et al.[72]	4	T_6-T_7 T_9-T_{11}	Midline	< 1 min	NA	Invos 5100 (Medtronic, Minneapolis, MN)
2008	Kunihara et al.[73]	14	Low lumbar	Midline	immediate	NA	OM-100A (Advanced Fiber Solutions, Easton, MA)
2016	Von Aspern et al.[75]	7	T_5-T_6 L_2-L_3	Paravertebral	immediate	< 40 s	Invos 5100
2017	Suehiro et al.[74]	4	T_6-T_7 T_9-T_{10}	Midline	NS	< 5 min	Invos 5100
2018	Shadgan et al.[71]	6	T_9	Spinal cord	NS	NS	OXT_5 (Pathonix Innovation, Vancouver, BC)
2019	Von Aspern et al.[76]	12	L_2-L_3	Paravertebral	< 1 min	NS	Invos 5100C (Medtronic, Dublin, Ireland)
2021	Von Aspern et al.[78]	18	L_2-L_3	Paravertebral	< 1 min	NS	Invos 5100C
2022	Von Aspern et al.[77]	10	T_4-T_6 T_7-T_9 T_{10}-T_{12} T_{13}-L_2 L_3-L_5	Paravertebral	NS	8 min NS NS NS NS	Invos 5100C (Medtronic, Dublin, Ireland) FORE-SIGHT (CAS Medical Systems, Branford, Conn)

Abbrevations: N: not applicable; NS: not specified; number: amount of animals included.

Table 2: Overview of literature in human studies.

Year	Author	Number	Level	Location	Onset	Return to baseline	Monitor
2011	Moerman et al.[80]	1	T_{10} L_2	Midline	NS	NA	Invos 5100
2011	Badner et al.[79]	2	T_1-T_3 T_8- T_{10}	Midline	NS	NA	Invos 5100
2013	Etz et al.[81]	20	T_5-T_7 L_1-L_3	Paravertebral	NS	NA	Invos 5100
2013	Demir et al.[82]	2	T_6-T_8 T_9- T_{11}	Midline	NS	NA	Invos 5100
2015	Boezeman et al.[83]	15	T_3 T_{12}	Midline	NS	NA	Invos 5100
2020	Kinoshita et al.[84]	18	T_3 T_{10}	Paravertebral	Immediate	Immediate	Invos 5100
2021	Von Aspern et al.[85]	1	T_4-T_5 T_7-T_8	Paravertebral	< 10 min	Immediate	Invos 5100

Abbrevations: NA: not applicable; NS: not specified; number: amount of patients included.

What is the optimal location for sensor application: midline or paravertebral?

To measure spinal saturation, NIRS optodes can be applied either on the midline[70–74,79,80,82,83] or paravertebrally.[76–78,81,84–86]

Midline application

The majority of information regarding this matter is derived from studies conducted on animals. Macnab et al. applied NIRS sensors at T_9-T_{10} on the spinous processes, the lamina and directly on the spinal cord in pigs.[70] Immediate changes in NIRS values at all three measuring sites were observed when arterial oxygenation was decreased or when spinal blood flow was impaired by distraction of the thoracic disc space. The authors concluded that changes in rS_tO_2 reflect spinal cord oxygenation.

Shadgan et al. applied NIRS sensors directly on the spinal cord at T_9 in pigs.[71] After hypoxia and acute spinal cord injury, NIRS-derived changes in oxyhemoglobin and deoxyhemoglobin corresponded to the arterial oxygenation of the spinal cord, measured by an intraparenchymal catheter inserted in the spinal cord.

Also in pigs, significant decreases in midline measured rS_tO_2 were reported within 1 minute after ligation of segmental arteries (T_6-L_1).[72] These findings were in accordance with the histopathological observations, revealing ischaemic changes in neurons. Likewise, an immediate decrease in oxyhaemoglobin following aortic cross-clamping was observed in a rabbit model.[73] Human case reports also have demonstrated variations in rS_tO_2 related to changes in spinal cord perfusion pressure, following increased blood pressure[79,80] aortic cross-clamping.[82] Midline measured rS_tO_2 could also be implemented to monitor conditions of imminent spinal cord ischaemia, reflected by decreased MEP.[83]

Paravertebral application

In pigs, a strong association was observed between the paraspinous collateral network blood supply (measured with NIRS) and directly measured thoracic and lumbar spinal cord oxygenation (measured with laser Doppler flowmetry).[75] Within 30 seconds after aortic cross-clamping, paravertebral lumbar rS_tO_2 decreased simultaneously with lumbar muscle and spinal cord oxygenation. All values were restored immediately after clamp removal. Von Aspern et al. have also demonstrated that decreases in rS_tO_2 from mid-thoracic to lumbar level following aortic cross-clamping were accompanied with decreases in spinal cord regional perfusion, obtained by injection of microspheres containing fluorescent dye.[77] Nevertheless, the changes during ischaemia and reperfusion were less pronounced in both mid-thoracic rS_tO_2 and rS_tO_2 in lower regions when compared to the regional

perfusion of the CN. In another study by von Aspern et al.[76] paravertebral lumbar optodes were bilaterally attached to 12 juvenile pigs. In the group where segmental arteries were subtotally occluded, higher lumbar $rS_{pv}O_2$ were observed compared to the group with total segmental artery occlusion. This finding was also supported by histopathological and clinical evidence, indicating a correlation with more severe tissue damage and permanent paraplegia in the group with total segmental artery occlusion. Consequently, the authors concluded that changes in lumbar $rS_{pv}O_2$ are indicative of neurologic outcomes. The same research group could also demonstrate that lumbar $rS_{pv}O_2$ independently responded to unilateral segmental artery occlusion.[78]

Similar changes were observed in an observational study including 15 patients scheduled for open TAAA repair.[81] After aortic cross-clamping, lumbar $rS_{pv}O_2$ significantly decreased to 74% ± 13% from baseline. After distal aortic perfusion, lumbar $rS_{pv}O_2$ increased to 80.9% ± 16% of baseline and restored completely after clamp release.

In a study conducted by Kinoshita et al. NIRS sensors were applied at T_3 and T_{10} in 18 consecutive patients undergoing total aortic arch replacement.[84] A rapid decrease in $rS_{pv}O_2$ was observed immediately after circulatory arrest at both thoracic levels and a return to baseline following resumption of the cardiopulmonary bypass. One case report also described the feasibility of a unilateral paravertebral application of NIRS optodes at T_4-T_5 (serving as control) and T_7-T_8 (to monitor saturation of the collateral network) during extended aortic arch surgery with a frozen elephant trunk.[85] Based on these data, it seems that both midline- and paraspinal-applied NIRS optodes are able to reliably measure rS_tO_2 of the collateral network, which supplies blood to the spinal cord.

Midline application of NIRS sensors measures rS_tO_2 in less vascularized biological tissues, in contrast to paraspinal application, where the extensive vascularized paraspinal musculature is located. Considering this, midline rS_tO_2 measurements might be more susceptible to errors, while it might be assumed that paravertebral rS_tO_2 approaches provide a more reliably measure of the oxygen content of the spinal cord blood supply.

What Is the Optimal Level for Sensor Application: Thoracic or Lumbar?

In most studies, spinal cord oxygenation is measured at the following two levels: upper level (thoracic) and lower level (low thoracic or lumbar). Interestingly, $rS_{pv}O_2$ at the midthoracic level seems to behave differently when compared to $rS_{pv}O_2$ measurements taken at lower levels.

Midthoracic Level

In four animal studies, the optodes were applied at the midthoracic level (T_5-T_7).[72,74,77,86] Out of these studies, only two experimental studies conducted in pigs could reveal a concomitant decrease

in both midthoracic and lumbar $rS_{pv}O_2$, which returned to their baseline values after aortic declamping.[74,77] However, it is worth noting that in the study by von Aspern et al., the reduction in midthoracic $rS_{pv}O_2$ was less pronounced compared to the decrease observed at the lumbar level.[77] In the remaining studies, the findings varied. One of them reported only a slight decrease in midthoracic $rS_{pv}O_2$ compared to $rS_{pv}O_2$ at the lower thoracic level following the ligation of segmental arteries (6% ± 8% vs. 39% ± 11%, respectively).[72] Another study reported no changes at all.[86]

The application of sensors at the mid-thoracic level was also conducted in human studies.[81,82,85] Stable midthoracic $rS_{pv}O_2$ values after aortic cross-clamping were observed in 20 patients during open and endovascular thoracoabdominal aneurysm repair.[81] Conversely, two case reports documented a decrease in $rS_{pv}O_2$ at the midthoracic level. In one instance, during a type B aortic dissection, $rS_{pv}O_2$ decreased in the T_6 to T_8 region, even after restoring distal aortic perfusion and cerebrospinal fluid drainage, whereas $rS_{pv}O_2$ at T_9 to T_{11} remained stable.[82] In another patient undergoing extensive aortic repair with antegrade cerebral perfusion, $rS_{pv}O_2$ measured at T_7-T_8 decreased to a larger extent compared to $rS_{pv}O_2$ measured at T_4-T_5, which served as a control (with an absolute decrease of 50% and 19%, respectively).[85]

Low Thoracic and Lumbar Level

In all animal studies, a consistent decrease in rS_tO_2 levels was demonstrated in the low thoracic (T_9-T_{12})[70,72,74,77] regions following impaired blood flow to the spinal cord. This pattern was also observed in human subjects undergoing open aortic surgery.[80–82] Significantly decreased low thoracic $rS_{T12}O_2$ (85.2% ± 18.4%) could be related to MEP ratios below 50%, as opposed to MEP ratios exceeding 50% where low thoracic rS_tO_2 was higher (94.6%± 10.0%).[83] Despite a combined decrease in MEP and low thoracic rS_tO_2, none of the patients experienced neurologic damage. Interestingly, Etz et al. were able to relate the occurrence of postoperative paraplegia to lower lumbar rS_tO_2.[81]

One case report was able to assess the real-time effect of surgical maneuvers.[82] After a massive bleeding, a substantial decrease in $rS_{T9\text{-}T11}O_2$ (34% decrease from baseline) was reported, which resolved after reimplantation of two segmental arteries. Furthermore, Kinoshita et al. observed the impact of antegrade cerebral perfusion on rS_tO_2 in 18 patients undergoing aortic arch surgery.[84] They measured rS_tO_2 at the level of T_3 and T_{10}. At the start of circulatory arrest, rS_tO_2 markedly decreased at both levels (from 60% and 80% at T_3 and T_{10}, respectively to approximately 40% at both levels). Following the onset of antegrade cerebral perfusion, rS_tO_2 at T_3 remained constant. However, rS_tO_2 at T_{10} continued to decrease and ultimately reached its nadir of barely 20%. This may indicate that collateral flow from antegrade cerebral perfusion is insufficient to reach the level of the lower spinal

cord during this type of surgery. After resumption of cardiopulmonary bypass, rS_tO_2 at both levels started to increase and recovered to baseline.

During thoracic endovascular aortic repair, no significant changes in rS_tO_2 at both T_5-T_7 and L_1-L_3 could be observed despite extended stent-graft coverage.[81] On the contrary, during a staged hybrid aortic repair, Moerman et al. observed a significant decrease in thoracic $rS_{T10}O_2$ after stent deployment, which could be resolved by increasing mean arterial pressure.[80] After stent deployment, a linear relationship was observed between mean arterial pressure and thoracic rS_tO_2, whereas lumbar rS_tO_2 remained unaffected. Based on these data, midthoracic rS_tO_2 seems to remain rather stable when blood supply to the spinal cord is compromised. Therefore, monitoring rS_tO_2 at the mid-thoracic level does not seem to provide additional information regarding the development of spinal cord ischaemia. Despite heterogenous study designs, preliminary evidence suggests that measurements at the low thoracic and lumbar levels adequately reflect oxygenation of the spinal cord blood supply. Because low thoracic and lumbar rS_tO_2 might behave differently,[80,82] it is recommended to monitor rS_tO_2 at both levels.

What Is the Response and Recovery Time of rS_tO_2 *After Surgical Interventions?*

The response time refers to the time frame from the event that compromised the spinal cord blood supply until the initiation of the rS_tO_2 decrease. From the available literature, no unequivocal response time can be identified. The response time varies between one second[70,73,75,84] and one minute.[72,76,78]

The lowest rS_tO_2 value is not always reached instantly. Following aortic cross-clamping, the nadir occurred as late as 8 to 12 minutes.[76,77,81,84–86] Even a decline of more than 60 minutes has been reported.[79] Boezeman et al. reported simultaneous decreases in MEP and NIRS values in two patients.[83] Unfortunately, they did not specify the time interval between aortic cross-clamping and the decrease in NIRS values or MEP alterations.

The literature often lacks precise specifications regarding recovery to baseline values. Reported recovery times range from less than 40 seconds to as long as 30 minutes.

What Extent of Decrease in rS_tO_2 *Is Associated with Adverse Clinical Outcomes?*

A key question is to what extent a decrease in rS_tO_2 can be tolerated, without the risk for spinal cord ischaemia. In animal studies, von Aspern et al. could demonstrate a correlation between paraplegia and lumbar rS_tO_2 decreases exceeding 30% from baseline.[76] They advise a 20 to 30 % decrease in rS_tO_2 from baseline as a cut-off value for diagnosis of potential spinal cord ischaemia.[78]

According to the observations of Etz et al., patients who developed paraplegia or paraparesis had a significantly greater decrease in lower lumbar rS_tO_2 (<75% of baseline for 15 ± 9 min) than those who

did not develop symptoms.[81] Boezeman et al. observed a 48% decrease of the low thoracic rS_tO_2, concomitant with a decrease in MEP response of 51% after aortic cross-clamping, which resolved after reattachment of segmental arteries and clamp removal.[83] On the contrary, Kinoshita et al. did not observe any cases of paraplegia or paraparesis in their study group of 18 patients, despite a decrease of rS_tO_2 at T_{10}, reaching as low as 20%.[84] Also, von Aspern et al. observed a 50% decrease in mid-thoracic rS_tO_2 which was not related to postoperative neurologic disorders.[85] However, both occurred during cardiopulmonary bypass and the application of deep cooling.

Issues to Be Solved

Given the devastating consequences of spinal cord ischaemia, there is an absolute need for real-time monitoring of the spinal cord oxygenation. The ideal monitor should have the capability to promptly detect spinal cord ischaemia, evaluate interventions (such as surgical reimplantation of segmental arteries, elevation of blood pressure, or cerebrospinal fluid drainage), and function as a postoperative monitor to prevent delayed paraplegia.

Although previous studies demonstrated the potential value of NIRS to monitor spinal cord perfusion, many questions and issues remain. In this context, it is important to emphasize that comparing studies conducted in different animal models can be misleading because of anatomical and physiological variations among these models. Additionally, because of factors such as a limited number of patients, a scarcity of control cases, interindividual variability, and the absence of outcome studies, it is difficult to make definitive recommendations on the use of NIRS as a monitoring tool for detecting spinal cord ischaemia.

The first question that arises is how a technology with a light penetration depth of only two to three cm would allow measurement of spinal rS_tO_2. While Lemaire et al. were able to show that a portion of the photons could penetrate the spinal cord,[72] it is evident that the measurement does not directly assess the oxygenation of the spinal cord itself; rather, it measures the oxygenation of the CN. As mentioned earlier, monitoring the rS_tO_2 of the CN is regarded as indicative of spinal cord oxygenation.[81] Supporting this theory is the observation that decreases in lumbar rS_tO_2, measured with NIRS, coincide with changes in spinal cord oxygenation or regional perfusion of the CN. These measurements were obtained using laser Doppler flowmetry or by quantifying fluorescent microspheres in relation to the cardiac output at that specific time point, respectively.[77,86] Furthermore, decreased rS_tO_2 values have been linked to histopathological findings that indicate a higher incidence of ischaemic neurons in the vulnerable spinal cord segments[72,74] and more extensive tissue damage in animals that developed permanent paraplegia.[76]

Another puzzling question is why most studies failed to show significant changes in rS_tO_2 at the mid-thoracic level after impairment of spinal cord blood flow.[72,81,86] The mid-thoracic spinal cord receives blood through the vertebral, intercostal, and upper thoracic segmental arteries, originating from the subclavian artery.[81] Due to an increased mean arterial pressure proximal to the aortic clamp, these arteries remain capable of providing
blood to the CN.[82,85] This contrasts with the reduction in lower thoracic and lumbar rS_tO_2 following aortic cross-clamping,[70–74,77,80–84] which may reflect a restricted collateral support system for the lumbar and lower thoracic paraspinous arterial network. Therefore, monitoring rS_tO_2 at the lumbar or lower thoracic level appears to be more effective in detecting spinal cord ischaemia.[81]

The safe zone wherein rS_tO_2 can fluctuate without compromising spinal cord function still remains to be elucidated. In patients undergoing carotid endarterectomy under regional anaesthesia, a cut-off value for cerebral rS_tO_2 of a 20% decrease from baseline demonstrated both a sensitivity and specificity of 83% and is considered the most suitable criterion.[50] However, it seems unlikely that the same cut-off values can be used for detection of spinal cord ischaemia. It could be argued that vascularization of the spinal cord is favoured with an extended amount of collaterals, serving as a reserve in case of decreased oxygen supply. Reports of rS_tO_2 decreases of 48% without symptoms of spinal cord ischaemia underscore this theory.[83] Of course, apart from the extent of decrease, it is essential to consider the duration of desaturation. Structural brain damage has been reported with rS_tO_2 reductions of 35% for more than 2 hours.[87] To date, no data regarding duration of spinal desaturation associated with spinal cord ischaemia are available.

Clinical Recommendations

Based on the currently available evidence, it is recommended to apply the NIRS optodes paravertebrally at the low thoracic and lumbar (L_1-L_3) levels. (Fig. 10)

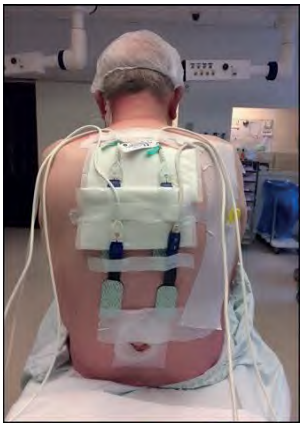

Fig. 10: Clinical application of NIRS sensors for monitoring spinal cord ischaemia

NIRS must be regarded as a trend monitor and the baseline needs to be set before induction of anaesthesia while the patient is breathing room air. While lacking concrete clinical evidence, an arbitrarily chosen cut-off value of a 20% decrease from the baseline should be considered as a warning sign for the potential development of spinal cord ischaemia. This choice aligns with the cut-off value utilized in cerebral oximetry, as the literature on cerebral oxygenation data in humans provides the only available information concerning ischaemia detection using NIRS. Optimization of oxygen delivery and spinal cord perfusion pressure obtained by increasing blood pressure and decreasing the intradural space pressure are adequate measures to increase rS_tO_2. In order to minimize the risk of delayed paraplegia,[88] continued NIRS monitoring for 48 to 72 hours postoperatively is recommended.

Conclusion

Due to its ease of use and noninvasiveness, NIRS is becoming increasingly popular for monitoring spinal cord ischaemia and evaluating protective strategies' effectiveness. Based on the available literature, paravertebral measurement of rS_tO_2 at the low thoracic and lumbar level seems to be the best approach. Future research should focus on determining the specific threshold levels and duration of low spinal rS_tO_2 values that are linked to adverse neurologic outcomes.

2.6. Strategies to prevent spinal cord ischaemia and improve spinal cord perfusion

The incidence of SCI in open aortic surgery directly depends on the duration of aortic cross-clamping. Therefore, long clamp times should be avoided in order to restore the spinal cord blood supply as fast as possible. This can be achieved by sequential aortic clamping, thereby enabling only a brief interruption of the perfusion of important feeding arteries to the spinal cord.[5] Besides this, the intraoperative construction of a left heart bypass with the preservation of distal perfusion has proven its value.[89]

In view of preserving the spinal cord blood supply, preoperative identification by means of imaging techniques and subsequent reimplantation of important feeding vessels to the spinal cord still remains a matter of debate.[33]

During normothermic conditions, neuronal injury can rapidly evolve. However, mild hypothermia (32-34°C) may have neuroprotective benefits by reducing the metabolic demands. But this may be accompanied with coagulopathy- related complications. In this light, selective cooling of the epidural space with normal saline at 4°C has been proposed, showing promising results.[90]

During TEVAR procedures with an extensive coverage of the intercostal arteries, the occurrence of SCI is directly related to the simultaneous occlusion of at least two major vascular regions (such as the left subclavian artery as well as the intercostal, lumbar and hypogastric arteries), especially in situations of persisting hypotension.[91] In this perspective, preoperative revascularization of the left subclavian artery is recommended by society guidelines.[92]

The corner stone of the anaesthetic management consists in optimization the spinal cord perfusion pressure (MAP – cerebrospinal fluid pressure) by means of increasing the MAP (> 80 mmHg) and decreasing the cerebrospinal fluid pressure (< 10 mmHg) through a spinal catheter.[92] However, insertion of a spinal catheter is not without risk. Serious and even fatal complications linked to its placement have been reported.[93]

In the past, pharmacological adjuncts, such as methylprednisolone,[94] naloxone[95] and intrathecal papaverine,[96] were recommended to reduce the metabolic demands of the spinal cord and to decrease the inflammatory response to ischaemia and reperfusion injury. However, to date there is no firm proof that these drugs effectively reduce the risk of SCI.[97]

2.7. References

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3

Effect of Endogenous Sympathetic-Mediated Blood Pressure Increase on Regional Paravertebral Oxygen Saturation

The beginning is the most important
part of the work.

