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Master thesis | Original study

Influence of contnuous administration of phenylephine versus dobutamine on paraspinal oxygen saturation

M. Besard[1], V. Bafort[1], M. Wolfskeil[1], A. Moerman[1], S. De Hert[1], C. Vanpeteghem[1]

[1]*Department of Anesthesiology, University of Ghent, Ghent University Hospital, Belgium.*

Corresponding author: Besard Milan, University of Ghent, Ghent University Hospital, Belgium. Jozef Plateaustraat 13, 9000 Ghent, Belgium. E-mail: milan.besard@ugent.be; milan.besard@telenet.be; +32 494 06 80 92

Abstract

Introduction: **This randomized controlled trial evaluates the effect of continuous administration of phenylephrine versus dobutamine on paraspinal oxygenation, measured by near-infrared spectroscopy (NIRS). Paraspinal NIRS-monitoring evaluates the spinal oxygenation in an indirect, continuous and real-time manner. The influence of these drugs on the paraspinal oxygenation is unknown, but can be highly relevant during major aortic repair.**

Methods: **This dissertation discusses a preliminary data analysis concerning the first twenty patients included. Phenylephrine or dobutamine were administered continuously during elective arterial dilation procedures of the lower limb. Adhering to a predefined protocol, drug administration was titrated to maintain normotension. The primary outcome variable is the NIRS-measured paraspinal oxygen saturation ($rS_{ps}O_2$), this at three distinct paraspinal levels (T3T4 – T9T10 – L1L2), and additionally at the deltoid muscle (rS_dO_2). A linear mixed modelling approach was used for statistical analysis. This manuscript adheres to the applicable CONSORT guidelines.**

Results: **Estimated mean relative NIRS-values (e.g. changes from baseline) were calculated at the different locations. We observed an overall positive effect on these oximetry values in the dobutamine administered group, this in contrast with an overall negative effect with phenylephrine administration. Significant differences in estimated mean relative values between the groups were observed at the lumbar level (-0.67% vs 2.97%) and at the deltoid muscle (-2.63% vs 2.01%), with significantly higher values during dobutamine administration.**

Conclusion: **By means of a mixed modelling approach to estimate mean relative values of $rS_{ps}O_2$ and rS_dO_2, we compared the effects of the administration of phenylephrine or dobutamine. Noticeable differences between the two groups were observed and seem to favour the use of dobutamine. Besides an overall positive effect of dobutamine administration, significant differences between the two interventions were observed at the lumbar level, in favour of dobutamine administration. Limitations of this analysis are the rather complex modelling, and the lack of implementation of cardiac output variables in the model.**

Keywords: **Spectroscopy, Near-Infrared, Dobutamine, Phenylephrine, Monitoring, Spinal Cord Ischemia.**

Dissertation promotors: Dr. Vanpeteghem Caroline, MD, Ghent University Hospital, Belgium; Dr. Moerman Anneliese, MD PhD, Ghent University Hospital, Belgium.

Principal investigator: Dr. Vanpeteghem Caroline, MD, Ghent University Hospital, Belgium.

Internal review board approval: - This trial (with EudraCT number 2018-003687-31) was approved by the Ghent University Hospital Ethics Committee (EC UZG 2018/1510, February 1st, 2019, Dr. D. Matthijs).

- Ghent University Hospital, C. Heymanslaan 10, 9000 Ghent, info@uzgent.be, +3293322111

- All participants provided written informed consent, in accordance with current GCP-guidelines.

- Patient enrolment occurred during the period July 2019 - May 2021.