Plato

3

Effect of Endogenous Sympathetic-Mediated Blood Pressure Increase on Regional Paravertebral Oxygen Saturation

Induction of anaesthesia is associated with hypotension due to the vasodilating properties of the administered drugs. Therefore, vasoactive agents are commonly used to restore the patient's blood pressure. It is well known that, depending upon the drug related vasoactive properties, optimization of haemodynamics may affect rS_cO_2 differently.

Before studying the effect of vasoactive agents on $rS_{pv}O_2$, we first examined the effect of endogenous catecholamines, epinephrine and norepinephrine, on $rS_{pv}O_2$ and aimed to investigate whether a strong endogenous sympathetic mediated stress response, induced by laryngoscopy, affects $rS_{pv}O_2$.

Laryngoscopy Mediated Stress Response Induces Opposite Effects on Cerebral and Paraspinal Oxygen Saturation

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Abstract

Background: Intraoperative sympathetic stimulation induces a cascade of metabolic and hormonal changes. It increases perfusion of vital organs, but also causes vasoconstriction of blood vessels supplying less vital organs, potentially leading to organ injury. To date, it is unknown how an endogenous stress reaction affects the spinal cord blood supply. Near-infrared spectroscopy (NIRS) can be applied paravertebrally to monitor the oxygenation of the collateral network, which contributes to the spinal cord blood supply. It has already been demonstrated that regional cerebral oxygen saturation (rS_cO_2) increases following sympathetic stimulation.

Objectives: We hypothesized that laryngoscopy would cause an increase in cerebral and paraspinal regional tissue saturations (rS_cO_2 and $rS_{ps}O_2$, respectively).

Design*:* Retrospective analysis of a previous conducted randomized trial.

Setting: Laryngoscopy in the operating room.

Methods: Data of 28 patients, scheduled for arterial dilation of the lower limb, were retrospectively analyzed. Before induction of anesthesia, standard monitoring, BIS and 8 NIRS sensors were applied (two on the forehead, six bilaterally on the back at T_3-T_4, T_9-T_{10} and L_1-L_2). Sympathetic stimulation was induced by laryngoscopy.

Main outcome measures*:* Changes in rS_tO_2 following sympathetic stimulation induced by laryngoscopy.

Results: Following laryngoscopy, rS_cO_2 significantly increased and $rS_{ps}O_2$ significantly decreased at T_9-T_{10} and L_1-L_2. The relative changes (regional tissue oxygen saturation (rS_tO_2) after intubation-rS_tO_2 before intubation)/ rS_tO_2 before intubation), at cerebral level, T_9-T_{10} and L_1-L_2 were 9%, -5% and -3%, respectively ($p < 0.01$). $rS_{ps}O_2$ at T_3-T_4 did not change significantly. Changes (Δ) in mean

arterial pressure following laryngoscopy were weakly correlated with ΔrS_cO_2 and moderately correlated with $\Delta rS_{ps}O_2$ at T_9-T_{10} and L_1-L_2.

Conclusions: Intraoperative sympathetic stimulation may decrease the oxygen supply to the spinal cord.

Trial registration: The trial was registered at ClinicalTrials.gov (NCT 03767296).

Keywords: Adrenergic receptor, ephedrine, laryngoscopy, near-infrared spectroscopy, sympathomimetic agents.

Introduction

Current guidelines advocate aiming for higher systemic blood pressures to prevent spinal cord ischemia in situations where regional blood perfusion of the spinal cord is at risk of being compromised.[1] This is usually obtained by pharmacological sympathetic stimulation, resulting in increased heart rate and blood pressure. The idea is that increased blood pressure automatically implies better regional spinal cord perfusion. Yet, evidence for such strategy is low (class III).[1]

Near-infrared spectroscopy (NIRS) enables the monitoring of changes in regional tissue oxygenation (rS_tO_2). Its use is widespread as a monitor of cerebral ischaemia,[2] but more recently, as a result of changed anatomical understanding and new research insights,[3-5] paravertebrally applied NIRS monitoring has also been advocated for non-invasive and indirect assessment of spinal cord perfusion. It measures the saturation of the collateral network, which is an extensive clew of interconnecting arteries and arterioles, located in the paravertebral tissues and contributing to the spinal cord blood supply.[6]

The present study aimed to investigate the effect of a strong endogenous sympathetic stimulation on cerebral and paravertebral oxygen saturation. Therefore, we analyzed NIRS data during laryngoscopy in order to identify the effects of a laryngoscopy-mediated stress response on regional cerebral oxygen saturation (rS_cO_2) and paravertebrally measured regional oxygen saturations ($rS_{ps}O_2$).

Methods

After approval of the Ghent University Hospital Ethics Committee for additional analysis (ERB

number: 2019/1603) and informed consent was obtained, data from a previously conducted prospective randomized trial (registered at ClinicalTrials.gov (NCT 03767296))[7] were retrospectively analyzed.

All 28 patients included in that study[7] were scheduled for an endovascular dilatation of arterial blood vessels of the lower limb. Exclusion criteria were BMI>30, previous aortic surgery, severe valvular disease, paraplegia or paraparesis and patients requiring renal replacement therapy. Baseline mean arterial pressure (MAP) was measured during the preoperative visit. Before induction of anesthesia, two disposable NIRS sensors (INVOS 5100C, Medtronic, Dublin, Ireland) were applied bilaterally on the forehead, as was one bispectral index sensor (BIS, Medtronic, Ireland). A further six NIRS sensors were applied bilaterally on the back of the patient, all in a paravertebral position, at thoracic level T_3-T_4, T_9-T_{10} and the remaining two at lumbar level L_1- L_2.[a]

Baseline NIRS levels were obtained before induction of anesthesia, with the patient in a supine position without supplemental oxygen. At this moment non-invasive blood pressure readings were obtained and set to repeated measurements at one-minute intervals. For induction of anesthesia, all patients received a standard dose of sufentanil (0.15 µg/kg) and propofol (1-2 mg/kg) until loss of consciousness, followed by cisatracurium (0.15 mg/ kg). After three minutes of manual ventilation with an inspiratory fractional oxygen concentration (F_iO_2) of 1.0 and BIS-titrated sevoflurane administration, the patient was intubated. Following intubation, F_iO_2 was immediately reduced to 0.4. Tidal volumes were set at 8 ml/kg ideal body weight. Respiratory rate was titrated to maintain end-tidal CO_2 readings between 35 and 45 mmHg. Sevoflurane was used for maintenance of anesthesia, with a target BIS range of 40-60.

Hemodynamic and respiratory data were acquired using a personal computer running dedicated data acquisition software (Dräger Data Grabber, Dräger Medical GmbH, Lübeck, Germany).

Primary outcome was the laryngoscopy-induced change in rS_tO_2 (rS_cO_2 and $rS_{ps}O_2$) as measured by NIRS. Blood pressure, heart rate, BIS and pulse oximetry (S_pO_2) were chosen as secondary endpoints.

Primary and secondary outcome data before and after laryngoscopy were compared. For the pre-laryngoscopy data, the value just before introduction of the laryngoscope was noted. For the post-laryngoscopy data, the maximum changed value within two minutes was recorded.

The relative changes (Δ) following laryngoscopy were calculated with the formula (post-laryngoscopy value minus pre-laryngoscopy value)/ pre-laryngoscopy value.

[a] Location of the sensor application is illustrated on p. 55.

Statistical analysis

Based upon the data of the previous trial,[7] a post- hoc power analysis[b] was performed for the present study. With a sample size of 28 and an alpha of 0.05, analysis revealed a power of 0.99 at the cerebral level and a power of 0.06, 0.98 and 0.99 at T_3-T_4, T_9-T_{10} and L_1-L_2, respectively.

Normality was tested with the Shapiro-Wilk test. Differences before and after laryngoscopy in primary and secondary outcomes were analyzed with the Wilcoxon Signed Ranks test and are presented as median [min, max]. Correlation between ΔMAP and ΔrS_tO_2 was performed with the Spearman correlation test. P-values < 0.05 were considered significant.

Results

All 28 patients from the previous trial were included in the present analysis. Patients' characteristics are presented in Table 1.

Table 1: Patients' characteristics.

Sex (male/female)	13/15
Length (cm)	168 [150, 190]
Weight (kg)	70 [42, 100]
BMI ($kg.m^{-2}$)	25.4 [17.5, 30.0]
Age (y)	67 [48, 87]
Arterial hypertension	24 (86)
Atrial fibrillation	5 (18)
Myocardial infarction	7 (25)
Diabetes mellitus	11 (39)
Pacemaker	1 (4)
ACE-inhibitors	12 (43)
b-blocking agents	14 (50)
Diuretics	8 (29)
Ca^{2+}-antagonists	5 (18)
Statins	17 (61)
Data are expressed as median [min, max] or number (percentage). BMI: body mass index; ACE: Angiotensin-converting enzyme.	

[b] The power analysis refers to a previous trial without specifying the details. In that study, a difference of 2% was observed between groups (receiving ephedrine and phenylephrine). This difference was used for calculating the post-hoc analysis in the current study.

Heart rate, MAP and BIS increased significantly following laryngoscopy, as depicted in Table 2. S_pO_2 did not change.

Table 2: Secondary outcome parameters before and after laryngoscopy with its relative change.

	Pre-laryngoscopy	Post-laryngoscopy	Relative change (%)	p-value
HR (bpm)	63 [58-77]	81 [69-93]	22 [13-40]	< 0.001
MAP (mmHg)	84 [64-95]	108 [83-122]	23 [8-38]	< 0.001
S_pO_2 (%)	99 [97-100]	99 [98-100]	0 [0.02-0.03]	ns
BIS	39 [27-46]	49 [35-68]	25 [16-55]	< 0.001

Data are presented as median [Q1-Q3]. HR: heart rate; bpm: beats per minute; MAP: mean arterial pressure; S_pO_2: peripheral oxygen saturation; BIS: bispectral index; relative change: (post-laryngoscopy – pre-laryngoscopy) /pre-laryngoscopy; ns: not statistically significant.

Table 3 presents the absolute values of rS_tO_2, measured before and after laryngoscopy, and the relative changes. Laryngoscopy provoked an opposite effect on rS_tO_2, with an increase in rS_cO_2 ($p<0.01$) and a decrease in $rS_{ps}O_2$ at T_9-T_{10} and L_1-L_2 ($p<0.01$ for both). No significant effect was observed at level T_3-T_4.

Table 3: Regional tissue oxygen saturation (rS_tO_2) before and after laryngoscopy with its relative change.

rS_tO_2	Pre-laryngoscopy	Post-laryngoscopy	Relative change (%)	p-value
rS_cO_2	68 [61-75]	76 [70-81]	9 [6-12]	<0.01
$rS_{T3-T4}O_2$	82 [78-89]	83 [76-89]	1 [-2, 1]	ns
$rS_{T9-T10}O_2$	78 [72-85]	74 [70-82]	-5 [-7, 1]	<0.01
$rS_{L1-L2}O_2$	81 [71-88]	77 [72-85]	-3 [-6, -1]	<0.01

Data are presented as median [Q1-Q3]. rS_cO_2: regional cerebral oxygen saturation, $rS_{T3-T4}O_2$: regional oxygen saturation at T3-T4, $rS_{T9-T10}O_2$: regional oxygen saturation at T9-T10; $rS_{L1-L2}O_2$: regional oxygen saturation at L1-L2, relative change: (post-laryngoscopy – pre-laryngoscopy)/pre-laryngoscopy, ns: not statistically significant.

Correlation analysis showed a weak positive correlation between ΔMAP and ΔrS_cO_2 ($r=0.49$, $p<0.05$) and a moderate negative correlation between ΔMAP and $\Delta rS_{ps}O_2$ at both T_9-T_{10} and L_1-L_2 ($r=0.59$ and $r=0.69$, respectively, $p<0.01$ for both). No correlation was found between ΔMAP and $\Delta rS_{T3-T4}O_2$. (Figure 1)

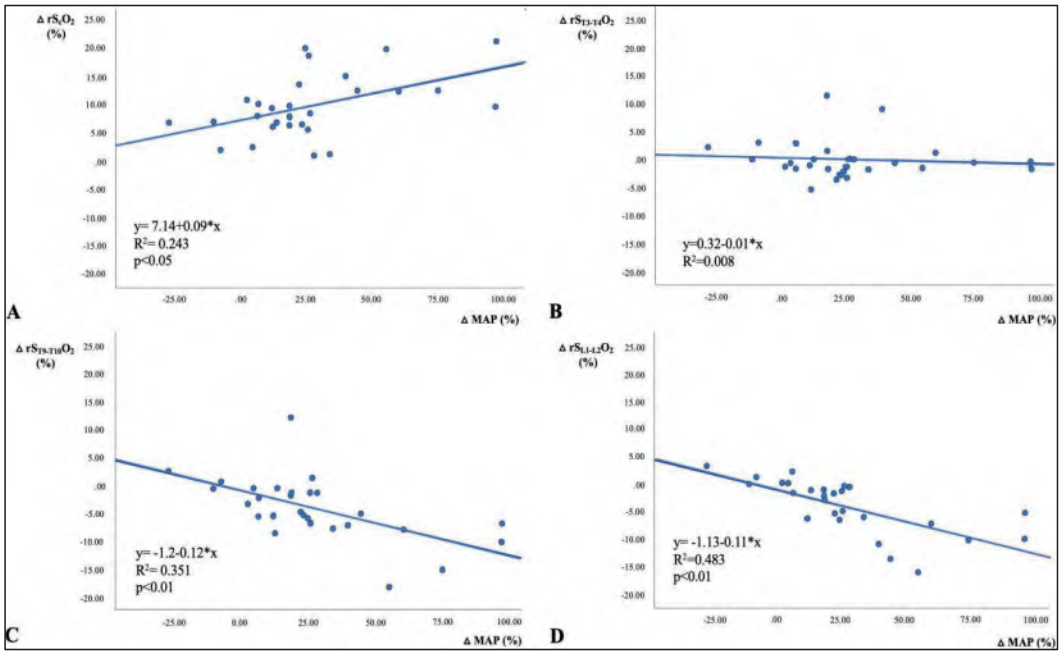

Figure 1: Correlation between relative changes in MAP and relative changes in regional tissue saturation.

Correlation analysis, demonstrating a weak positive correlation between changes (Δ) in MAP and ΔrScO2 (A), no correlation between ΔMAP and ΔrST3-T4O2 (B) and a moderate negative correlation between ΔMAP and both ΔrST9-T10O2 (C) and ΔrSL1-L2O2 (D).

Δ: relative change, rS_cO_2: regional cerebral oxygen saturation, $rS_{T3\text{-}T4}O_2$: regional oxygen saturation at T3-T4, $rS_{T9\text{-}T10}O_2$: regional oxygen saturation at T_9-T_{10}; $rS_{L1\text{-}L2}O_2$: regional oxygen saturation at L_1-L_2. MAP: mean arterial pressure.

Discussion

Laryngoscopy mediated stress response was accompanied with an increase in rS_cO_2. However, despite higher MAPs, a decrease in $rS_{ps}O_2$ was observed. NIRS technology was used to observe the effect of laryngoscopy on rS_cO_2 and $rS_{ps}O_2$. Based on data of previous studies[3], measuring $rS_{ps}O_2$ at low thoracic and lumbar levels seems to adequately reflect the oxygenation of the collateral network. Therefore, the T_9-T_{10}- and L_1-L_2-level were both chosen for sensor application. The level of T_3-T_4 was chosen as a control measurement. NIRS measures rS_tO_2 of the underlying region at a depth of

approximately 2.5 to 3 cm. Hence, the question may rise if oxygenation of the subcutaneous tissue has been measured instead of oxygenation of the collateral network. Indeed, although the spatial resolution technique reduces the influence of outer layers, not all extraspinal structures may have been excluded. Therefore, patients with a BMI of more than 30 were excluded to minimize this possible confounding factor, in accordance with the exclusion criteria stated in previous studies on NIRS and spinal cord oxygenation.[8]

Also, the study population existed of vascular burdened patients with concomitant diseases such as diabetes mellitus (39%) and atherosclerosis (100%). (Table 1) The inherent microangiopathy accompanying both conditions may influence reactivity of the targeted vascular structures (at cerebral and paravertebral level), hence influencing the changes in rS_tO_2 following laryngoscopy. Moreover, 86% of our study population suffered from arterial hypertension and were treated with antihypertensive medication. (Table 1) It might be that the antihypertensive drugs have affected the vascular wall and hereby have affected the measured changes in rS_tO_2 following laryngoscopy. Despite these possible confounding factors, our measurements all trended in the same direction.

We have previously[c] demonstrated that administration of ephedrine, a commonly used α- and ß-sympathomimetic drug failed to improve $rS_{ps}O_2$ (-0.7% and -1.3% at T_9-T_{10} and L_1-L_2, respectively) despite substantially rising MAP (12 mmHg).[7] The results of the current study confirm this sympathetic mediated response in $rS_{ps}O_2$(-4% at both T_9-T_{10} and L_1-L_2) with increased blood pressure (MAP increase of 24 mmHg). These findings suggest that an increased sympathetic stimulation seems indeed associated with decrease in $rS_{ps}O_2$ and this effect appears more pronounced with a more important rise in MAP.

This is an unexpected finding as the current strategy to preserve spinal cord blood supply is to augment MAP, presuming that increasing blood pressure automatically implies better tissue perfusion.[9]

To date, research on how physiologic responses affect $rS_{ps}O_2$ remains scarce. The current initial data suggest that an endogenous stress response following laryngoscopy may induce a decrease in $rS_{ps}O_2$, indicating that sympathetic stimulation may adversely affect (para)spinal tissue oxygenation.

Limitations

In this study, the spinal cord oxygenation was not directly measured. Instead, we measured $rS_{ps}O_2$,

[c] These are the results of a previous conducted RCT (NCT03767296) studying the differences in effect of ephedrine and phenylephrine on the regional paravertebral tissue saturations. The results of this study will be discussed in Chapter 4.

which reflects the oxygenation of the underlying paravertebral tissues. Since this vasculature takes part in the collateral network, several landmark papers postulate that it contributes substantially to the spinal cord blood supply.[3-5]

Nevertheless, the spinal cord blood supply is not solely dependent on blood supply from the collateral network. Hence, the observed changes of $rS_{ps}O_2$ following laryngoscopy – presumably due to vasoactive changes in the paravertebral vasculature- may not necessarily imply that the spinal cord blood supply is at stake. Therefore, further investigation is needed to study the effect of sympathetic stimulation on $rS_{ps}O_2$ with simultaneous imaging of the spinal cord perfusion, using fMRI, for example.

Arterial partial pressure of carbon dioxide (P_aCO_2) plays a significant role in vascular tone and might therefore influence rS_cO_2. We did not obtain P_aCO_2 data, but as part of our routine anesthetic monitoring, end tidal CO_2 was measured and per protocol maintained at a level between 35 and 45 mmHg. No outliers of end tidal CO_2 were detected in our dataset.

Post-hoc power analysis is sometimes criticized as a means of assessing validity of determining whether the sample size of a secondary data analysis is adequate for a proposed analysis.[10] Sensitivity analysis has been proposed as a possible means to address this problem. The most relevant variables potentially influencing the current study results would be outliers and missing data, none of which were present in this study.[11]

Conclusion

Although paraspinal NIRS monitoring has to date not been validated to indirectly assess spinal cord oxygen saturation, the results of the present study should be an incentive to specifically analyze the effects of sympathetic stimulation on $rS_{ps}O_2$.

Funding and conflict of interest:

This study was supported by the Research Grant Program of the Belgian society of anesthesiology, resuscitation, perioperative medicine and pain management (BeSARPP). The authors declare no conflicts of interest.

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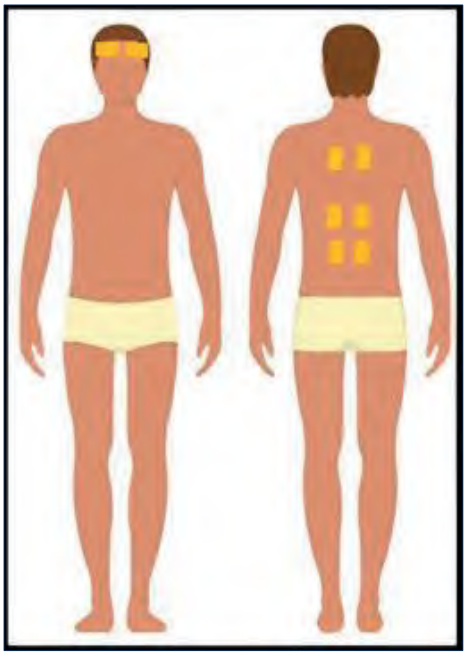
Addendum Chapter 3



Location of sensor application.

4

Effect of a Bolus Administration of Ephedrine and Phenylephrine on the Paravertebral Tissue Oxygen Saturation

Once upon a time...

Inclusion of the first study patient...

Cluster 6, Operating Room 14
Ghent University Hospital, Belgium

Ft. Isabeau Lecoutere, MD
(with permission)

4

Effect of a Bolus Administration of Ephedrine and Phenylephrine on the Paravertebral Tissue Oxygen Saturation

In Chapter 3, we illustrated the contrasting effects of a sympathetic-mediated stress response induced by laryngoscopy on cerebral and paravertebral tissue oxygen saturations. In Chapter 4, we present a study that investigates whether vasoactive drugs also produce opposite effects. Moreover, previous research has already demonstrated the distinct effects of ephedrine and phenylephrine on cerebral tissue oxygen saturation (rS_cO_2). In this same study, we also assessed whether both drugs exhibit analogous differential effects on paravertebral tissue oxygen saturation ($rS_{pv}O_2$).

Ephedrine and phenylephrine induce opposite changes in cerebral and paraspinal tissue oxygen saturation,measured with Near-infrared spectroscopy: a randomized controlled trial

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Abstract

While the effects of phenylephrine (PE) and ephedrine (E) on cerebral oxygen saturation (rS_cO_2) already have been studied, the effect on paraspinal oxygen saturation ($rS_{ps}O_2$) is still unexplored. This study aims to assess the effect of PE and E on rS_cO_2 and $rS_{ps}O_2$, measured with near-infrared spectroscopy. A randomized 4-treatment cross-over trial was designed in 28 patients under BIS-titrated anaesthesia with sevoflurane. If MAP decreased more than 20% from baseline, incremental doses of PE and/or E were given according to the randomization (group I: E–PE–E, group II: PE–E–PE, group III: E–E–E, group IV: PE–PE–PE). rS_cO_2 and $rS_{ps}O_2$ on T_3–T_4, T_9–T_{10} and L_1–L_2 were recorded. Differences in rSO_2 (post-pretreatment) within each group were analyzed with paired Student's *t* test. Differences in effects of PE and E on rS_cO_2 and $rS_{ps}O_2$ were analyzed with linear mixed modelling. Following PE administration, rS_cO_2 decreased significantly (– 2.7% ± 3.5), while it remained stable following E (– 0.6% ± 3.6). Contrastingly, $rS_{ps}O_2$ at T_3–T_4, T_9–T_{10} and L_1–L_2 slightly increased following PE (0.4% ± 2.5, 0.7% ± 2.0 and – 0.1% ± 1.4, respectively), while it decreased after E administration (– 1.3% ± 3.4%, – 0.7% ± 2.6% and – 1.3% ± 2.7%, respectively). Compared to E, PE administration was associated with a significant decrease in rS_cO_2 (– 2.1%, 95% CI [– 3.1%, – 1.2%], $p < 0.001$). In contrast, compared to PE, E was associated with a significant decrease in $rS_{ps}O_2$ at T_3–T_4, T_9–T_{10} and L_1–L_2 (– 2.0%, 95% CI [– 2.8, – 1.1], $p < 0.001$; – 1.4%, 95% CI [– 2.4%, – 0.4%], $p = 0.006$; and – 1.5%, 95% CI [– 2.3%, – 0.8%], $p < 0.001$, respectively). An opposite effect on rS_cO_2 and $rS_{ps}O_2$ was observed after bolus administration of PE and E.

Keywords: Ephedrine · Near-infrared spectroscopy · Paraspinal · Phenylephrine

Introduction

Controversy remains on how perioperative hypotension is best treated. In the absence of important fluid shifts or blood losses, a liberal fluid administration is not recommended, and maintenance of blood pressure is therefore often achieved by administration of vasoactive agents.

Near-infrared spectroscopy (NIRS) is considered to be a reliable monitor for the detection of cerebral ischaemia.[1] Several studies have demonstrated a beneficial effect of ephedrine (E) compared to phenylephrine (PE) on cerebral oxygenation, measured with NIRS.[2-4]In recent years, NIRS is gaining popularity as a noninvasive monitor of oxygenation of the paraspinal musculature, as a reflection of blood supply to the spinal cord, thereby allowing detection of spinal ischaemia.[5,6]Until now, the effect of E or PE on paraspinal muscle oxygenation remains to be elucidated. We aimed to investigate whether oxygen saturation of the paraspinal muscles is different depending on the type of vasopressor used. We chose a study population of patients scheduled for arterial dilation of the lower limbs, as the course of this procedure entails minimal haemodynamic fluctuations. In accordance with the effect on cerebral oxygenation, we hypothesized that E and PE would exert a similar effect on paraspinal muscle oxygenation.

Materials and methods

The trial was registered at ClinicalTrials.gov (NCT03767296). After approval of the University Hospital Ghent Ethics Committee (EC 2016/0644, June 7th 2016, D Matthijs) and written informed consent, patients scheduled for a percutaneous transluminal angioplasty of the lower limb were included between February and September 2017. Patients < 18 years old, with a body mass index > 30 kg/m^2, severe valvular disease, paraplegia or paraparesis, patients who previously underwent aortic surgery, and patients who required renal replacement therapy were excluded.

This manuscript adheres to the applicable CONSORT guidelines. Included patients were randomly assigned into four groups. The CONSORT diagram is represented in Fig. 1.

Baseline mean arterial pressure (MAP) was defined during the preoperative consultation. Before induction of anaesthesia, six disposable NIRS sensors (INVOS 5100C; Medtronic, Minneapolis, MN, USA) were applied bilaterally on the back of the patient at three levels: two sensors at thoracic level T_3–T_4, two at thoracic level T_9–T_{10} and two at lumbar region L_1–L_2. Two NIRS sensors were additionally placed on the forehead to measure regional cerebral oxygen saturation (rS_cO_2).[d]

[d] Location of the sensor application is illustrated on P. 55.

Baseline was set in the supine position, breathing room air. A bispectral index (BIS) monitor (BIS™, Covidien, MA, USA) was used to measure depth of anaesthesia. Blood pressure was measured noninvasively every minute. All patients received sufentanil (0.15 μg/kg), propofol (1–2 mg/kg until loss of consciousness) and cisatracurium (0.15 mg/kg) for induction of anaesthesia. Following intubation, inspired oxygen fraction was decreased to maintain an end tidal oxygen concentration of 40%. Tidal volume was preset at 8 ml/kg ideal body weight and adapted in order to maintain end-tidal CO_2 between 35 and 45 mmHg. Anaesthesia was maintained with sevoflurane to keep the BIS within a range of 40–60. The study protocol is presented in Fig. 3. Vasopressor agents were administered through a dedicated intravenous line. The MAP limit was predefined as a 20% decrease from baseline. If MAP was lower than this limit, a bolus of E or PE was administered, according to the group the patient was randomized to. Several bolus administrations and incremental bolus dosages could be administered. The ethical committee required a restriction of the total amount of E and P to 140 mg and 1500 μg, respectively. The study was completed when MAP decreased more than 20% from baseline for the fourth time or when the maximum dose of vasopressors was reached. If administration of the study medication did not achieve the expected result, management of haemodynamics was left to the discretion of the attending anesthesiologist and the patient was excluded from further data analysis.

All haemodynamic and respiratory data were recorded using a personal computer with dedicated data acquisition software (Dräger Data Grabber, Dräger AG).

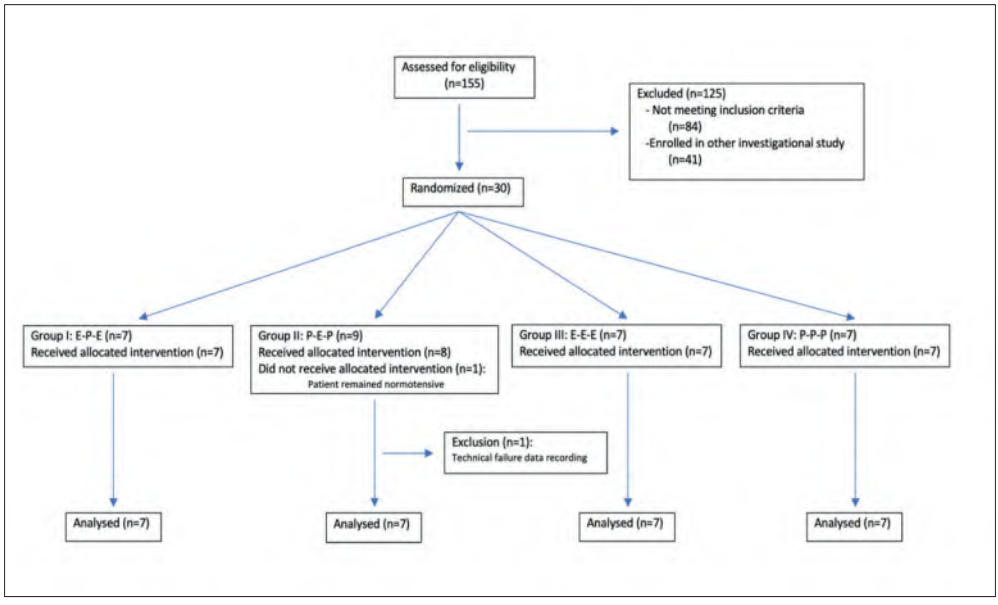

Figure 1: CONSORT diagram

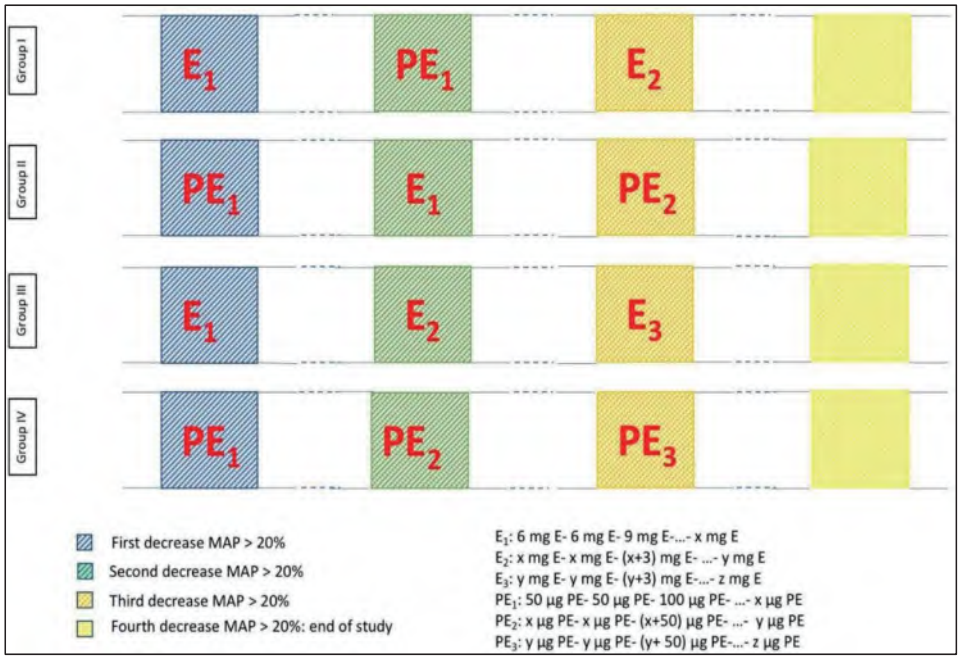

Figure 2: Study protocol

Statistical analysis

Sample size calculation was based on the data published by Pennekamp et al.[2] They observed a difference in response between PE and E of 4%. For a power of 0.8 and an alpha of 0.05, seven patients in each observation arm were calculated to be necessary to address the experimental question.

Differences in patient characteristics and drug doses were calculated with the Kruskal–Wallis test or Fisher exact's test, as appropriate and were presented as median (min–max). Differences in doses of PE and E were analyzed with one way ANOVA. Differences in haemodynamics and rSO_2 (post-pretreatment) within each group were analyzed with paired Student's t-test and are presented as mean (SD).

For analysis of differences in effects between PE and E, a linear mixed model with an unstructured covariance matrix and saturated mean model was used to verify whether there was a carry-over effect between E and PE on rS_cO_2 and $rS_{ps}O_2$ at all three spinal levels. No carry-over effect between E and PE could be demonstrated at none of the measurement levels. Therefore, data of E and PE treatment were clustered and patients were divided into two groups for further analysis: the E-group and the PE-group.

A linear mixed model with covariance pattern modelling, applying an unstructured or compound symmetry covariance structure depending on the Akaike information criterion, with stepwise backward selection was applied to measure the effect of E and PE on rS_cO_2 and $rS_{ps}O_2$. Differences between the E and PE group are presented as mean [95% CI].

Results

Thirty patients were included and were randomly assigned into four groups. (Fig. 1) We had two drop-outs: in one patient MAP did not decrease more than 20% from baseline and therefore the patient did not receive the allocated treatment. The second patient had incomplete data recording due to a technical failure.

Twenty-eight patients completed the study. No significant differences in patient characteristics were observed between the four groups. (Table 1)

Patients' haemodynamics were significantly different pre- and post-administration for heart rate and MAP in both groups, but not for BIS and oxygen saturation (SpO_2). (Table 2)

The median cumulative dose was 18 mg (6–144) for E and 100 µg (50–500) for PE.

Figure 3 depicts the absolute differences in rSO_2 after vasopressor administration at the three time points (MAP decrease > 20% from baseline). In Table 2, the absolute values of rS_cO_2 and $rS_{ps}O_2$ and their differences (post-pretreatment) are shown for both groups.

Table 1: Patient characteristics

	Group I (E–P–E) (n = 7)	Group II (P–E–P) (n = 7)	Group III (E–E–E) (n = 7)	Group IV (P–P–P) (n = 7)
Sex (m/f)	4/3	6/1	1/6	3/4
Age (y)	70 (56–81)	61(48–84)	66 (54–83)	67 (52–87)
BMI (kg m^{-2})	23.5 (17.5–25.8)	27.4 (19.3–29.9)	27.6 (18.4–30.0)	24.6 (19.6–27.3)
AHT	6	6	6	6
DM	3	1	3	4
β-LYTICS	3	4	2	5
ACEI	4	2	4	2
CCB	1	2	1	1

Data are presented as median (min–max) or number (n)

m male, *f* female, *y* year, *BMI* body mass index, *AHT* arterial hypertension, *DM* diabetes mellitus, *ACEI* angiotensin-converting-enzyme-inhibitors, *CCB* calcium channel blocking agents

Table 2: Patient haemodynamics and regional tissue saturations before (pre) and after (post) treatment

	Ephedrine-group			Phenylephrine-group		
	Pre	Post	Δ	Pre	Post	Δ
HR (bpm)	58 ± 11	61 ± 11	3 ± 6*	60 ± 12.0	57 ± 12	−3 ± 5*
MAP (mmHg)	68 ± 10	80 ± 12	12 ± 9*	73 ± 11	86 ± 12	13 ± 8*
BIS	41 ± 11	41 ± 12	0 ± 9	44 ± 12	43 ± 11	−1 ± 6
SpO_2 (%)	98 ± 3	97 ± 3	0 ± 1	99 ± 1	99 ± 1	0 ± 1
rS_cO_2 (%)	65.3 ± 8.3	64.7 ± 7.7	−0.6 ± 3.6	66.4 ± 8.9	63.7 ± 9.1	−2.7 ± 3.5*
$rS_{T3-T4}O_2$ (%)	78.4 ± 7.4	77.1 ± 8.6	−1.3 ± 3.4‡	79.5 ± 8.3	79.9 ± 7.7	0.4 ± 2.5
$rS_{T9-T10}O_2$ (%)	73.4 ± 10.9	72.6 ± 11.4	−0.7 ± 2.6	74.7 ± 8.9	75.4 ± 8.8	0.7 ± 2.0‡
$rS_{L1-L2}O_2$ (%)	76.0 ± 11.8	74.7 ± 12.3	−1.3 ± 2.7†	76.0 ± 10.5	75.9 ± 10.2	−0.1 ± 1.4

Data are presented as mean ± standard deviation

Δ = posttreatment–pretreatment, *HR* heart rate, *MAP* mean arterial pressure, *BIS* bispectral index, SpO_2 oxygen saturation by pulse oximetry, rS_cO_2 cerebral tissue oxygenation, $rS_{T3-T4}O_2$, regional tissue oxygenation at high thoracic level (T_3–T_4), $rS_{T9-T10}O_2$ regional tissue oxygenation at low thoracic level (T_9–T_{10}), $rS_{L1-L2}O_2$ regional tissue oxygenation at lumbar level (L_1–L_2)

*p < 0.001; †p < 0.01; ‡p < 0.05 (post vs. pre, Paired Student's t-test)

Following PE, rS_cO_2 was significantly lower (– 2.1% [– 3.1%, – 1.2%], p < 0.001), compared to E. In contrast, $rS_{ps}O_2$ was significantly lower following E administration compared to PE at T_3–T_4, T_9–T_{10} and L_1–L_2 (– 2.0% [– 2.8, – 1.1], p < 0.001; – 1.4% [– 2.4%, – 0.4%], p = 0.006 and – 1.5% [– 2.3%, – 0.8%], p < 0.001, respectively).

Correlation analysis showed a significant, negative correlation between MAP and rS_cO_2 for PE (– 0.482, p = 0.001). No correlation was found between MAP and rS_cO_2 for E nor between MAP and $rS_{ps}O_2$ for E and PE. (Fig.4)

Discussion

The present study revealed that, in contrast to our hypothesis, E and PE induced opposite changes in rS_cO_2 and $rS_{ps}O_2$: PE induced a decrease in rS_cO_2 and an increase in $rS_{ps}O_2$, whereas after E administration rS_cO_2 did not change and $rS_{ps}O_2$ decreased.

Effect of E and PE on cerebral oxygenation

The decrease in rS_cO_2 after administration of PE has previously been related to a decrease in cardiac output (CO).[3] However, decreases in rS_cO_2 after PE administration were also observed without any changes in CO.[4] This discrepancy might be explained by the opposite effects of PE on CO.[7,8] PE can increase CO by mobilizing the unstressed volume (i.e. blood volume not participating in the patients'

haemodynamics), thereby increasing preload. On the other hand, PE can also decrease CO by either decreasing heart rate or increasing afterload and/or by increasing venous resistance. The net effect depends on both physiological variables (such as rhythm control, fluid status and position on the Frank–Starling curve) and vasopressor related variables (such as drug dose, the sensitivity of the individual patient and the corresponding tissues.[7,9]

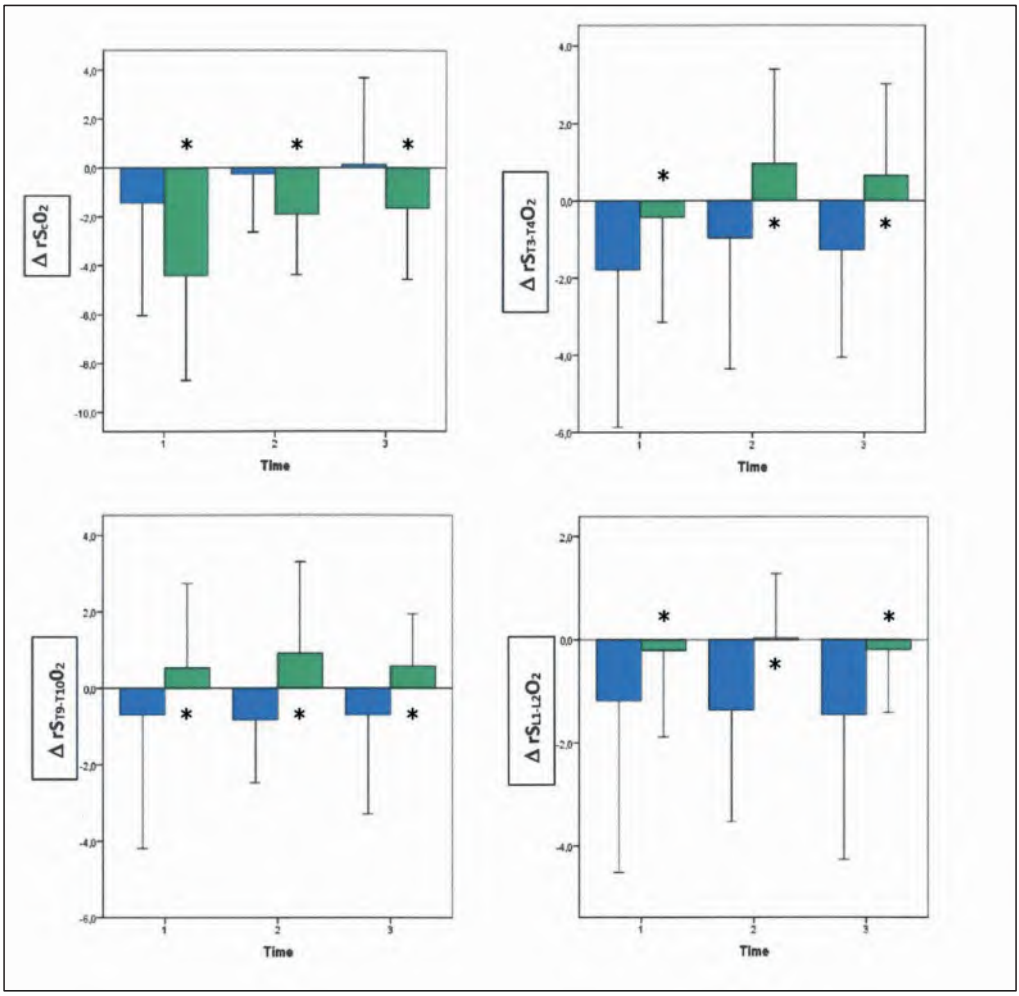

Figure 3: Changes in regional tissue saturation following vasopressor treatment at different time points.