Introduction

Paraplegia or paraparesis remains one of the most devastating complications after extensive surgical aortic repair. During the past decades, extensive research has been conducted regarding strategies to limit the occurrence of this complication. Essentially, the underlying mechanism is a compromised perfusion of the spinal cord (spinal cord ischemia – SCI). The underlying mechanism and severity of SCI in thoracoabdominal aneurysm repair is multifactorial, and a number of risk factors has been identified[1–4]. Despite the perioperative use of neuroprotective strategies during high-risk procedures, the occurrence of this complication remains significant[1,5]. An overview of the neuroprotective strategies is beyond the scope of this dissertation. One of the newer techniques to monitor perioperatively the integrity of the spinal cord is NIRS-measured regional tissue oxygenation (rS_tO_2) of the paraspinal musculature. This method assesses the spinal oxygenation in a continuous, indirect, real-time and non-invasive manner by evaluating the paraspinal musculature and the paraspinal collateral network[1-3,5]. Traditionally, the most prominent segmental artery (artery of Adamkiewicz) was thought to be essential in the blood supply of the distal two-thirds of the spinal cord. Sudden interruption of this artery would irrevocably lead to spinal cord ischemia. However, this assumption is not entirely accurate. Nowadays an extensive intraspinal and paraspinal collateral network (psCN) is believed to contribute substantially to the blood supply of the spinal cord[1,2,5-10]. This collateral network is located mainly in the paraspinal musculature. It essentially consists of interconnecting arteries between the direct spinal cord blood supply and the blood supply to the paravertebral tissues and muscle groups. Due to a significant blood volume capacity, this psCN could act as a buffer system in the event of an interruption of the direct spinal blood supply. Based on the psCN-concept, we can make an indirect estimate of the spinal oxygenation at the paraspinal level ($rS_{ps}O_2$). Both midline and paraspinal applied NIRS-optodes are able to reliably measure the oxygenation of the spinal cord. Experimental research confirms that the $rS_{ps}O_2$ strongly correlates with spinal oxygenation[1]. Furthermore, MEP-based comparative data showed that lower $rS_{ps}O_2$ values associate strongly with a loss of integrity and functionality of the spinal cord[1]. Current evidence states to apply the optodes paravertebrally at the lower thoracic and lumbar levels. It is primarily at the lumbar levels that significant changes in $rS_{ps}O_2$ are detected during ischemia and reperfusion[1,5]. Animal research confirmed this correlation between neurological deficits and a refractory decrease in $rS_{ps}O_2$ measurements at the lumbar level[1]. The optodes at high thoracic levels appear to detect little or no changes, and should therefore be regarded as reference measurements[5]. Until now, there are no published randomised controlled trials (RCTs) involving humans on the use of cnNIRS for the detection of SCI. Most of the evidence is based on experimental analyses. Despite the lack of validation of this technique in both open and endovascular repair of thoracoabdominal aneurysms, current evidence and guidelines support the perioperative use to monitor spinal oxygenation[1-3,5,11]. Similar to the experimental technique MIS²ACE (Minimally-Invasive Staged Segmental Artery Coil- and plug Embolisation), the validity of cnNIRS is currently being investigated as part of the PAPA-ARTiS trial[1]. Currently, Oostveen et al. is evaluating the validity of this technique as well[11].

SCI and vasoactive drugs

Optimal haemodynamic management and cerebrospinal fluid drainage with subsequent optimization of the spinal perfusion pressure can significantly reduce secondary damage and the associated excitotoxic response[12-14]. The presence of vasoactive drugs within the management of SCI is therefore paramount. The perioperative correction of hypotension significantly affects the neurological outcome[12-14]. However, the evidence regarding the use of permissive hypertension in case of spinal cord ischemia is less compelling[15-17]. Current guidelines recommend increasing mean systemic blood pressures to 85-90 mmHg for five to seven days after onset of ischemia[13,14,15]. Until now, there is no strong evidence to support one vasoactive drug above another. Very little is known about the effect of different vasoactive drugs on spinal perfusion and oxygenation, not to mention the ideal hemodynamic targets in the individual patient.

Confounders

When interpreting the tissue oxygenation values patient, one has to keep in mind the possible confounders when using vasoactive agents. Most evidence for these confounders is found at the cerebral and muscular level. It is paramount to understand the importance of these confounders. The discussion of the evidence of these (possible) confounders is beyond the scope of this dissertation. To summarize, NIRS-technology evaluates the mixed (arterial – venous – capillary) tissue oxygen saturation within an optical field. A change of the blood flow within this field is very likely to alter the measurements. However, a change in blood flow does not necessarily give a proportional

change in NIRS-measured values, since there are circumstances that alter the oxygen demand and/or the regional blood volume. One of these major influencing factors is the use of vasoactive drugs.

Spinal oxygenation and vasoactive drugs

In following paragraph, the current evidence specifically at the spinal level is discussed. The effect of vasoactive agents on the microvasculature of the damaged central nervous system is largely unknown and unpredictable. To illustrate the known local effects of different vasoactive agents on spinal perfusion and oxygenation, some comparative studies are discussed below.

Firstly, some remarkable findings were published by Streijger et al.[15] Both phenylephrine and noradrenaline were able to optimize nearby spinal blood flow and oxygenation (measured by invasive sensors), this in the event of a temporary spinal cord compression in pigs at the low thoracic level. Noradrenaline was superior in blood flow and oxygenation restoration (compared to phenylephrine). Both products resulted in a limited beneficial metabolic effect (lactate/pyruvate ratio, glutamate content) after decompression. Additionally, both vasopressors (phenylephrine more than noradrenaline) were associated with an increase in local spinal cord haemorrhage. Interestingly, this association of noradrenaline and local spinal cord haemorrhaging was observed as well in a recent animal trial by Williams et al.[19] This was not seen with dobutamine administration. They hypothesized that an alpha-adrenergic vasoconstriction can increase vascular resistance in the intact spinal vasculature, with redistribution to the damaged areas. In contrast, by beta-adrenergic stimulation (and vasodilation), dobutamine can optimize this redistribution in the spinal tract.