*Mean absolute differences in regional oxygen saturation (ΔrSO_2) after vasopressor administration (posttreatment–pretreatment) on four levels: cerebral (rS_cO_2), T_3–T_4 ($rS_{T3–T4}O_2$), T_9–T_{10} ($rS_{T9–T10}O_2$) and L_1–L_2 ($rS_{L1–L2}O_2$) (Y-axis) at three time points (MAP decrease > 20% from baseline) (X-axis). The blue bars represent mean absolute differences in oxygen saturation following ephedrine treatment, the green bars represent mean absolute differences in oxygen saturation following phenylephrine treatment. Whisker: equals 1 standard deviation. *Significantly different from ephedrine.*

Related to the selected study population, no invasive monitoring such as arterial line and CO measurement was used. Therefore, no firm and final conclusions can be made regarding the vasopressor related effects of changes in CO on rS_cO_2 and $rS_{ps}O_2$. Additionally, the decrease in rS_cO_2 might be related to a direct α_1 adrenergic receptor (AR)-mediated vasoconstriction by the agonistic effect of PE on the α_1-AR-subtype.[2,10]

Similar to Nissen and Meng[3,4], we did not observe any changes in rS_cO_2 following E administration. Since E is known to increase CO[11] and assuming that rS_cO_2 varies with changes in CO[3], this is an unexpected finding. Although E is a mixed α- and β-AR agonist, it exerts primarily a β-AR-mediated effect on vascular smooth muscle cells, resulting in vasodilation.[12] Vasodilation of the cerebral vasculature is mainly β_1-mediated. As E is however most potent on β_2-AR[13,14], this might explain why rS_cO_2 remains unaffected following E administration in patients without carotid artery disease. Of note, in patients with carotid disease on the contrary, a different response was observed following E administration with a significant increase in rS_cO_2.[2]

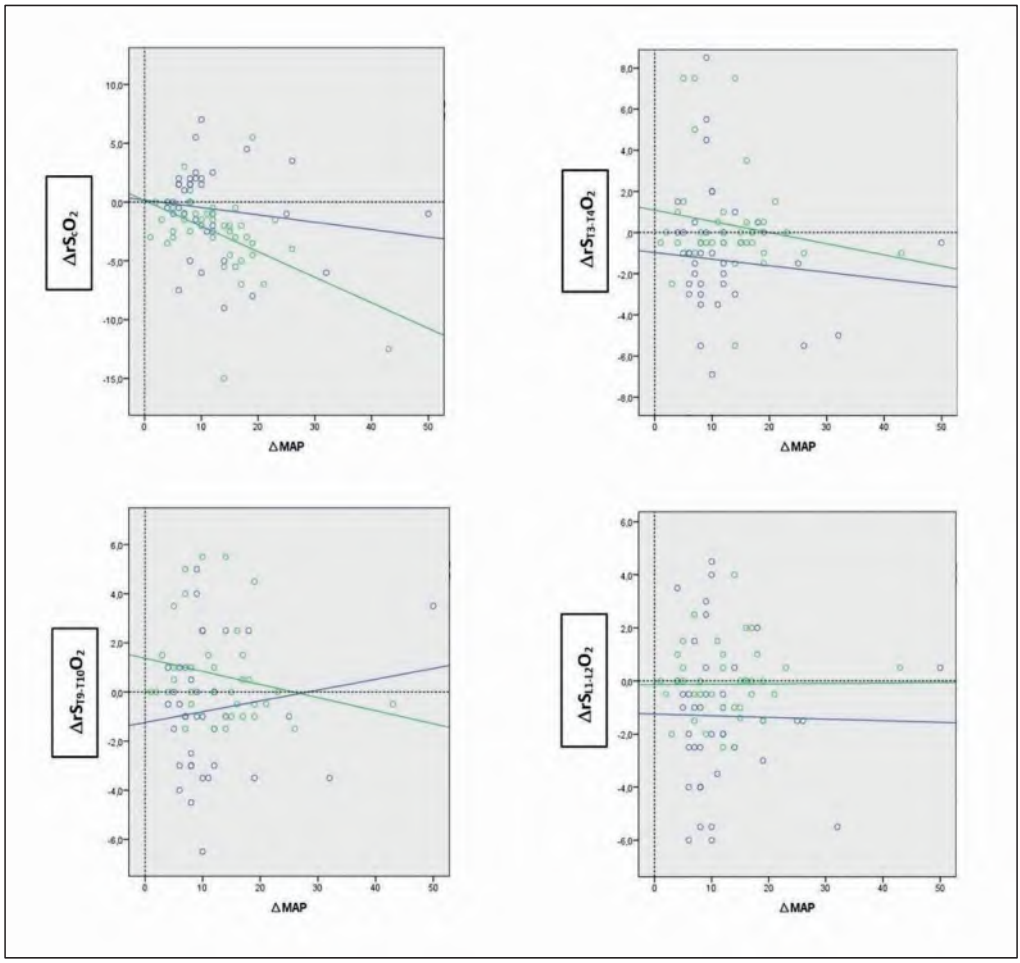

Figure 4: Correlation between MAP and absolute differences in rSO_2.

Correlation between mean arterial pressure and absolute differences in regional oxygen saturation (post-pretreatment). Blue dots represent ephedrine, green dots represent phenylephrine. Δ: absolute difference (post-pretreatment); rS_cO_2: cerebral oxygen saturation; $rS_{T3–T4}O_2$: oxygen saturation at high thoracic level (T_3–T_4); $rS_{T9–T10}O_2$: oxygen saturation at low thoracic level (T_9–T_{10}); $rS_{L1–L2}O_2$: oxygen saturation at lumbar level (L_1–L_2)

Effect of E and PE on paraspinal muscle oxygenation

It is suggested that measurement of the oxygen saturation of the paraspinal musculature reflects blood supply to the spinal cord, thereby providing a potential means for monitoring spinal ischaemia. This notion is based on the collateral network concept.[15] The collateral network is a network of arteries within the paraspinous muscles and the paravertebral tissues, interconnected with the feeding arteries of the spinal cord. According to the collateral network concept, this network

contributes extensively to the blood supply of the spinal cord and might act as a buffer in case of decreased blood supply to the spinal cord. This collateral network concept and the ability of NIRS to guide for spinal oxygen saturation monitoring has gained acceptance in situations of global tissue hypoperfusion with aortic cross-clamping, However, it should be acknowledged that the extent to which this hypothesis might also apply in case of vasoconstrictive pharmacological effects- primarily presenting at the level of the resistance vessels, which are located deeper in the muscular tissue- remains to be confirmed.

Regarding our data on paraspinal muscle oxygenation, we observed an opposite effect on $rS_{ps}O_2$ compared to rS_cO_2: $rS_{ps}O_2$ increased after PE administration whereas a slight, although significant decrease was observed following E administration. From global haemodynamic point of view, pharmacological effects on cardiac performance should be expected to have similar effects on tissue oxygenation throughout the body. The results from the present study underscore that this is not the case. The present study design however does not allow to identify possible underlying mechanisms for these different responses of both drugs at cerebral and paraspinal tissue level. It might be considered that vasoconstriction of the resistance vessels at spinal level results in a steal phenomenon with an increased blood flow to the spinal muscles, which is then reflected in a preserved or even improved tissue oxygenation. In such case, paravertebral tissue oxygenation measurements will not reflect what is happening at spinal level. Alternatively, it may be hypothesized that the opposite effects reflect the different actions of vasoactive drugs on the specific ARs of the local vasculature. Further studies regarding which ARs and subtypes are localized in the human cerebral and spinal vascular bed are needed to explore this hypothesis. This in order to gain more insight in cerebral and spinal haemodynamics following vasopressor administration.

Conclusion

An opposite effect was observed after bolus administration of PE and E on both rS_cO_2 and $rS_{ps}O_2$. PE caused a decrease in rS_cO_2 and an increase in $rS_{ps}O_2$, whereas with E no changes in rS_cO_2 and a decrease in $rS_{ps}O_2$ were observed. These findings indicate that effects of vasoactive agents on regional tissue oxygenation may differ substantially and that observations from one tissue cannot necessarily be extrapolated to other tissues. Further studies are needed to explore the AR distribution in the different vascular beds in order to get a better insight in drug-mediated effects on regional tissue oxygenation.

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Compliance with ethical standards

Conflict of interest
The authors declare that they have no conflict of interest.

Ethical approval
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (University Hospital Ghent Ethics Committee (EC 2016/0644, June 7th 2016, D Matthijs) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent
Written informed consent was obtained from all individual participants included in the study.

Research involving human participants
Protocol: AGO/2016/006, EudraCT number: 2016-001839-13, Clinical Trial number: NCT03767296.

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5

Effect of a Continuous Administration of Dobutamine and Phenylephrine on the Paravertebral Oxygen Saturation

5

Effect of a Continuous Administration of Dobutamine and Phenylephrine on the Paravertebral Oxygen Saturation

In Chapter 4, it was noted that the effect of administering ephedrine and phenylephrine as a bolus did not yield consistent results on $rS_{pv}O_2$. Attempting to obtain a haemodynamic steady state condition, we administered a continuous infusion of vasoactive drugs. In Chapter 5, our objective is to investigate the effect on $rS_{pv}O_2$ of a continuous administration of two vasoactive drugs, phenylephrine and dobutamine, which operate through distinct mechanisms.

Blood pressure control with phenylephrine or dobutamine: a randomized controlled trial comparing effects on cerebral and paravertebral tissue oxygen saturation measured with near-infrared spectroscopy

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Abstract

Preserving haemodynamics is expected to positively affect tissue oxygen saturation. We hypothesized that maintaining mean arterial blood pressure (MAP) (using phenylephrine (PE) or dobutamine (Dobu)) would equally affect regional cerebral and paravertebral tissue saturation (rS_cO_2 and $rS_{pv}O_2$, respectively). Thirty-four patients were randomly assigned to receive either PE or Dobu, in order to keep MAP within 20% of the preoperative value. Their effect on haemodynamics, rS_cO_2 and $rS_{pv}O_2$ at thoracic level T_3-T_4, T_9-T_{10} and lumbar level L_1-L_2 was calculated at different doses. Drug-induced haemodynamic effects differed between groups (ΔMAP: -2%±21 and − 19%±17, ΔCI: -14.6%±14.6 and 24.1%±49.9,
ΔHR: -21%±21 and 0%±16 for PE and Dobu, respectively). Both groups exhibited a significant decrease in rS_cO_2, with a more pronounced decline in the PE group (-14.1%±16.1) compared to the Dobu group (-5.9%±10.6). There were no significant changes at the paravertebral level in either group, but a slight but statistically significant difference was detected between the two groups at T_3-T_4 and L_1-L_2. Current guidelines advocate maintaining adequate systemic blood pressures to prevent spinal cord ischaemia in specific procedures. However, it is still unknown which circulatory supportive drug is more beneficial for maintaining spinal cord perfusion. Our data indicates that, when used for maintenance of blood pressure within a 20% range of preoperative values, neither phenylephrine nor dobutamine affect paravertebral tissue saturation.

Keywords: Cerebral, Dobutamine, Near-infrared spectroscopy, paravertebral, Phenylephrine

Introduction

Impaired tissue oxygenation may negatively affect organ function and thereby jeopardize postoperative outcome.[1] Maintaining adequate blood and oxygen supply is therefore a prime goal in improving postoperative patient's outcome.[2] Looking specifically at the level of the central nervous system, many studies using near-infrared spectroscopy (NIRS) have demonstrated that maintaining stable haemodynamics resulted in a better cerebral oxygen saturation (rS_cO_2).[3,4]

In contrast to the amount of data available for the cerebral circulation, hardly any information has been published on another important part of the central nervous system, namely the spine and the spinal blood circulation. Yet, current guidelines advocate aiming for adequate systemic blood pressures to prevent spinal cord ischaemia in procedures where spinal cord perfusion might be at risk.[5] However, to date, firm experimental data supporting such statement is lacking.

Based on the observations that avoiding cerebral hypoperfusion by maintaining or optimizing blood pressure was associated with improved cerebral tissue oxygenation, we hypothesized that a similar phenomenon would be present at the level of the spine. To address this question, we aimed to evaluate the effects on both rS_cO_2 and paravertebral oxygen saturation ($rS_{pv}O_2$) of two different types of circulatory support by continuous administration of either phenylephrine or dobutamine in order to maintain systemic blood pressure within a range of 20% of its preoperative value. Both phenylephrine and dobutamine are perioperatively used vasoactive drugs, albeit with a different mode of action. Phenylephrine acts as a pure vasoconstrictor, while dobutamine has an inodilating effect. In this study we aimed to assess whether this different mode of action influences effects of hemodynamic support on regional paraspinal tissue oxygenation.

Materials and methods

The trial was registered at ClinicalTrials.gov (NCT03846765) and approved by the University Hospital Ghent Ethics Committee (EC 2018/1510 on January 31st, 2019, D. Matthijs). After written informed consent, 34 patients scheduled for an arterial dilation of the lower limb were included. Exclusion criteria were patients < 18 years old, body mass index > 30 $kg.m^{-2}$, paraplegia or paraparesis, severe valvular disease, atrial fibrillation or flutter, lactation or pregnancy, patients with a pacemaker, patients who previously underwent aortic surgery or required renal replacement therapy, patients who had ACE-inhibitors at the morning of surgery, patients with a difference in systolic blood pressure between left and right arm of at least 20 mmHg, and patients simultaneously involved in another interventional trial.

The included patients were randomly assigned into two groups according to the study medication

administered: in group Dobu, MAP was kept within 20% of the preoperative value with dobutamine, while in group PE, phenylephrine was used.

Preoperative mean arterial blood pressure (MAP_{preop}) was defined during the preoperative visit.

According to the standard anaesthesia protocol, a non- invasive blood pressure cuff was applied. For the purpose of the study, a cardiac output monitor (ClearSight System™, Edwards Lifesciences Corp, Irvine CA, USA) was additionally applied to the patient's contralateral side.

All patients had two intravenous lines at the side of the ClearSight System™: one for administration of intraoperative drugs other than the study medication and crystalloids to support basal fluid need (3 $ml.kg^{-1}.h^{-1}$) and one serving as a dedicated line for continuous administration of dobutamine or phenylephrine.

Eight disposable NIRS sensors (INVOS 5100 C; Medtronic, Minneapolis, MN, USA) were applied: two NIRS sensors were applied bilaterally on the patient's forehead to measure rS_cO_2, one sensor at the deltoid region, ipsilateral to the dedicated line for study drug administration, to measure muscle saturation, and five in paravertebral position on the back of the patient: one at thoracic level T_3-T_4, two bilaterally at both thoracic level T_9-T_{10} and lumbar level L_1-L_2.[e]

Depth of anaesthesia was monitored with a bispectral index (BIS) monitor (BIS™, Covidien, MA, USA). For induction of anaesthesia, all patients received sufentanil (0.15 $\mu g.kg^{-1}$), propofol (1–2 $mg.kg^{-1}$) until loss of consciousness and cisatracurium (0.15 $mg.kg^{-1}$). Tidal volume was preset at 8 $ml.kg^{-1}$ ideal body weight and end-tidal CO_2 was maintained between 35 and 45 mmHg. End tidal oxygen concentration was aimed at 40% and sevoflurane was administered for maintenance of anaesthesia, aiming for a BIS between 40 and 60.

Two minutes following stabilization of haemodynamic and respiratory variables after intubation a continuous phenylephrine or dobutamine infusion was initiated at 0.2 and 2 $\mu g.kg^{-1}.min^{-1}$, respectively. The values of regional tissue oxygen saturation (rS_tO_2) and haemodynamic parameters measured two minutes after the start of the study drug infusion were defined as the start values for this study (T0). At that time point, we considered a minimal residual effect of the laryngoscopy-mediated stress reaction and the pre-oxygenation at F_iO_2 of 1.0, and yet no effect of the circulating study drug.

The dosage scheme is depicted in Fig. 1. Every two minutes, the infusion rate could be adapted based on the MAP as measured by the ClearSight System™. The MAP cutoff was set at 20% decrease from

[e] Location of NIRS sensor application is illustrated on P. 84.

MAP_{preop}. If MAP lowered below this limit, the drug infusion rate was augmented (red arrows on Fig. 1). If MAP was within the normal range (less than 20% decrease from MAP_{preop}), the drug infusion rate remained unchanged and if MAP reached higher values than MAP_{preop}, the drug infusion rate was decreased according to the dosage scheme (green arrows on Fig. 1).

The study was ended after 30 min of continuous drug administration or in case MAP did not increase despite the maximum dose of phenylephrine (1 $\mu g.kg^{-1}.min^{-1}$ for 4 min) or dobutamine (10 $\mu g.kg^{-1}.min^{-1}$ for 4 min).

A personal computer with dedicated acquisition software (Dräger Data Grabber, Dräger AG) was used to

record all haemodynamic and respiratory data.

Statistical analysis

Sample size calculation was based on previous data from our study group.[6] We observed a statistically significant difference of effects on tissue oxygenation between phenylephrine and ephedrine of 2%. To obtain the same difference in response between phenylephrine and dobutamine with standard deviation of 2% for a power of 0.8 and a p-value of 0.05, 17 patients in each observation arm were calculated to be necessary to address the experimental question. Drop- outs were replaced.

The effect of phenylephrine and dobutamine on rS_tO_2 and on haemodynamic parameters was calculated at different dose categories (D2 representing 2 $\mu g.kg^{-1}.min^{-1}$ dobutamine or 0.2 $\mu g.kg^{-1}.min^{-1}$ phenylephrine; D4 representing 4 $\mu g.kg^{-1}.min^{-1}$ dobutamine or 0.4 $\mu g.kg^{-1}.min^{-1}$ phenylephrine, D6 representing 6 $\mu g.kg^{-1}.min^{-1}$ dobutamine or 0.6 $\mu g.kg^{-1}.min^{-1}$ phenylephrine, D8 representing 8 $\mu g.kg^{-1}.min^{-1}$ dobutamine or 0.8 $\mu g.kg^{-1}.min^{-1}$ phenylephrine, D10 representing 10 $\mu g.kg^{-1}.min^{-1}$ dobutamine or 1.0 $\mu g.kg^{-1}.min^{-1}$ phenylephrine). Data were analyzed with SPSS Statistics for Windows Version 28.

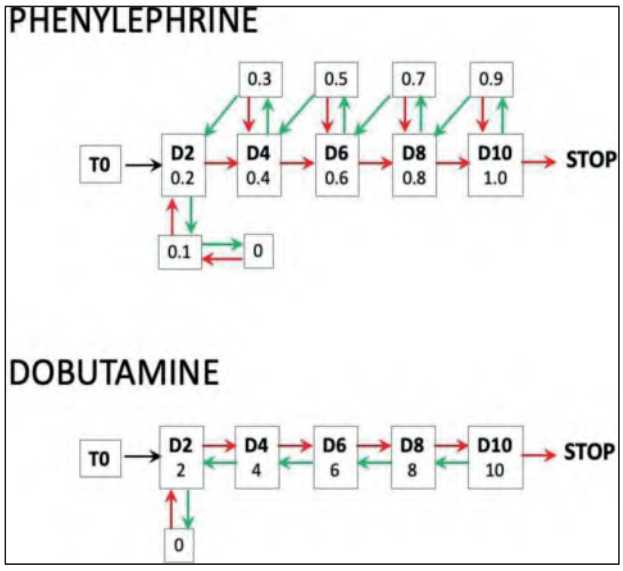

Figure 1: Dosage scheme.

Study protocol in group PE (phenylephrine administration) and group Dobu (dobutamine administration). T0: start of the measurements at 2 min after intubation. Continuous administration is expressed in µg.kg^{-1}.min^{-1}. If MAP > MAP$_{preop}$: green arrow, if MAP < MAP$_{preop}$-20%: red arrow.

Differences in patients' demography and baseline characteristics were calculated using a standard unpaired two- sided Student's t-test. Changes of rS_tO_2 and haemodynamic parameters at different dose categories were compared within and between groups with Wilcoxon signed ranks test and Mann-Whitney U, respectively. Covariates were explored by means of an analysis of covariance.

Results

Thirty-six patients were included in the study. After replacement of two drop-outs (one patient preferred local anaesthesia and another patient was simultaneously enrolled in a surgical interventional trial), 34 patients were randomly assigned to one of the two groups and completed the study. The CONSORT diagram is depicted in Figure 2.

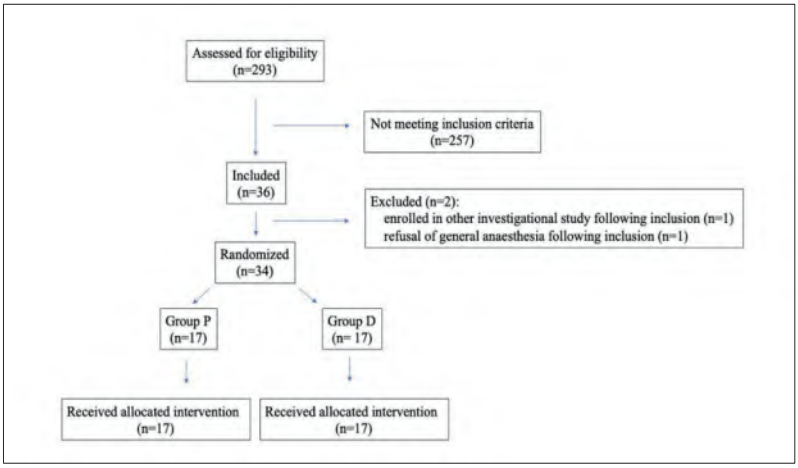

Figure 2: Consort Diagram

Not all patients received study medication at the highest dose categories, because the study was either ended after 30 min or because the maximal dose administration had been reached before the end of the 30 min study period. Only 16 patients in both groups received study medication at D6. At D8 and D10, 13 and 16 patients received the study drug in group PE and group Dobu, respectively. Patient characteristics are presented in Table 1. Body mass index (BMI) differed between the two groups with a lower BMI in group P. Preoperative treatment with angiotensin-converting-enzyme inhibitors differed as well (70% in group PE vs. 35% in group Dobu), but as required by trial inclusion, this therapy was interrupted the day before.

Table 1: Demographic data.

	Group PE (n=17)	**Group Dobu** (n=17)
Gender (male/female)	10/7	12/5
Age (years)	67.5 ± 10.6	71.7 ± 5.8
BMI ($kg.m^{-2}$)	24.5 ± 2.4*	26.8 ± 2.1*
Smoker (yes/no)	13/4	13/4
Beta-lytics (yes/no)	9/8	9/8
CCB (yes/no)	9/8	5/12
ACE-I (yes/no)	12/5*	6/11*

Data are presented as mean ± standard deviation or number (n).
*BMI: body mass index, CCB: calcium channel blocking agents, ACE-I: angiotensin-converting-enzyme inhibitors, *: significant difference between group PE and group Dobu*

Mean pre-op MAP (± SD) was 104 mmHg (± 11) and 104 mmHg (± 13) in the PE and the Dobu group, respectively. Haemodynamic characteristics and rS_tO_2 at the start of the study protocol are presented in Table 2. No statistical differences were observed between groups. F_iO_2 was not identified as a covariate, influencing changes in rS_tO_2.

Table 2: Patients' haemodynamics and regional tissue oxygen saturation at the start of the study.

	Group PE (n=17)	**Group Dobu** (n=17)
MAP (mmHg)	85.0 ± 20	79.0 ± 15
HR (bpm)	66.0 ± 12	64.0 ± 10
CI (L.min^{-1})	4.7 ± 1.7	4.0 ± 1.3
S_aO_2 (%)	99.0 ± 1.3	99.0 ± 2.1
rS_cO_2 (%)	74.3 ± 10.0	74.3 ± 9.2
rS_dO_2 (%)	82.8 ± 7.2	81.4 ± 5.1
$rS_{T3T4}O_2$ (%)	82.8 ± 9.6	81.5 ± 6.3
$rS_{T9T10}O_2$ (%)	75.6 ± 7.5	75.4 ± 9.0
$rS_{L1L2}O_2$ (%)	81.6 ± 7.4	80.7 ± 6.3

Data are expressed as mean ± standard deviation. MAP: Mean arterial blood pressure, HR: heart rate, bpm: beats per minute, CI: cardiac index, S_aO_2: arterial oxygen saturation, S_cO_2: regional cerebral tissue oxygen saturation, rS_aO_2: regional tissue oxygen saturation at deltoid level, $rS_{T3T4}O_2$: regional tissue oxygen saturation at T_3-T_4, $rS_{T9T10}O_2$: regional tissue oxygen saturation at T_9-T_{10}, $rS_{L1L2}O_2$: regional tissue oxygen saturation at L_1-L_2.

Figure 3 and Table 3 present the relative differences compared to the values measured at the start of the study protocol for the haemodynamic data in both groups at the different dose categories. Maintenance of blood pressure was better in group PE. Cardiac index (CI) decreased in group PE while an increase was observed in group Dobu. Heart rate decreased in group PE and remained essentially unchanged in group Dobu. The expected increase in heart rate in group Dobu may have been blunted by the intake of β-blockers by 52.9% of the patients in this group.

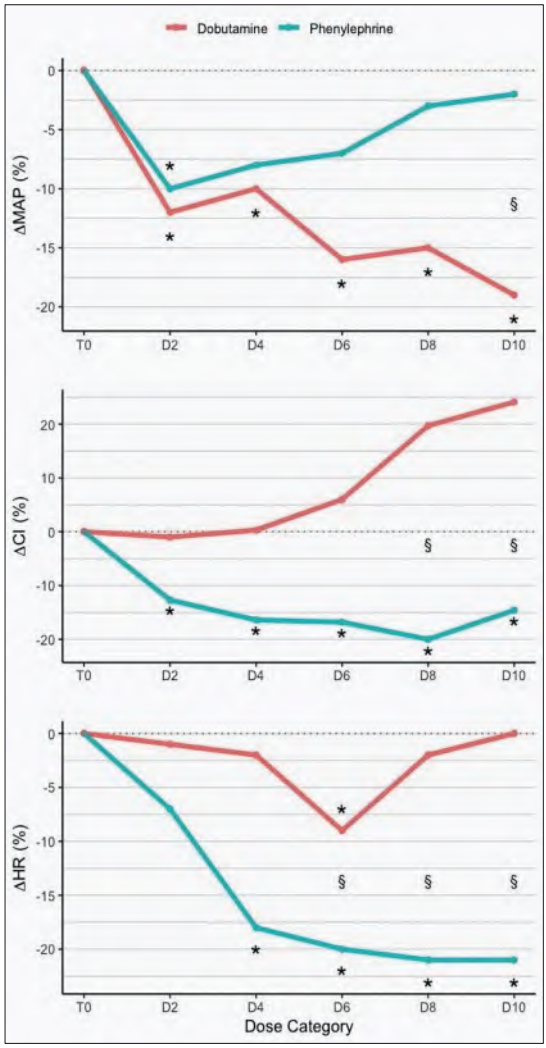

Figure3: Relative differences in haemodynamics at the different dose categories

Group PE: receiving phenylephrine, Group Dobu: receiving dobutamine,
T0: start of the measurements at 2 min after intubation, D2: dose category representing 0.2 µg.kg^{-1}.min^{-1} phenylephrine or 2 µg.kg^{-1}.min^{-1} dobutamine, D4: dose category representing 0.4 µg.kg^{-1}.min^{-1} phenylephrine or 4 µg.kg^{-1}.min^{-1} dobutamine, D6: dose category representing 0.6 µg.kg^{-1}.min^{-1} phenylephrine or 6 µg.kg^{-1}.min^{-1} dobutamine, D8: dose category representing 0.8 µg.kg^{-1}.min^{-1} phenylephrine or 8 µg.kg^{-1}.min^{-1} dobutamine, D10: dose category representing 1 µg.kg^{-1}.min^{-1} phenylephrine or 10 µg.kg^{-1}.min^{-1} dobutamine, Δ: relative difference from start of the study protocol, calculated as (value minus start value)/ start value, MAP: mean arterial blood pressure, CI: cardiac index, HR: heart rate
*§: significant difference between group PE and group Dobu, *: significant difference from start value within the group*

Table 3: Relative differences in haemodynamic data from the start of the study at the different dose categories in both groups.

	Dose category	Δ MAP(%)	Δ CI(%)	Δ HR (%)
Group PE	D2 (n=17)	-10 ± 15*	-12.7 ± 8.0*	-7 ± 14
	D4 (n=17)	-8 ± 19	-16.4 ± 12.2*	-18 ± 13*
	D6 (n=16)	-7 ± 18	-16.8 ± 15.4*	-20 ± 14*§
	D8 (n=13)	-3 ± 22	-20.0 ± 14.5*§	-21 ± 13*§
	D10 (n=13)	-2 ± 21§	-14.6 ± 14.6*§	-21 ± 21*§
Group Dobu	D2 (n=17)	-12 ± 13*	-1.0 ± 31.2	-1 ± 17
	D4 (n=17)	-10 ± 15*	0.3 ± 35.0	-2 ± 24
	D6 (n=16)	-16 ± 23*	6.0 ± 39.5	-9 ± 14*§
	D8 (n=16)	-15 ± 22*	19.7 ± 37.9§	-2 ± 12§
	D10 (n=16)	-19 ± 17*§	24.1 ± 49.9§	0 ± 16§

Group PE: receiving phenylephrine, Group Dobu: receiving dobutamine,
D2: dose category representing 0.2 µg.kg^{-1}.min^{-1} phenylephrine or 2 µg.kg^{-1}.min^{-1} dobutamine, D4: dose category representing 0.4 µg.kg^{-1}.min^{-1} phenylephrine or 4 µg.kg^{-1}.min^{-1} dobutamine, D6: dose category representing 0.6 µg.kg^{-1}.min^{-1} phenylephrine or 6 µg.kg^{-1}.min^{-1} dobutamine, D8: dose category representing 0.8 µg.kg^{-1}.min^{-1} phenylephrine or 8 µg.kg^{-1}.min^{-1} dobutamine, D10: dose category representing 1 µg.kg^{-1}.min^{-1} phenylephrine or 10 µg.kg^{-1}.min^{-1} dobutamine, n: amount of patients, Δ: relative difference from the start of the study, calculated as (value minus start value)/ start value, MAP: mean arterial blood pressure, CI: cardiac index, HR: heart rate
*§: significant difference between group PE and group Dobu, *: significant difference from the start value within the group.*

Figure 4 and Table 4 present the relative differences in rS_tO_2 at the different locations and at the different dose categories. The data shows that the effect of the study drugs on rS_tO_2 differed depending on the measurement area. At the cerebral level, rS_cO_2 significantly decreased in both groups, with a significant lower value in group PE compared to group Dobu at D8 (-12.3%±15.3 and − 5.4%±9.2, for group PE and group Dobu, respectively) and at D10 (-14.1%±16.1 and − 5.9%±10.6, for group PE and group Dobu, respectively). At the muscular and paravertebral levels, no statistically significant changes in rS_tO_2 could be observed within groups. Only at paravertebral level T_3-T_4 and L_1-L_2, a clinically small but statistically significant difference in rS_tO_2 was observed between both groups (at D10 for paravertebral level T_3-T_4 (-1.6%±4.0 and 2.1%±4.4 for group PE and group Dobu, respectively) and for paravertebral level L_1-L_2 at D4 (-1.3%±3.2 and 1.2%±3.2 for group PE and group Dobu, respectively) and at D6 (-1.0%±2.8 and 1.6%±3.4 for group PE and group Dobu, respectively).

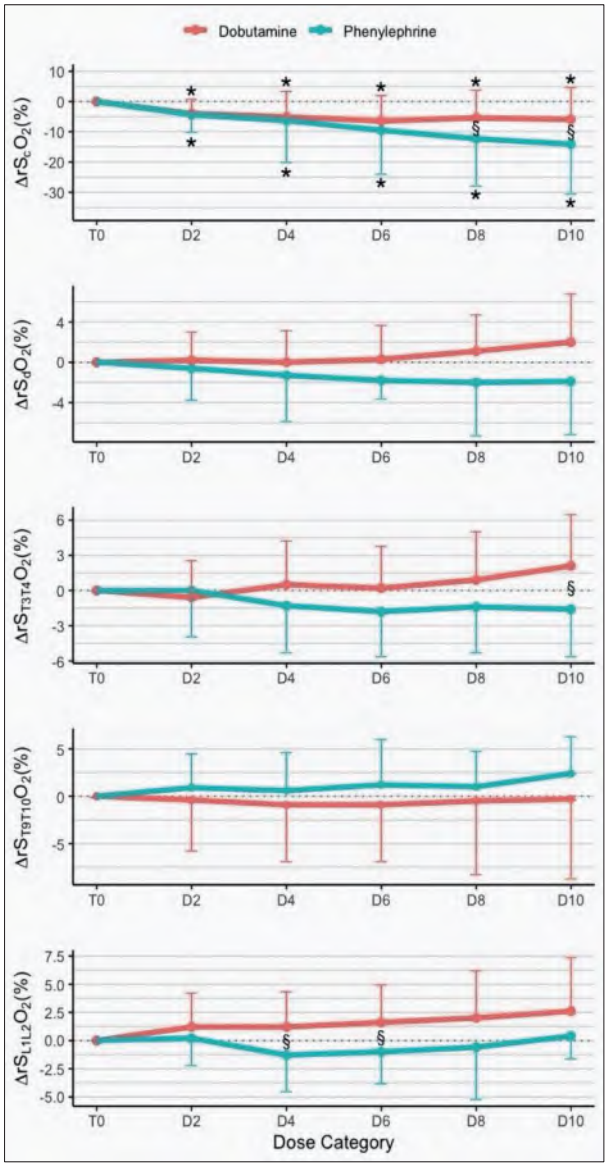

Figure 4: Relative differences in regional tissue saturation at the different locations and dose categories.

*T0: start of the measurements at 2 min after intubation, D2: dose category representing 0.2 µg.kg^{-1}.min^{-1} phenylephrine or 2 µg.kg^{-1}.min^{-1} dobutamine, D4: dose category representing 0.4 µg.kg^{-1}.min^{-1} phenylephrine or 4 µg.kg^{-1}.min^{-1} dobutamine, D6: dose category representing 0.6 µg.kg^{-1}.min^{-1} phenylephrine or 6 µg.kg^{-1}.min^{-1} dobutamine, D8: dose category representing 0.8 µg.kg^{-1}.min^{-1} phenylephrine or 8 µg.kg^{-1}.min^{-1} dobutamine, D10: dose category representing 1 µg.kg^{-1}.min^{-1} phenylephrine or 10 µg.kg^{-1}.min^{-1} dobutamine, Δ: relative difference from baseline, calculated as (value minus start value)/ start value, rS$_c$O$_2$: regional cerebral oxygen saturation, rS$_d$O$_2$: regional oxygen saturation at deltoid level, rS$_{T3T4}$O$_2$: regional oxygen saturation at T$_3$-T$_4$, rS$_{T9T10}$O$_2$: regional oxygen saturation at T$_9$-T$_{10}$, rS$_{L1L2}$O$_2$: regional oxygen saturation at L$_1$-L$_2$. §: significant difference between group PE and group Dobu, *: significant difference from start value within the group.*

Table 4: Relative differences in regional oxygen tissue saturation from the start of the study at the different dose categories in both groups.

	Dose category	Δ rS_cO_2 (%)	Δ rS_dO_2 (%)	Δ $rS_{T3T4}O_2$ (%)	Δ $rS_{T9T10}O_2$ (%)	Δ $rS_{L1L2}O_2$ (%)
Group PE	D2 (n=17)	-4.4±5.7*	-0.6±3.1	0.0±3.9	0.9±3.6	0.2±2.4
	D4 (n=17)	-6.3±13.8*	-1.3±4.5	-1.3±3.9	0.6±4.0	-1.3±3.2§
	D6 (n=16)	-9.5±14.3*	-1.8±4.7	-1.8±3.8	1.2±4.8	-1.0±2.8§
	D8 (n=13)	-12.3±15.3*§	-2.0±5.2	-1.4±3.9	1.0±3.8	-0.6±4.6
	D10 (n=13)	-14.1±16.1*§	-1.9±5.2	-1.6±4.0§	2.4±4.0	0.4±2.0
Group Dobu	D2 (n=17)	-3.9±4.6*	0.2±2.8	-0.6±3.2	-0.4±5.3	1.2±3.0
	D4 (n=17)	-5.1±8.8*	0.0±3.2	0.5±3.8	-0.9±6.0	1.2±3.2§
	D6 (n=16)	-6.4±8.6*	0.3±3.4	0.2±3.6	-0.9±6.0	1.6±3.4§
	D8 (n=16)	-5.4±9.2*§	1.1±3.7	0.9±4.2	-0.5±7.8	2.0±4.2
	D10 (n=16)	-5.9±10.6*§	2.0±4.9	2.1±4.4§	-0.3±8.3	2.6±4.8

Group PE: receiving phenylephrine, Group Dobu: receiving dobutamine,
D2: dose category representing 0.2 µg.kg.min-1 phenylephrine or 2 µg.kg.min-1 dobutamine, D4: dose category representing 0.4 µg.kg.min-1 phenylephrine or 4 µg.kg.min-1 dobutamine, D6: dose category representing 0.6 µg.kg.min-1 phenylephrine or 6 µg.kg.min-1 dobutamine, D8: dose category representing 0.8 µg.kg.min-1 phenylephrine or 8 µg.kg.min-1 dobutamine, D10: dose category representing 1 µg.kg.min-1 phenylephrine or 10 µg.kg.min-1 dobutamine,
n: amount of patients, Δ: relative difference from the start value, calculated as (value minus value at the start of the observation period)/ start value, rS_cO_2: regional cerebral oxygen saturation, rS_dO_2: regional oxygen saturation at deltoid level, $rS_{T3T4}O_2$: regional oxygen saturation at T_3-T_4, $rS_{T9T10}O_2$: regional oxygen saturation at T_9-T_{10}, $rS_{L1L2}O_2$: regional oxygen saturation at L_1-L_2. §: significant difference between group PE and group Dobu, *: significant difference from the start value within the group.

Discussion

In this study, we assessed the effects of continuous administration of phenylephrine and dobutamine on rS_tO_2 at cerebral, muscular, and paravertebral level. Both drugs were used in order to maintain blood pressure within a 20% range of the baseline preoperative values. However, rS_cO_2 decreased significantly, with a more pronounced decrease in the PE group compared to the Dobu group. At the muscular and the paravertebral levels, no differences compared to the start values were observed in neither group, whereas at T_3-T_4 and L_1-L_2 a small but statistically significant difference was observed between both groups.

Most anaesthetists continue to consider the decrease in MAP during induction of anaesthesia as due not only to decrease in systemic vascular resistance but also to cardiac depression.[7] In clinical practice, phenylephrine

and dobutamine are commonly used in cardiovascular compromised patients to support the

circulation and maintain blood pressure within a clinically acceptable range. Both drugs however have a different mode of action. While dobutamine is an inodilator, phenylephrine has a pure vasoconstricting effect which may affect

regional tissue blood flow. Based on the current observations, it seems that neither drug, when used to maintain blood pressure within a 20% range of the baseline preoperative values, negatively affects paraspinal tissue oxygenation.

In the present study, NIRS technology was used to assess non-invasively tissue oxygen saturation. NIRS monitoring is now widely implemented for monitoring of cerebral oxygen saturation.[8] Previous studies already have demonstrated that the type of vasoactive drug may affect rS_cO_2.[9,10] In the present study, we observed a significant decrease in rS_cO_2 in both groups. In group PE, this decrease occurred in the presence of a significantly decreased CI, despite a well-maintained MAP, which is consistent with previous reports.[9,10] On the other hand, rS_cO_2 also significantly decreased in group Dobu, but to a lesser extent compared to group PE (− 5.9% and − 14.1% in group Dobu and group PE, respectively). CI increased during dobutamine administration, but blood pressure could not be restored and even decreased. This could be explained by the findings of Saugel et al.[11] Using a finger-cuff method for measuring haemodynamic variables, they observed that hypotension following induction of anaesthesia with propofol and sufentanil was predominantly caused by arterial vasodilation with a concomitant decrease in systemic vascular resistance, rather than by a reduced myocardial contractility or venous dilation.