Secondly, Kurita et al.[20] measured the regional spinal oxygenation ($rS_{sp}O_2$) in pigs, using invasive NIRS technology. Phenylephrine was administered under hypovolemic and normovolemic conditions. The effect of phenylephrine on $rS_{sp}O_2$ was very condition-dependent, with a more prominent increase in $rS_{sp}O_2$ seen under hypovolemic conditions. The authors established that even under hypovolemic conditions, spinal oxygenation is blood pressure dependent. In hypovolemic conditions, fluid resuscitation provided little improvement of $rS_{sp}O_2$, in contrast to subsequent association of phenylephrine. They observed that under the inflicted hypovolemia, the spinal cord blood supply was fairly volume tolerant. They attributed this to a presumed redistribution of blood to the central nervous system. Subsequent volume resuscitation mainly seemed to restore peripheral tissue perfusion. The authors noted that phenylephrine most likely exerts venous recruitment and cutaneous vasoconstriction in hypovolemic conditions.

Finally, we would like to mention a third study, by Vanpeteghem et al. [21] This trial investigated the effect of boluses of phenylephrine and ephedrine on cerebral (rS_cO_2) and paraspinal ($rS_{ps}O_2$) NIRS-measured local tissue oxygenation. An increase in $rS_{ps}O_2$ was observed in response to phenylephrine administration. In contrast, ephedrine produced a decrease. The hypothesis of local redistribution and venous recruitment was also mentioned here. Phenylephrine would presumably cause a redistribution of blood to the paraspinal collateral network, and thus improve the local paraspinal oxygenation.

Materials and methods

This master's dissertation is a preliminary data analysis of the research conducted at the Ghent University Hospital, Belgium. This data analysis concerns the first ten patients included in each treatment arm in the original trial. The first patient was excluded because of drug administration errors. All relevant information regarding the trial execution is added in the attachments, with addition of a CONSORT-diagram and checklist.

Objectives and goals of the dissertation

The objective of this dissertation is to investigate the influence of the continuous administration of phenylephrine or dobutamine on NIRS-measured paraspinal regional tissue oxygenation ($rS_{ps}O_2$). This trial included patients scheduled for elective arterial dilation procedures of the lower limb. Most patients experience a period of hypotension during this type of procedure. Vasoactive agents are therefore frequently administered. The physiological properties of phenylephrine and dobutamine are completely different. Phenylephrine causes peripheral vasoconstriction (pure alpha1-agonist). Any increase in blood pressure mediated by dobutamine is mainly caused by an increase in cardiac output (beta-agonist with limited alpha-adrenergic activity). To date, this is the first randomized controlled trial that investigates the influence of continuous administration of phenylephrine and dobutamine on $rS_{ps}O_2$ in human participants.

Trial design and general information

This research was initiated as a single centre, prospective RCT. The trial (EudraCT number 2018-003687-31) was approved by the Ghent University Hospital Ethics Committee (EC UZG 2018/1510,

February 1st, 2019, Dr. D. Matthijs). During this RCT two vasoactive substances were administered. All patients received either phenylephrine or dobutamine in a continuous intravenous manner, according to a predefined protocol and flowchart. Drug dosing, labelling and storage conditions were closely guarded. The drug administration flowcharts are added in the attachments as well. All participants provided written informed consent, in accordance with current Good Clinical Practice (GCP) guidelines.

Patient selection and criteria

Patient enrolment occurred during the period July 2019 - May 2021. During this period 34 adults were included in the trial, according to prior sample size calculation. All of these patients were admitted adults (≥18 years of age) in the Ghent University Hospital, who were electively scheduled for an arterial dilatation and/or stenting of lower limb blood vessels. Patients were excluded if they were minors (< 18 years of age), obese (BMI > 30 $kg.m^{-2}$), underwent previous aortic surgery, suffered from severe valvular disease, paraplegia or paraparesis, if they required renal replacement therapy, if a pacemaker was implanted, if patients were pregnant or lactating, if there was preoperative use of Angiotensin Converting Enzyme Inhibitors (ACE-I) or if there was no sinus rhythm on preoperative ECG or at induction of anaesthesia (patients with a history of atrial fibrillation were included if they had a sinus rhythm on their preoperative ECG). There were no restrictions, no possible advantages nor additional risks related to the trial inclusion, with the exception of the risks inherent to the administration of vasoactive drugs. Two patients were excluded from participating. One enrolled simultaneously in a second interventional study. The second patient had the procedure under local anaesthesia, because of preoperative confirmation of severe coronary artery disease. These participants were considered as dropouts.