During the past ten years, NIRS technology has gained interest as a non-invasive monitor for measuring $rS_{pv}O_2$ to assess the spinal cord blood perfusion.[12] Paravertebrally applied optodes measure the saturation of the underlying, paravertebral tissues. These comprise paravertebral blood vessels, contributing to the collateral network. This network is an extensive vascular clew of arteries and arterioles, all interconnecting with each other and providing blood supply to the spinal cord.[13] Several animal and human studies have demonstrated the usefulness of NIRS-monitoring of the collateral network to detect spinal cord ischaemia in an experimental setting or during thoraco-abdominal aortic surgery.[12,14]

Current guidelines advocate maintaining adequate systemic blood pressures to prevent spinal cord ischaemia in procedures where spinal cord perfusion might be at risk.[5] However, it is still unknown which vasoactive drug is more beneficial for maintaining spinal cord perfusion. Therefore, we applied five optodes in paravertebral position (one at T_3-T_4 and four bilaterally at both T_9-T_{10} and L_1-L_2) to observe the effect on $rS_{pv}O_2$ following a continuous administration of phenylephrine or dobutamine.

As a control, we applied NIRS optodes at the deltoid to measure muscle oxygen saturations.

When used for maintenance of MAP between a range of 20% of its baseline preoperative value, neither drug affected rS_dO_2. Also, at levels $rS_{T3T4}O_2$ and $rS_{L1L2}O_2$ neither drug significantly altered tissue oxygen saturation. Yet, statistically significant differences between groups were observed at certain dose categories. Of note, the differences between groups observed at the different measurements are very small and within the limits of the SD's and therefore, most probably, of minimal or even no clinical relevance.

This absence of clinically relevant effects on tissue saturation at paravertebral level was observed despite important different effects of both drugs on systemic haemodynamics. Indeed, maintenance of MAP was obtained in group PE but not in group Dobu. As expected, CI decreased with phenylephrine but not with dobutamine. A similar response was observed for heart rate.

These data together seem to indicate that neither drug has a clinically relevant effect on paravertebral tissue saturation, when used for maintenance of blood pressure within a 20% range of preoperative values. Alternatively, it might be postulated that NIRS technology when applied at paravertebral level does not allow to diagnose potential effects of the haemodynamic alterations within a 20% range of preoperative MAP on paraspinal tissue oxygen concentration. The design of the present study does not allow to give an answer to this question.

In this respect, it is important to note that according to the findings of a previous study, administration of a bolus of ephedrine or phenylephrine to restore a MAP decline > 20% of baseline values also failed to change $rS_{pv}O_2$ despite substantially rising MAP.[6] However, with strong sympathetic stimulation, leading to a MAP increase of a median of 23% (min – max: 27–97%) a significant decrease in $rS_{pv}O_2$ was observed suggesting that application of NIRS technology at paraspinal level is able to detect tissue saturation changes, provided the induced alterations in MAP are of sufficient magnitude.[15]

Limitations

The spinal cord oxygenation was not directly measured in this study. Instead, NIRS technology was used to measure $rS_{pv}O_2$, reflecting the oxygenation of the paravertebral tissues, from which the vasculature contributes to the collateral network.[12,13]

Arterial partial pressure of carbon dioxide (P_aCO_2) may significantly affect the vascular tone and therefore influence rS_tO_2. In this study, P_aCO_2 data were not obtained, but end tidal CO_2 was measured. As per protocol, end tidal CO_2 was maintained at a level between 35 and 45 mmHg. This data- set does

not contain outliers of end tidal CO_2.

Due to the protocol, not all patients in both groups received study medication at the highest dose category. As a consequence, the study might not be sufficiently powered to obtain a sufficiently high sample size for drawing reliable conclusions at certain dose categories. In group Dobu, more than half of the patients received treatment with beta-blocking agents. This may have impacted their haemodynamic response to dobutamine and, as a result the NIRS-readings in that group.

In conclusion, current guidelines recommend maintaining adequate systemic blood pressures to prevent spinal cord ischaemia in specific procedures. However, it is still unknown which circulatory drug is more beneficial for maintaining spinal cord perfusion. The results of the present study suggest that with both phenylephrine and dobutamine, when used for maintenance of MAP within the 20% range of preoperative baseline, paraspinal tissue oxygen saturation values do not substantially alter throughout the observation period. Further studies will have to elucidate whether this reflects the inability of both drugs - when used in this specific indication – to maintain paravertebral tissue oxygenation or whether this is merely the reflection of insufficient sensitivity of the NIRS technology for detecting drug induced paravertebral tissue oxygen changes.

Acknowledgements

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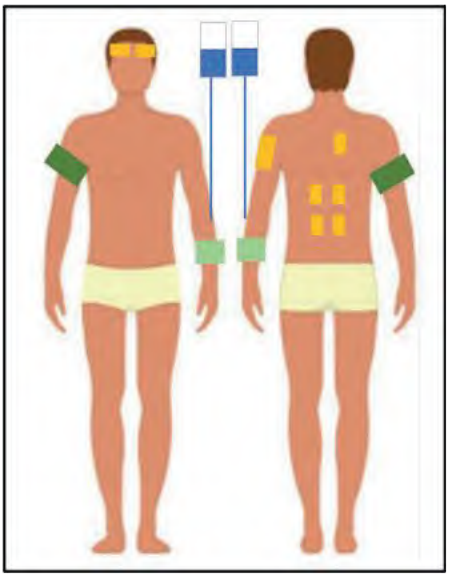
ADDENDUM CHAPTER 5



Location of sensor application.

6

Does the Administration of Vasoactive Agents Interfere with Blood Pressure Measurements?

6

Additional research related to this thesis:

Does the Administration of Vasoactive Agents Interfere with Blood Pressure Measurements?

In the study described in Chapter 5, two distinct types of non-invasive blood pressure monitors were used: the standard intermittent brachial cuff blood pressure monitor and the continuous ClearSight (Edwards Lifesciences) blood pressure monitor. Surprisingly, we observed instances where the blood pressure readings obtained simultaneously from both devices did not consistently match. Given that we employed two different types of vasoactive agents, phenylephrine and dobutamine, our objective was to investigate whether the choice of vasoactive agent had an impact on blood pressure measurements obtained from both monitors. We sought to determine if any discrepancies were influenced by the administration of phenylephrine or dobutamine.

Continuous non-invasive blood pressure measurement with "ClearSight" compared to standard intermittent blood pressure measurement in patients with peripheral arterial disease. Are potential differences influenced by phenylephrine or dobutamine?

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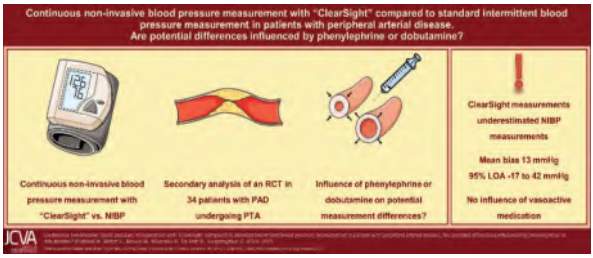
J Cardiothorac Vasc Anesth. 2023;37:2470-4



Abstract

OBJECTIVES To investigate the agreement between continuous non-invasive blood pressure measurement with the ClearSight system (cNIBP-CS) and standard intermittent non-invasive blood pressure measurement (iNIBP) in patients with peripheral arterial disease (PAD). Additionally, the influence of vasoactive medication on potential measurement differences was assessed.

DESIGN Secondary analysis of a randomized controlled trial.

SETTING University Hospital

PARTICIPANTS Thirty-four patients with PAD undergoing percutaneous transluminal angioplasty of the lower limbs.

INTERVENTIONS None

MEASUREMENTS AND MAIN RESULTS Continuous non-invasive blood pressures were measured with the "ClearSight" system and compared to standard intermittent non-invasive blood pressures. Bland-Altman analysis revealed a mean bias of 13 mmHg (± 15) between cNIBP-CS and iNIBP, with 95% limits of agreement ranging from -17 to 42 mmHg. When comparing both medication groups, a similar mean bias was found for phenylephrine and for dobutamine (12 mmHg (± 13) and 13 mmHg (± 13), respectively).

CONCLUSION In this study in PAD patients, cNIBP-CS showed an underestimation of blood pressure compared to iNIBP, both in phenylephrine and dobutamine-treated patients. Larger bias and wider 95% limits of agreement were found compared to previous studies.

KEYWORDS: ClearSight, continuous non-invasive blood pressure measurement, peripheral arterial disease, phenylephrine, dobutamine

Introduction

Patients with peripheral arterial disease (PAD) presenting for surgical revascularization techniques have a high incidence of coronary artery disease and an increased risk of perioperative myocardial injury, which makes them particularly vulnerable to intraoperative hypotension.[1-3] Adequate perioperative hemodynamic monitoring and prompt treatment of hypotension is a key concept for safe anesthesia.[2] With standard intermittent brachial cuff blood pressure measurements, there may be a delay in the detection of hypotension.[4] Continuous blood pressure monitoring may facilitate early detection and prompt treatment of hypotension and therefore be more suited for PAD patients.[5,6]

As direct arterial cannulation may be considered too invasive for blood pressure measurements in minor surgical procedures, a non-invasive continuous blood pressure measurement device such as the ClearSight system (Edwards Lifesciences, Irvine, California, U.S.A) could be an alternative. Reports on the reliability and accuracy of continuous non-invasive blood pressure measurement with the ClearSight system (cNIBP-CS) are conflicting and differ among patient populations. Some studies have shown that cNIBP-CS reliably reflects standard blood pressure measurement in patients with and without PAD, as well as in patients treated with vasopressors.[7-11] However, another study has shown important inaccuracies with Nexfin (Edwards Lifesciences, Irvine, California, U.S.A.), the former ClearSight system, especially in critically ill patients treated with norepinephrine.[12] Moreover, a study in patients with American Society of Anesthesiologists (ASA) physical status I or II reported a poor performance of cNIBP-CS.[13] Finally, a recent review and meta-analysis indicated that devices with finger cuff technologies, such as the ClearSight system, are not interchangeable with the standard in acute care conditions.[14]

The aim of the current study was to investigate the accuracy of cNIBP-CS as alternative for standard intermittent non-invasive blood pressure measurement (iNIBP) in patients with PAD undergoing percutaneous transluminal angioplasty (PTA) of the lower limb. In addition, we analyzed whether potential measurement differences were influenced by two different types of vasoactive agents, phenylephrine and dobutamine.

Methods

In this secondary analysis, data were used from a previous prospective randomized controlled trial (RCT) designed to assess the effect of continuous administration of phenylephrine or dobutamine for hemodynamic support on spinal oxygenation.[15] This previous RCT was approved by the University Hospital Ghent Ethics Committee (EC 2018/1510 on January 31st, 2019) and registered at ClinicalTrials.gov (NCT03846765). The current secondary analysis was approved on February 9th, 2022 (BC 04033 E03). Exclusion criteria were age < 18 years, BMI > 30, severe valvular disease, previous aortic surgery, interarm blood pressure difference of 20 mmHg or more, paraplegia/paraparesis, kidney replacement therapy, pacemaker presence, pregnancy, lactation, ACE-inhibitor use on surgery day, and lack of sinus rhythm on preoperative ECG or at anesthesia induction.

On the day before surgery, non-invasive blood pressure was measured bilaterally on the upper arm with the Spot Vital Signs Device (Welch Allyn, Auburn, New York, U.S.A.), while patients were sitting relaxed in their rooms. The highest of both pressures was used as preoperative baseline value. The ClearSight system was used for cNIBP-CS on the arm with the highest preoperative blood pressure. Contralaterally, iNIBP was measured with the Dräger Infinity Acute Care System (Dräger AG, Lübeck, Germany), at an interval of 2 minutes. All hemodynamic and respiratory data were recorded using a personal computer with dedicated data acquisition software (Dräger Data Grabber, Dräger AG, Lübeck, Germany) and the ClearSight system.

Statistical analysis was performed with SPSS Statistics 28 (IBM, Armonk, New York, U.S.A). Differences in patient characteristics and baseline values between both groups were compared using unpaired Student's t-test for numerical outcome variables with normal distribution, Mann-Whitney U tests for numerical outcome variables without normal distribution and Chi^2-test (all cell counts > 5) for categorical outcome variables. If Levene's test was significant for normal distributed numerical outcome variables, Mann-Whitney U-test was used instead of Student's t-test. The measurement differences between iNIBP and cNIBP-CS were analyzed using Bland-Altman analysis for repeated measurements. A correlation analysis between measurement differences and mean arterial blood pressure was conducted. An alpha-level of 0.05 was considered as statistically significant.

Results

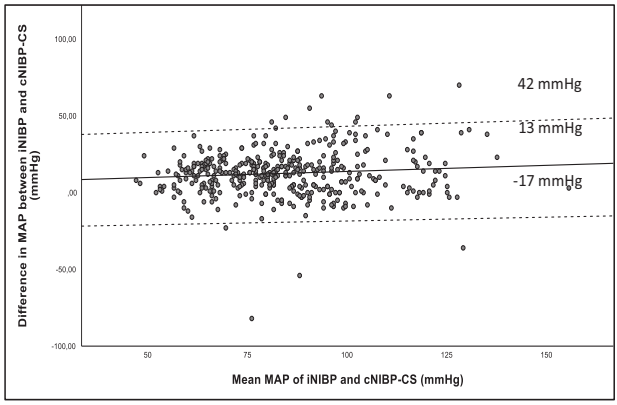
Patient characteristics are listed in table 1. Except for BMI and ACE-inhibitor treatment, no differences were observed between the phenylephrine and the dobutamine group.

Table 1 Patient characteristics

		Phenylephrine group		Dobutamine group		Total	
		N	**%**	**N**	**%**	**N**	**%**
Gender (male/female)		10/7	59%/41	12/5	71%/29	22/12	65%/35%
Smoking		13	77%	13	77%	26	77%
Diabetes		5	29%	8	47%	13	38%
Beta-blocker		9	53%	9	53%	18	53%
Calcium channel blocker		9	53%	5	29%	14	41%
ACE-inhibitor*		12	71%	6	35%	18	53%
		N	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
Age (years)		17	67.5 (10.6)	17	71.7 (5.8)	34	69.6 (8.7)
Weight (kg)		17	71 (10)	17	75 (10)	34	73 (10)
Length (cm)		17	170 (9)	17	167 (9)	34	169 (9)
BMI (kg/cm^2)*		17	24.5 (2.4)	17	26.8 (2.1)	34	25.6 (2.5)

*Statistically significant difference between groups. N = number of patients; ACE = Angiotensin converting enzyme; BMI = body mass index; SD = standard deviation. Bland-Altman analysis for agreement of both blood pressure measurement methods is presented in figure 1.

a.



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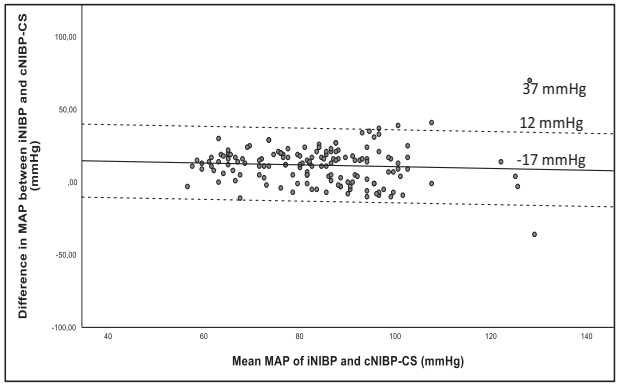

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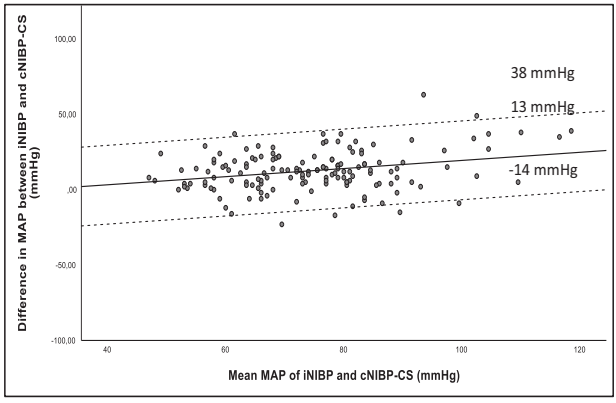

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Figure 1: Bland-Altman plots of agreement between continuous non-invasive blood pressure measurement with the ClearSight system and standard intermittent non-invasive blood pressure measurement for **a.** all measurements **b.** measurements in the phenylephrine group and **c.** measurements in the dobutamine group.

The bias is represented by a solid line, the 95% LOA by dashed lines.

MAP = mean arterial blood pressure; cNIBP-CS = continuous non-invasive blood pressure measurement with the ClearSight system; iNIBP = standard intermittent non-invasive blood pressure measurement; LOA = limits of agreement.

Including all measurement points (n=392), a mean bias of 13 mmHg (± 15) was observed between cNIBP-CS and iNIBP, with 95% limits of agreement (LOA) ranging from -17 to 42 mmHg. When comparing the phenylephrine group to the dobutamine group, a mean bias was observed of 12 mmHg (±13) for phenylephrine and of 13 mmHg (±13) for dobutamine, with 95% LOA of -17 to 37 mmHg and -14 to 38 mmHg, respectively. The difference between both blood pressure measuring methods was statistically significant ($p<0.001$). There was, however, no statistically significant difference between the phenylephrine group and the dobutamine group ($p = 0.793$).

We observed some proportional increase in measurement differences towards higher mean arterial pressures (MAP), as seen in figure 2. To further investigate this phenomenon, we conducted a Spearman's correlation test. A positive correlation was observed ($r_S= 0.340$, $p < 0.001$).

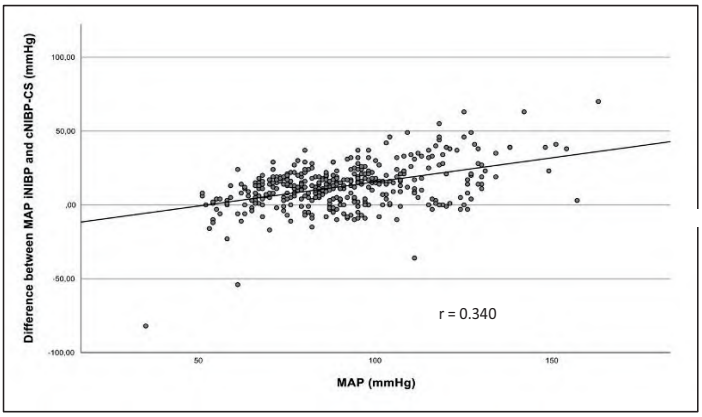

Figure 2: Correlation between measurement differences and MAP.

MAP = mean arterial blood pressure; cNIBP-CS = continuous non-invasive blood pressure measurement with the ClearSight system; iNIBP = standard intermittent non-invasive blood pressure measurement; r = Spearman's correlation coefficient.

Discussion and conclusion

This retrospective observational study, comparing cNIBP-CS to iNIBP, observed a mean bias (± SD) of 13 mmHg (± 15) along with a wide 95% LOA ranging from -17 to 42 mmHg in patients with PAD undergoing PTA of the lower limbs. Blood pressure seemed to be underestimated by cNIBP-CS compared to iNIBP.

In comparison to earlier studies, also using standard non-invasive blood pressure measurement at the brachial level as the reference method, our study revealed a larger mean bias and standard deviation. Previous studies reported a mean bias of -3.8 mmHg (± 8.1) in breast cancer surgery[16], of

0.68 mmHg (± 13.76) for parturients undergoing caesarean section[17], of -0.9 mmHg (± 11.0) in patients undergoing shoulder surgery in the beach chair position and of -4.9 mmHg (± 11.8) in patients undergoing shoulder surgery in the supine position.[18]

It should, however, be noted that in a Bland-Altman analysis not only the mean bias value should be considered but also the data distribution. A larger standard deviation and wide limits of agreement indicate a greater variability or inconsistency in the differences between the two methods being compared. This implies less agreement between the methods, even with a very small mean bias close to zero.

We do not have a straightforward explanation for the larger bias between both measurement methods in our study. However, the previous reports were in patients without any vascular compromise, whereas the current observations were obtained in PAD patients. The applicability of cNIBP-CS in patients with PAD remains a subject of debate. In previous research, PAD was often an exclusion criterion for comparison studies.[19-21] However, several studies have included patients with known or presumed PAD. An important difference to our study is that these studies compared cNIBP-CS to invasive arterial blood pressure measurement. Two studies in carotid endarterectomy patients found mean biases of 4 mmHg (± 7.8) and -6.8 mmHg (± 6.7).[7,9] A study in patients undergoing transcatheter aortic valve replacement identified a mean bias of 0.3 mmHg (± 7.4)[8] and a study in patients undergoing unspecified cardiovascular surgery found a mean bias of -9.1 mmHg (± 7.3).[11] In patients with PAD Fontaine stage ≥ II, scheduled for vascular surgery, Klose et al. found a mean bias of 2.46 mmHg (± 18.24), which is the highest standard deviation observed in our literature search. Moreover, they observed a wider distribution in patients with MAP higher than 105 mmHg: a mean bias 17.16 mmHg (± 19.11).[2] Of note, this study was conducted with the previous ClearSight technology, Nexfin.

Other factors than PAD can affect blood pressure measurement accuracy, such as the use of vasoactive medication. For this study, we hypothesized that administration of phenylephrine or dobutamine might differently affect potential measurement discrepancies between iNIBP and cNIBP-CS, given their different mode of action on the systemic vascular resistance (SVR). Phenylephrine is a potent vasoconstrictor due to its strong α-adrenergic activity, increasing blood pressure by elevating SVR.[22] In contrast, dobutamine is an inodilator with varying dose-related effects on peripheral vasculature. Dobutamine directly stimulates β_1-receptors and α_1-receptors, but has weak affinity for β_2-receptors, leading to an increase in stroke volume and cardiac output. The counterbalancing effects of α_1-mediated vasoconstriction and β_2-mediated vasodilatation result in a net effect of mild

vasodilation at lower doses and vasoconstriction in doses above 15 µg/kg/min.[22] Upon comparing the phenylephrine group to the dobutamine group in our study, we found a mean bias of 12 mmHg (± 13) with 95% LOA -14 to 37 mmHg and of 13 mmHg (± 13) with 95% LOA -14 to 39 mmHg, respectively. One study in cardiac surgery patients investigated the impact of changes in SVR after administration of phenylephrine or ephedrine on the measurement differences between cNIBP-CS and invasive arterial blood pressure. The mean biases for low, normal, and high SVR states were 6.9 mmHg (± 6), -5.2 mmHg (± 8.5) and -7.1 mmHg (± 7.9), respectively.[10] A study in critically ill patients on the ICU, using the earlier Nexfin system, showed a mean bias of 6 mmHg (± 13) for patients receiving norepinephrine; however, this was comparable to the patients who did not receive vasoactive agents.[12]

In the current study, we compared cNIBP-CS to iNIBP. The ClearSight system uses a "volume clamp technique" and "Physiocal method". With an inflatable finger cuff, containing a plethysmograph and sensors, it detects blood volume changes in the finger. Cuff pressures are continuously adjusted to maintain a constant arterial diameter. Continuous recording of the finger cuff pressure is then converted into a brachial artery pressure waveform by using filtering and transfer functions.[23,24] The "Physiocal method" determines the artery's "unloaded volume" and adjusts for vascular tone changes.[23]

Standard iNIBP devices employ the oscillometric method via an inflatable cuff placed on the upper arm. This technique measures changes in cuff pressure that occur when blood flow through the brachial artery resumes during cuff deflation. The amplitude is near maximal when the cuff is deflated at MAP. Systolic and diastolic pressures are then estimated using algorithms unique to each manufacturer and should not be considered as accurate as MAP.[25] Accuracy of iNIBP can further be influenced by various factors such as incorrect cuff size, patient movement, external pressure at the level of the cuff, arterial stiffness, arrhythmias etc.[26]

While direct arterial cannulation is considered the true gold standard, its use is typically confined to long-lasting surgeries and high-risk patients. It is widely considered as too invasive for our study population, undergoing minor vascular surgery. Moreover, some researchers consider non-invasive brachial blood pressures to represent central blood pressures more accurately compared to invasive radial blood pressure measurements.[27,28]

In our study, we focused on the mean arterial pressure for several reasons. Firstly, MAP is the most important determinant of organ perfusion when compared to systolic and diastolic pressures.[29] Secondly, with the oscillometric method employed in iNIBP, MAP is the measured parameter, while systolic and diastolic pressure are calculated from this measurement.

Our study has several limitations that should be acknowledged when interpreting the results. Although we collected a total of 392 measurement points to compare, these were repeated measurements in a relatively small study population of only 34 patients, with 17 patients in each medication group. This limits the generalizability of our findings.

Secondly, we observed significant outliers in both directions of which we could not identify a clear cause. These outliers were not caused by patient movements (actively nor passively by surgeons), recalibrations of the devices nor objectifiable measurement failure. Thirdly, we used both arms for the measuring devices since inflation of the iNIBP cuff would have compromised the simultaneous reading of the cNIBP-CS. The preoperative interarm difference, measured bilaterally with iNIBP, was 4 mmHg (± 3) in the entire group. When comparing the phenylephrine group to the dobutamine group, those were 3 mmHg (± 3) and 4 mmHg (± 2), respectively. While these interarm differences in the current study can be considered as minimal, the potential differences need to be taken into account when assessing blood pressure systems with the investigated device on one arm and the standard comparator in the contralateral arm.

In conclusion, in this study of 34 patients with PAD undergoing PTA of the lower limb, continuous non-invasive blood pressure measurement with the ClearSight system underestimated blood pressure compared to standard intermittent non-invasive blood pressure measurement. We found larger biases and wider limits of agreement than most previous studies, suggesting less agreement in our study population. Whether these findings are caused solely by the PAD or potentially other confounding factors are involved, remains to be established.

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7

Discussion

7

Discussion

Endovascular or open thoraco-abdominal aneurysm repair procedures entail a significant risk of paraparesis and paraplegia because these procedures inherently compromise blood flow to the spinal cord.[1] Not only is this complication an independent risk factor for mortality , but it also severely debilitates patients, demanding exceptional care and substantial financial resources from the community.[2]

Given these challenges, it is crucial for all stakeholders involved to have access to a rapid and reliable method for detecting SCI, to enable precise and real-time adjustments in haemodynamic management and interventions aimed at enhancing spinal cord perfusion.

Currently, monitoring MEPs serves as the gold standard for reliably detecting SCI. However, MEP signals are affected by anaesthetics and, therefore, necessitate personalized anaesthetic plans.[3] Furthermore, interpreting these signals requires specialized healthcare personnel, and MEP monitoring is not feasible for awake patients due to its painful nature.[4]

Given the challenges associated with MEP monitoring, there has been a growing interest in NIRS as a non-invasive and easily interpretable method for detecting SCI. Numerous studies, both in animals and humans, have demonstrated the reliability of NIRS in detecting SCI.[5] Moreover, it has been shown that changes in blood pressure can affect NIRS values, measuring the saturation of the paravertebral CN.[6–8]

In ***this thesis***, our primary focus was to investigate whether increases in blood pressure, either occurring through endogenous stimulation or induced by medication, equally affect paravertebral NIRS values and to what extent. Additionally, we aimed to examine whether a specific type of vasoactive medication administered to restore normotension is more effective in preserving the saturation of the paravertebral collateral network.

The studies implemented in this thesis were conducted in vascular burdened patients, all of whom were scheduled for a lower limb arterial dilation procedure. This patient population was selected because the surgical procedure (i.e., needle puncture) is minimally invasive and does not typically trigger a pronounced sympathetic-mediated haemodynamic response. Consequently, all patients experienced a condition of hypotension following anaesthesia induction, necessitating the use of vasoactive drugs to restore blood pressure. In this context, since there was no surgery-induced sympathetic reaction, it was possible to examine the isolated effects of vasoactive drugs on $rS_{pv}O_2$ during normotension.

In ***chapter 3*** we observed a significant decrease in $rS_{pv}O_2$ during the sympathetically mediated stress response following laryngoscopy, with reductions of 5% at T9-T10 and 3% at L1-L2.[9] This aligns with the results of another study[10] that observed the effect of ephedrine, an α- and ß-sympathomimetic drug, on $rS_{pv}O_2$. Both an endogenous sympathetic reaction and ephedrine appeared to have a negative effect on $rS_{pv}O_2$, despite an increase in MAP in both situations (24 mmHg and 12 mmHg, respectively). These results also indicate that the greater the increase in MAP, the more negatively $rS_{pv}O_2$ is affected. This finding is intriguing, especially considering that increasing blood pressure is a fundamental approach to prevent and treat SCI by enhancing spinal cord perfusion.[11] It raises the question whether different types of vasoactive drugs might have varying effects on $rS_{pv}O_2$.

In ***chapter 4*** we demonstrated that a bolus of phenylephrine induced a significant, though clinically irrelevant, increase in $rS_{pv}O_2$ compared to a bolus dose of ephedrine. This result may reflect the impact of phenylephrine on CO. On one hand, phenylephrine may increase CO by mobilizing the unstressed volume, which is the portion of blood not actively participating in the patient's circulatory system, potentially leading to increased preload.[12,13] On the other hand, phenylephrine might negatively affect CO by increasing afterload, venous resistance, or both. Ultimately, the overall effect of phenylephrine on CO is dependent on various physiological variables like heart rate, fluid status, and the position on the Frank-Starling curve, as well as drug-related variables including dosage and individual tissue sensitivity.[12,14]

Still, one might expect that ephedrine, a well-known inotropic drug, would also positively affect $rS_{pv}O_2$. Based upon the results of this study, this assumption cannot be confirmed. However, it is

important to note that providing a precise explanation for the exact mechanism remains speculative, especially since in that study we did not measure CO.

Another hypothesis explaining the phenylephrine-related increase in $rS_{pv}O_2$ might be its vasoconstrictive effect on the spinal resistance vessels, deviating the blood flow to the spinal muscles. When this is the case, $rS_{pv}O_2$ does not reflect the situation at the spinal level.

In ***chapter 5*** the use of a non-invasive CO monitor, ClearSight (Edwards Lifesciences, Irvine, California, U.S.A), was implemented.[15] Despite the differential effects on CO (24% ± 50% for dobutamine and -15 % ± 15 for phenylephrine), no significant effect on $rS_{pv}O_2$ could be observed. There was only a small statistically significant difference between dobutamine and phenylephrine at T_3-T_4 and L_1-L_2. This could be attributed to the fact that not all patients in this study reached the higher dose categories. Therefore, these data lack the statistical power to draw reliable conclusions. Nevertheless, this raises the question whether factors other than haemodynamics may affect rS_tO_2.

Regarding the conducted studies, a potential drug-related effect on metabolism cannot be excluded. However, taking into account the dose and duration of the administered drugs is very limited, it seems not very likely that these would have induced a substantial change in metabolism and oxygen consumption during the current observation periods. Moreover, if such mechanism would have played a substantial role, a similar effect on tissue oxygenation would be expected in the different regions studied, which was not the case in our observations.

It also has to be acknowledged that vasoactive agents may differently affect arterioles, capillaries and venules.[16]

One possible explanation for the differing effects of vasoactive drugs on $rS_{pv}O_2$ may be related to their distinct actions on adrenergic receptors in the local (para)spinal vasculature. However, the current methodology does not enable commentary on or identification of the extent to which each compartment is involved in the observed NIRS changes across the different observed regions. Further research is needed to investigate the specific types and subtypes of adrenergic receptors located in the CN.

It is important to recognize that in both studies (Chapters 4 and 5), vasoactive medications were administered to preserve normotension. It is conceivable that in hypertensive situations, the effect on $rS_{pv}O_2$ could be more pronounced. Additionally, it is plausible that the limited impact on $rS_{pv}O_2$ is due to the presence of intact spinal cord autoregulation, which maintains a constant spinal cord blood flow.

Another possible reason for the minor changes in $rS_{pv}O_2$ could be that NIRS monitoring may lack the sensitivity to accurately detect these effects. The true value of NIRS in evaluating SCI through the

measurement of $rS_{pv}O_2$ can only be determined by a comparison with the gold standard for SCI monitoring, which is MEPs. This is currently being investigated in a randomized, multicenter observational trial that involves patients scheduled for aortic repair at three tertiary referral centers.[17] As of now, we are still awaiting the results.

It has to be acknowledged that observations made in the studies underscore the important role of the reliability of the measurement techniques in the reading of data and hence the reliability of the observations and conclusions.

Limitations

This work did not intend to examine the drug-related effects on $rS_{pv}O_2$ in patients with T(A)AA, but only focus on the isolated effect of vasoactive drugs on $rS_{pv}O_2$ in normotensive conditions.

It is also important to note that in this research, we did not directly measure spinal cord oxygenation. Instead, we utilized NIRS to measure the rS_tO_2 of the CN, as a surrogate marker for spinal cord oxygenation.

Commercially available NIRS monitors only measure rS_tO_2 at a depth of 2.5 to 3 cm, which raises the question of whether the measured values represent the oxygenation of the subcutaneous fatty tissue rather than the underlying collateral network. Therefore, patients with a BMI exceeding 30 were excluded to minimize the potential influence of adipose tissue on rS_tO_2.

To date, several reports have observed that changes in cutaneous circulation affect cerebral NIRS measurements.[18] Indeed, despite the spatial resolution's ability to reduce the interference on rS_tO_2 of more superficially located layers, it does not eliminate all outer layers. However, it is still unknown to what extent the measured values are influenced by extracranial contamination (rS_tO_2 of skin, temporal muscle, skull, dura, frontal sinus, cerebrospinal fluid). It is well known that adipose tissue reduces the penetration of light, while in thinner individuals, optical density is higher.[19] Until now, the impact of 'extra-collateral' contamination, referring to the influence of measured rS_tO_2 from non-targeted biological tissues such as skin and adipose tissue in situations where the CN is the region of interest, has remained an entirely unexplored domain. Also, the effect of myoglobin on NIRS measurements is still unknown.[20] However, in analogy with NIRS derived rS_cO_2, it seems plausible that $rS_{pv}O_2$ readings are also influenced to some degree by 'extra-collateral' contamination. Thus, the paravertebrally measured saturation may not entirely reflect the oxygenation status of the CN.

Furthermore, the utilization of NIRS has gained acceptance as a monitoring tool for detecting SCI in situations involving aortic cross clamping and concurrent distal hypoperfusion.[5] Whether NIRS is

sensitive enough to reliably detect and evaluate the differential effects of vasoactive medication on the resistance vessels of the CN remains to be confirmed.

All the studies conducted in this thesis were carried out on patients already burdened with vascular issues and concurrent diseases like diabetes, atherosclerosis, and more. Additionally, the majority of these patients were being treated with antihypertensive medications. It is plausible that the vascular issues and the medications might have had an effect on the vascular wall, potentially interfering with the changes in $rS_{pv}O_2$.

It also has to be acknowledged that the studies presented in Chapter 3 and Chapter 4 were conducted in the same study population. In this light it may be possible that individual patient characteristics and behavior may have influenced the results.

The presence of inherent microangiopathy may have masked or modulated the effects of the drugs on $rS_{pv}O_2$. This consideration also applies to the period of microvascular recovery that follows each inflation of the finger cuff, when employing the ClearSight system for blood pressure measurements in one of our studies.[15] Notably, we have observed that ClearSight tended to underestimate MAP readings when compared to the standard NIBP measurements, with wide limits of agreement.[21]

For the purpose of the studies, no imaging technology was used to identify the specific anatomy of the patient's spinal cord blood supply. Therefore, the individual anatomy and extent of the collateral network, together with its specific contribution to the spinal cord blood supply is unknown in this patient population and may have affected the results of our research.

Conclusion

The current strategy for treating or preventing SCI during aneurysm surgery recommends maintaining adequate systolic blood pressures to preserve appropriate spinal cord perfusion. Spinal cord oxygenation can be indirectly measured using NIRS. However, how $rS_{pv}O_2$ is affected by physiologic responses and vasoactive medication remains a largely unexplored domain of research.

We have observed that endogenous sympathetic activation negatively affects $rS_{pv}O_2$, but whether this has clinical relevance is yet to be determined. In contrast, drug-mediated blood pressure increases do not significantly affect $rS_{pv}O_2$, even in conditions where CO is significantly altered. This raises questions about the sensitivity of NIRS monitoring in the paravertebral region in the specific situation of detecting differential effects of vasoactive drugs during normotensive conditions.

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8

Future Perspectives

Caelum non est finis.

The sky is not the limit.

Ellison Onizuka, NASA astronaut
(1946-1986)

8

Future Perspectives

It is widely recognized that maintaining adequate spinal cord perfusion through the augmentation of blood pressure is the corner stone of treatment and prevention of spinal cord ischaemia. The question arises which vasoactive agent is most effective in preserving spinal cord perfusion.

The use of NIRS as a monitoring tool for spinal cord perfusion has been proven to be both feasible and reliable for detecting the occurrence of spinal cord ischaemia in clinical situations as well as in experimental animal studies. However, several unresolved issues persist.

Based on the findings of this thesis, it appears that studying the effects of vasoactive medications on $rS_{pv}O_2$ under normotensive conditions may not be ideal.

Therefore, it should be of interest to examine their effect on $rS_{pv}O_2$ in situations where hypertension is critical to ensure adequate spinal cord perfusion pressure. The context of open surgery with clamping of the aorta with or without the installation of a left heart bypass is ideal for studying the effect of drug-induced maintenance of spinal cord perfusion. On the other hand, TEVAR procedures are often associated with delayed paraplegia. Therefore, it could be of interest to continue monitoring the spinal oxygen saturations during the postoperative period, even in the awake patients to study the relation between the NIRS measurements, (drug mediated) blood pressure and the patient's clinical condition. Additionally, it would be of interest to study if vasoactive medication differently affects $rS_{pv}O_2$ in patients with and without β-lytic therapy.

Another outstanding challenge is the extent to which surrounding tissues, not being part of the CN, can influence NIRS readings.

Relating NIRS readings to MEPs in clinical settings would also be valuable. This approach would allow us to determine the threshold at which a decrease in $rS_{pv}O_2$ poses an effective risk of spinal cord ischaemia.

Due to the lack of data on how the anatomy of the CN changes in patients with aortic aneurysms, it would be interesting to investigate this through imaging techniques. Additionally, it would be intriguing to be able to study the extent to which the CN adapts following aortic surgery.

At experimental level, a validation of the technology should include comparisons with a means of directly measuring spinal cord blood flow where potential changes in spinal cord blood flow using different therapeutic interventions (pharmacological, spinal drainage, etc.) are directly assessed and compared to the response of NIRS.

In addition, this experimental setting is also well-suited for studying the spinal cord autoregulation.

9

Summary

9

Summary
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Summary

Despite new insights and surgical techniques, spinal cord ischaemia still remains a feared complication after surgical repair of the thoraco-abdominal aorta. During this procedure, it is therefore necessary to monitor the perfusion of the spinal cord. Motor evoked potentials are still the gold standard for detecting spinal cord ischaemia. However, this monitoring technique requires specifically experienced personnel, demands an adjustment of the anaesthetic management and is also painful for the awake patient. Over the last decade, a new, non-invasive monitoring technique has gained popularity, namely near-infrared spectroscopy. This technique measures regional tissue saturations of the underlying tissues and has been extensively studied as a monitor for cerebral oxygenation. When the optodes are applied paravertebrally, they measure the saturation of the collateral network, a surrogate for the spinal cord blood supply.

Maintaining adequate perfusion pressure is the cornerstone of the treatment and prevention of spinal cord ischaemia. But it has also been reported that vasoactive drugs, depending on the type, can exert a differential effect on saturation values, as is observed at the cerebral level.

In this thesis it was first investigated whether an endogenous, sympathetically mediated catecholamine release has an influence on the paravertebral measured tissue saturations. This stress-mediated decrease is significant and more pronounced than the investigated effects of a bolus administration (ephedrine and phenylephrine) or a continuous infusion (phenylephrine and dobutamine) on paravertebral tissue saturations. To what extent this offers clinical relevance remains to be further investigated. In contrast, the administration of vasoactive medications, with the aim of maintaining normotension, produces little or no change in paravertebral saturations, even in situations of significantly altered cardiac output. This raises the question whether the technique of near-infrared spectroscopy is sensitive enough to detect drug effects of vasoactive medication on paravertebral saturations during normotensive conditions.

Samenvatting

Ondanks nieuwe inzichten en chirurgische technieken blijft ruggenmergischemie nog steeds een gevreesde complicatie na chirurgisch herstel van de thoraco-abdominale aorta. Tijdens deze procedure is het dan ook noodzakelijk om de bevloeiing van het ruggenmerg te monitoren. Nog steeds zijn Motor Evoked Potentials de gouden standaard om ruggenmergischemie te detecteren. Echter deze monitor techniek vereist hierin specifiek ervaren personeel, dwingt tot een aanpassing van het anesthetisch beleid en is bovendien pijnlijk bij de wakkere patiënt. Het laatste decennium heeft een nieuwe, niet-invasieve monitor techniek aan populariteit gewonnen, namelijk de nabij-infraroodspectroscopie. Deze techniek meet de regionale weefselsaturaties van de onderliggende weefsels en is reeds uitvoerig bestudeerd als monitor voor de cerebrale oxygenatie. Wanneer de optoden paravertebraal worden aangebracht meten ze de saturatie van het collateraal netwerk, een surrogaat voor de ruggenmergbevloeiing.

Het behoud van een adequate perfusiedruk is de hoeksteen van de behandeling en preventie van ruggenmergischemie. Maar het is ook beschreven dat vasoactieve geneesmiddelen, afhankelijk van het type, een verschillend effect kunnen uitoefenen op de saturatiewaarden, althans op cerebraal niveau.

In deze thesis wordt eerst nagegaan of een endogene, sympathisch gemedieerde catecholaminevrijstelling een invloed heeft op de paravertebraal gemeten weefselsaturaties. Deze stress-gemedieerde daling is significant en meer uitgesproken dan de onderzochte effecten van een bolustoediening (ephedrine en phenylephrine) of een continu infuus (phenylephrine en dobutamine) op de paravertebraal gemeten weefselsaturaties. In welke mate dit klinische relevantie biedt, dient nog verder onderzocht worden. De toediening van vasoactieve medicatie daarentegen, met het oog op behoud van normotensie, brengt weinig of geen verandering van paravertebraal gemeten saturaties teweeg, zelfs niet in situaties van significant gewijzigde cardiac output. Dit doet de vraag rijzen of de techniek van nabij-infraroodspectroscopie gevoelig genoeg is om medicamenteuze effecten van vasoactieve producten op de paravertebraal gemeten saturaties te detecteren tijdens normotensieve condities.

10

Acknowledgements

Quousque tandem abutere, Carolina,
patientia mea?

How much longer, Caroline,
will you test my patience?

Ramses Forsyth,
Adapted from Cicero

10

Acknowledgements
Dankwoord

Ooit heeft een wijze vrouw mij gezegd:
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Neem voor uw dankwoord een goed glas champagne… en schrijf!
Je zult zien: het gaat vanzelf!”
Gedwee als ik ben, heb ik haar woorden ter harte genomen.
Deze wijze vrouw is Professor Moerman en mag ik met veel trots mijn promotor noemen.

Het klinkt cliché, maar dat is het allerminst…
Het maken van een thesis gebeurt niet door 1 persoon. Het is een proces waarbij tal van mensen zijn betrokken en heel veel ondersteuning komt bij kijken. Ik wil dan ook tot alle personen die deze thesis mee tot stand hebben gebracht, een oprechte en warme “dank je wel!” zeggen.

Vooreerst wil ik mijn promotor, Prof. Dr. Annelies Moerman bedanken.
Reeds heel erg lang heb ik enorm veel respect voor u als self-made woman en krachtige vrouw. Ik was dan ook vereerd dat u de taak op zich wou nemen om als promotor mij onder uw vleugels te nemen. Ik wil graag mijn dankbaarheid uiten voor uw bereidheid om mij vanaf het begin te coachen bij het schrijven van artikels. Om mij nadien te begeleiden bij mijn onderzoek en alle facetten dat dit met zich mee heeft gebracht. Om steeds voor mij klaar te staan wanneer ik hunkerde naar informatie of feedback, ook toen u het ontzettend druk had.
Dank je wel!

Figuurlijk uitgedrukt gingen mijn promotor, Prof. Dr. Annelies Moerman en co-promotor, Prof. Dr. S. De Hert heel vaak hand in hand. Van deze tandemfunctie en quasi onbegrensde beschikbaarheid van Prof. De Hert (alle dagen van de week, alle weken van het jaar, jaar in en jaar uit) heb ik dan ook gretig gebruik kunnen en mogen maken.
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Graag wil ik ook Prof. Isabelle Van Herzeele bedanken als lid van de begeleidingscommissie. Ik weet hoe druk u het heeft met zowel kliniek als wetenschap. Ik was dan ook bijzonder gecharmeerd dat er vrijwel onmiddellijk een bevestigend antwoord kwam op de vraag of u in mijn begeleidingscommissie zou willen zetelen.
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Isabelle, dank je wel!

Ook Prof. Thierry Bové verdient een speciale vermelding als voorzitter van de examencommissie. U was steeds toegankelijk voor vragen en praktische regelingen.
Aansluitend wil ik natuurlijk ook de interne en externe juryleden bedanken voor hun tijd, interesse en constructieve opmerkingen: Prof. Dr. Patrick Wouters, Prof. Dr. Frank Vermassen, Prof. Dr. Kirsten Colpaert, Prof. Dr. Mona Momeni, Prof. Dr. Daniel De Backer en Dr. Ignace Tielliu.
Dank je wel!

In deze lijst mag ook zeker het team vasculaire chirurgen niet ontbreken, die me de kans hebben gegeven om deze onderzoeken uit te voeren.
Dank je wel voor deze opportuniteit en fijne samenwerking.

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administratieve en ondersteunende bijdrage mogen er wezen! Jouw werk schittert als een parel in de zon!
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Jullie hebben er altijd alles aan gedaan om zowel Ramses als mezelf de kans te bieden om onze professionele en academische carrière te kunnen uitbouwen. Dit vertaalt zich in de zorg om de kinderen, die steeds bij jullie terecht konden en kunnen. Naschoolse opvang, ziekenbedjes, opvang tijdens congressen of late shiften…en vooral het eten…dat lekkere eten…
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“The sky is not the limit! It is just the beginning…”

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11

Curriculum Vitae

11

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Curriculum Vitae

Caroline M. VANPETEGHEM

Personalia

Date of Birth: May 27th, 1974

Marital status: Married with Ramses Forsyth, mother of Anaïs (°09/12/2002), Toulouse (°09/07/2004) and Parcifal (°24/08/2007).

Nationality: Belgian.

Education

1986-1992: Humaniora St. Pietersinstituut Gent (direction: Latin-Mathematics).
1992-1999: Medical Doctor (Ghent University, Belgium)
1999-2004: Residency in Anesthesia and Reanimation (University Hospital Ghent)
2004- now: Staff Member Anesthesia and Reanimation (University Hospital Ghent)

Interests and Experience

Senior staff member thoracic and vascular anesthesiology since 2004.
Senior staff member anesthesia for robotic surgery since 2013.
Anesthesia for liver transplantations.

Professional Memberships

European Association of Cardiothoracic Anaesthesia and Intensive Care (EACTAIC):

- Active member of EACTAIC thoracic subcommittee since 2014
- National representative 2021-2023
  Regular invited speaker

- European Society of Anaesthesiology and Intensive Care (ESAIC):
  Active member of the scientific committee 'Lung' (elected in octobre 2023)
  Regular Invited speaker

Congress organization

Second Thoracic Masterclass, Brussels (March 2023)

Other Professional Commitments

Rijksinstituut voor ziekte- en invaliditeitsverzekering (RIZIV): Member of 'paritair comité' since 2022.

Teaching Experience

AVU interuniversity course: "Anaesthetic management in patients with endocrine disorders"
Ghent 03.03.2007
Ghent 23.02.2008
Antwerp 23.02.2009
Antwerp 06.03.2010
Antwerp 26.02.2011.

Participation in center of excellence: "Use of sevoflurane in respiratory compromised patients."
Ghent 04.02.2010
Ghent 04.03.2010
Ghent 29.04.2010
Ghent 02.06. 2010
Ghent 24.05.2011
Ghent 27.05.2011
Ghent 17.05.2012
Ghent 24.10.2013.

Research Experience

2002-2003: Active participation in multicenter study 'A double blind, placebo controlled, paralleled group study of the effect of 'Zoniporide' on perioperative cardiac events in high-risk subjects undergoing non-cardiac surgery (Pfizer) (Princ. Local Invest. Prof De Baerdemaeker; Ghent University)

2005-2008: Active participation in 'SSI-study '(P.I. prof. dr. M. Struys, Ghent University)

2008: Active participation in 'surgical stress and telomere length reduction in clinical samples' (P.I. Ramses Forsyth, Ghent University)

2008- 2009: Active participation in study called 'influence of recruitment maneuver, FIO2 and ventilatory pattern on oxygenation during one- and two lung ventilation in COPD-patients and patients with a normal lung function' (P.I. dr. L. Szegedi, Ghent University)

2011-2014: Active participation in multicenter study 'POISE II' (Principal Local Investigator: Prof. S. De Hert, University of Ghent)

2015-2016: Active participation in multicenter study APRICOT (Principal Local investigator: Prof. S. De Hert; University Hospital Ghent)

2017: Principal investigator monocentric study: influence of bolus administration of phenylephrine and ephedrine on regional tissue oxygen saturation.

2019-2021: Principal investigator monocentric study: influence of continuous administration of phenylephrine and dobutamine on regional tissue oxygen saturation.

2022-…: Active participation in monocentric study: operative room black box analysis.

Active participation in thoracic workshops

1. BVAR Oostende (Belgium) 2011: difficult airway.
2. EACTA Basel (Suisse) 2016: one lung ventilation.
3. ESCOP Ghent (Belgium) 2016: one lung ventilation.
4. EACTA Berlin (Germany) 2017: thoracic epidural.
5. EACTA Manchester (UK) 2018: bronchial blocker.
6. EACTA Ghent (Belgium) 2019: EZ blocker.
7. EACTA thoracic masterclass Charleroi (Belgium) 2019: use of fiberoptics and tracheobronchial anatomy.
8. EACTAIC, Napoli (Italy) 2022: Double Lumen Tubes.
9. EACTAIC Thoracic Masterclass, Brussels (Belgium) 2023: Bronchial Blockers.

Session Chairs

1. SARB, Wavre (Belgium) (2006): research meeting.
2. LICAGE, Ghent (Belgium) (2012): 4th ELITA liver split course.
3. ESCOP, Ghent (Belgium) (2014).
4. EACTAIC, Ghent (Belgium)(2019): thoracic session.
5. ESAIC, Milan (Italy) (2022): joint session EACTAIC-ESAIC. TOSSCA airway recommendations. Update.
6. ESCVES, Liege (Belgium) (2022): vascular session.
7. EACTAIC, Napels (Italy) (2022): Thoracic anaesthesia: state of the art.
8. EACTAIC, Napels (Italy) (2022): thoracic workshop.
9. ESAIC, Glasgow (Scotland) (2023): a truly difficult airway.

Invited International Lectures

1. Anaesthetic management for robotic associated urologic surgery in children. ORSI, Melle (Belgium) (2016).
2. One lung ventilation in patients with a difficult airway. EACTA, Manchester (UK) (2018).
3. Role of Near-infrared spectroscopy as a neuromonitor. ESA, Vienna (Austria) (2019).
4. Total intravenous anesthesia versus inhalation anesthesia during one lung ventilation in thoracic surgery. EACTA, Ghent (Belgium) (2019).
5. One lung ventilation in patients with a difficult airway. EACTA, Ghent (Belgium) (2019).

6. Colloids and blood transfusion in thoracic surgery. EACTA Thoracic Masterclass, Charleroi (Belgium) (2019).

7. Patient positioning during anesthesia. CEEA, Antwerpen (Belgium) (2020).

8. Anesthesia during low impact surgery. ORSI, Melle (Belgium) (2020).

9. Neuromonitoring: an update. CEEA, Antwerpen (Belgium) (2021).

10. Risk/benefit balance of regional versus general anaesthesia for vascular surgery patients. ESAIC, online (2021).

11. TOSSCA airway recommendations. Update. ESAIC, Milan (Italy) (2022).

12. Near-infrared spectroscopy during TEVAR. ESCVS, Liege (Belgium) (2022).

13. Difficult airway management in thoracic anaesthesia. EACTAIC, Napoli (Italy) (2022).

14. One lung ventilation: do's and don'ts. CEEA, Antwerpen (Belgium) (2023).

15. ERAS in thoracic anaesthesia: inhalation anaesthesia or intravenous anaesthesia? EACTAIC Thoracic Masterclass, Brussels (Belgium).

16. Local or general anaesthesia in endovascular aortic aneurysm repair? ESAIC, Glasgow (Scotland) (2023).

17. A truly difficult airway in thoracic anaesthesia: options for laryngoscopy. ESAIC, Glasgow (Scotland) (2023).

18. Extreme positionings during surgery. CEEA, Rotterdam (The Netherlands) (2024).

Masterthesis co-promotorship

1. 'Impact of compliance with enhanced recovery after surgery (ERAS) guidelines for anatomic pulmonary resection.' Anne-Katrien Scheire (2023).

ManaMa promotorships

1. 'Spinal anesthesia near-infrared spectroscopy in care of patients during thoracoabdominal aortic repair procedures: narrative review of its clinical efficacy.'
   Leen Van De Moortel, MD (2018).

2. ‘Influence of a bolus administration of ephedrine or phenylephrine on paraspinal oxygen saturation, measured with NIRS.’ Bas Bruneel, MD (2019).

3. ‘Pharmacologically versus endogenously induced variations in tissue oxygenation as measured by near-infrared spectroscopy (NIRS).’ Bram Van Overmeire, MD (2019)

4. ‘Influence of continuous administration of phenylephrine versus dobutamine on paraspinal oxygen saturation measured with near-infrared spectroscopy: preliminary data.’ Milan Besard, MD (2022).

5. ‘Effect of continuous administration of phenylephrine versus dobutamine on cerebral oxygenation, as measured with near-infrared spectroscopy (NIRS): a preliminary analysis.’ Vincent Bafort, MD (2023).

6. ‘Continuous non-invasive blood pressure measurement with “ClearSight” compared to standard intermittent blood pressure measurement in patients with peripheral arterial disease. Are potential differences influenced by phenylephrine or dobutamine?’ Martha Wolfskeil, MD (2023).

7. ‘Does the choice of anaesthesia affect cancer? A molecular crosstalk between theory and practice.’ Wiebrecht Debel, MD (2023).

8. ‘Medical device development and product communication: an ergonomical solution for the steep trendelenburg. position.’ Elien Verhoeve, industrial sciences, UGent (2019).

Manama Jury Member

1. ‘Serratus intercostal plane (sip) block in video-assisted thoracic surgery (vats).’
   Isaure Musschoot, MD (2019).

2. ‘Effect of skin perfusion on the measurement of oxygen level in the brain. NIRS and extracranial contamination in cardiac surgery.
   Virginia Liberton, MD (2023).

Grants

SARB graduation day (04.04.2016): 15000€.
‘Influence of a bolus administration ephedrine and phenylephrine on the spinal oxygen saturation, measured by NIRS.’

Publications

1. Struys MM, **Vanpeteghem C**, Huiku M, Uutela K, Blyaert NB, Mortier EP. Changes in a surgical stress index in response to standardized pain stimuli during propofol-remifentanil infusion. *Br J Anaesth.* 2007;99(3):359-67.

2. Moerman A, Van Herzeele I, **Vanpeteghem C**, Vermassen F, Francois K, Wouters P. Near-infrared spectroscopy for monitoring spinal cord ischemia during hybrid thoracoabdominal aortic aneurysm repair. *J Endovasc Ther* 2011; 18:91–95.

3. Devereaux PJ, Sessler DI, Leslie K, ***et al***. (The POISE-2 Investigators) Clonidine in patients undergoing noncardiac surgery. *NEJM* 2014; 370:1504–13.

4. Devereaux PJ, Mrkobrada M, Sessler DI, ***et al.*** (The POISE-2 Investigators) Aspirin in patients undergoing noncardiac surgery. *NEJM* 2014; 370:1494–1503.

5. **Vanpeteghem C,** Moerman A., De Hert S. Perioperative hemodynamic management of carotid artery surgery. *J Cardiothorac Vasc Anesth* 2016 Apr; 30: 491-500.

6. Habre W, Disma N, Virag K, Becken K, Hansen T, Jöhr M, ***et al.*** Incidence of severe critical events in paediatric anaesthesia (APRICOT): a prospective multicentre observational study in 261 hospitals in Europe. *Lancet Resp Med* 2017; 5: 412-25.

7. Abbott TEF, Ahmad T, Phull MK, Fowler AJ, Hewson R, Biccard BM, Chew MS, Gillies M, Pearse RM, **International Surgical Outcomes Study (ISOS) group.** The surgical safety checklist and patient outcomes after surgery: a prospective observational cohort study, systematic review and meta-analysis *Br. J Anaesth* 2018;120: 146-155.

8. **International Surgical Outcomes Study (ISOS) group.** Prospective observational cohort study on grading the severity of postoperative complications in global surgery research. *Br J Surg* 2019; 106: e73-e80.

9. Spinoit AF, Moreels N, Raes A, Prytula A, De Groote R, Ploumidis A, De Bleser E, Randon C, **Vanpeteghem C**, Walle JV, Van Laecke E, Vermassen F, Decaestecker K. Single setting Robot-Assisted Kidney Transplantation (RAKT) in a child consecutive to single-port laparoscopic nephrectomy in the child and robot-assisted living-related donor nephrectomy: initial Ghent experience. *J Pediatr Urol.* 2019; 15: 578-9.

10. **Vanpeteghem C**, Bruneel B, Lecoutere I, De Hert S, Moerman A. Ephedrine and phenylephrine induce opposite changes in cerebral and paraspinal tissue oxygen saturation, measured with near-infrared spectroscopy: a randomized controlled trial. *J Clin Monit Comput*. 2020; 34: 253-9.

11. **Vanpeteghem C**, Van de Moortel L, De Hert S, Moerman A. Assessment of spinal cord ischemia with near-infrared spectroscopy: myth or reality? *J Cardiothorac Vasc Anesth*. 2020;34: 791-6.

12. Van Praet C, Lambert E, Desender L, Van Parys B, **Vanpeteghem C**, Decaestecker K. Total intracorporeal robot kidney autotransplantation: Case report and description of surgical technique. Front Surg. 2020 11;7: 65.

13. Şentürk M, El Tahan MR, Szegedi LL, Marczin N, Karzai W, Shelley B, Piccioni F, Granell Gil M, Rex S, Sorbello M, Bence J, Cohen E, Gregorio GD, Kawagoe I, Globokar MD, Jimenez MJ, Licker MJ, Mourisse J, Mukherjee C, Navarro R, Neskovic V, Paloczi B, Paternoster G, Pelosi P, Salaheldeen A, Stoica R, Unzueta C, **Vanpeteghem C**, Vegh T, Wouters P, Yapici D, Guarracino F. Thoracic anesthesia of patients with suspected or confirmed 2019 novel coronavirus infection: preliminary recommendations for airway management by the European Association of Cardiothoracic Anaesthesiology Thoracic Subspecialty Committee. *J Cardiothorac Vasc Anesth*. 2020;34:2315-27.

14. Grammens J, Schechter MY, Desender L, Claeys T, Sinatti C, VandeWalle J, Vermassen F, Raes A, **Vanpeteghem C**, Prytula A, Silay MS, Breda A, Decaestecker K, Spinoit AF. Pediatric challenges in robot-assisted kidney transplantation. *Front Surg*. 2021 8: 649418.

15. Şentürk M, El Tahan MR, Shelley B, Szegedi LL, Piccioni F, Licker MJ, Karzai W, Gil MG, Neskovic V, **Vanpeteghem C**, Pelosi P, Cohen E, Sorbello M, MBChB JB, Stoica R, Mourisse J, Brunelli A, Jimenez MJ, Drnovsek Globokar M, Yapici D, Morsy AS, Kawagoe I, Végh T, Navarro-Ripoll R, Marczin N, Paloczi B, Unzueta C, Gregorio GD, Wouters P, Rex S, Mukherjee C, Paternoster G, Guarracino F. Thoracic anesthesia during the COVID-19 pandemic: 2021 updated recommendations by the European Association of Cardiothoracic Anaesthesiology and Intensive Care (EACTAIC) Thoracic Subspecialty Committee. *J Cardiothorac Vasc Anesth*. 2021;35:3528-46.

16. Dillemans J, Van Gompel C, Wouters P, **Vanpeteghem C**. Technical failure of the EZ-blocker™ causing serious adverse events during one lung ventilation: a case series. *Anaesth Rep*. 2022 13;10: e12160.

17. Zwaenepoel B, Vandewiele K, Peperstraete H, De Ryck F, **Vanpeteghem C**, Malfait T, Herck I, Vandenberghe W, Van Laethem L, Defreyne L, Van Braeckel E, Depuydt P, Schaubroeck H. Video-assisted thoracic surgery in critically ill COVID-19 patients on venovenous extracorporeal membrane oxygenation. *Perfusion*. 2022: 2676591221119319.

18. **C.M. Vanpeteghem**, S.G. De Hert, A.T.Moerman. Laryngoscopy mediated stress response induces opposite effects on cerebral and paraspinal oxygen saturation. Acta Anaesth Bel, 2022, 73: 201-5.

19. Debel W, Ramadhan A, **Vanpeteghem C**, Forsyth RG. Does the choice of anaesthesia affect cancer? A molecular crosstalk between theory and practice. *Cancers*. 2023; 15:209.

20. **Vanpeteghem CM**, De Hert SG, Moerman AT. Blood pressure control with phenylephrine or dobutamine: a randomized controlled trial comparing effects on cerebral and paravertebral tissue oxygen saturation measured with near-infrared spectroscopy. J Clin Monit Comput. 2023; 37:1161-9.

21. Wolfskeil M, Bafort V, Besard M, Moerman A, De Hert S, **Vanpeteghem C**. Continuous noninvasive blood pressure measurement with "ClearSight" compared to standard intermittent blood pressure measurement in patients with peripheral arterial disease. Are potential differences influenced by phenylephrine or dobutamine? J Cardiothorac Vasc Anesth. 2023; 37: 2470-4.