Randomisation process

The randomisation process is to be seen as a 'simple randomisation'. This process was generated before the start of the trial and was organised by means of sequentially numbered sealed envelopes. Allocation remained concealed until after patient enrolment.

Trial intervention and drug administration protocol

During the preoperative evaluation of each participant, bilateral baseline blood pressure measurements were registered. Six NIRS-sensors (INVOS 5100C, Medtronic, USA) were applied to the back of the patient upon procedural instalment, this according to the spinal anatomical reference points. We placed one sensor at the upper thoracic level (T3-T4), two sensors bilaterally at the lower thoracic level (T9-T10) and two bilaterally at the lumbar level (L1-L2). The last sensor was placed on the deltoid muscle, opposite of the drug administration side. To titrate the drugs a non-invasive cardiac output monitor (Clearsight, EdwardsTM LifeScience, USA) was used. This monitor provides a non-invasive arterial pressure waveform and instant evaluation of blood pressure. The interventional drugs were administered through a dedicated large bore intravenous line, with a continuous fluid push-bolus to secure optimal drug administration. A second intravenous line was placed for standard anaesthesia care. An oscillometric non-invasive blood pressure was measured every minute, this at the opposite side of the drug administration.

After a standardized induction of anaesthesia, an endotracheal tube was placed. On this exact moment, the administration of the interventional drug started. Mechanical ventilation settings were altered following a predetermined protocol. Anaesthesia was maintained with sevoflurane and titrated according to BIS-values. For each treatment group we adhered to a well described drug administration flowchart protocol (see Attachments). The drugs were administered in order to maintain blood pressure within a predetermined range from normal (preoperative) values. If systemic blood pressures (MAPs) decreased to values lower than preop values minus 20%, a higher dose of vasopressor was administered. If MAPs increased to values above preop values, the dosing rate was decreased. We performed this hemodynamic evaluation and titration every two minutes after intubation. The data collection was terminated after 30 minutes of hemodynamic support (i.e. 30 minutes after intubation) or if administration of phenylephrine or dobutamine exceeded 1µg/kg/min or 10 µg/kg/min respectively, and this for three consecutive evaluations. If administration of the study medication was not able to achieve the desired result, hemodynamic management was left to the discretion of the anaesthesiologist, and the patient was excluded from analysis.

Data collection and management

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

from the Clearsight and INVOS 5100C monitor were downloaded to the same personal computer. Additional parameters were manually acquired on the patient's Case Report Forms.

Statistical analysis

Initial trial sample size calculation was based on previous data from the principal investigator. We observed a statistically significant difference in response 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 an p of 0.05, 17 patients in each observation arm were calculated to be necessary to address the experimental question. Dropouts were replaced following trial protocol, to give a total number of 34 participants.

Statistical analysis

In pursuit of a comprehensive statistical approach, the help of the Statistical Department, Ghent University was called upon. Given the trial design, continuous drug administration, possible hemodynamic changes and repeated measurements within the same patient, a linear mixed modelling approach was applied for this preliminary analysis. This preliminary analysis and choice of statistical approach has in no manner influenced the patient enrolment or data acquisition. The complete statistical analysis was completed using the SPPS Statistical 28 software package. After construction of the SPSS-database, a standard descriptive statistical approach was used. Differences in patient and baseline characteristics were calculated using a standard unpaired two-sided Student's t-test. Throughout this analysis, an alpha of 0.05 is used as the cut-off for significance.

Because of the possible major hemodynamic fluctuations after intubation and possible delay of administration of the vasoactive drugs, an artificial baseline moment was created. This baseline moment was chosen to be two minutes after intubation (T2), and therefore two minutes after start of drug administration. By using this artificial baseline moment, we could analyse the effect of these drugs compared to realistic baseline measurements. Furthermore, there was a need for an artificial scaling of the administered drug dosages. Given the difference in blood pressure supporting effect and the obvious differences in physiologic properties, a transformation to a group-specific z-score was made (see Figure 1). By this adaptation, a comparison between the two vasoactive drugs could be made.

Linear mixed modelling

After analysis of the trial set-up, possible mediators and possible intra-individual interactions a random intercept - random slope model was constructed. This model was used to determine predicted mean values of rS_tO_2 values at four different locations. By means of a forward and backward-stepping model building strategy (using the Akaike's information criterion), we tried to identify the most realistic model. This resulted in exclusion of the variable FiO_2, since no differences in outcome were seen after exclusion. As main determining covariates we selected (a) the mean blood pressures (measured by the Clearsight device), (b) the drug dosage (i.e. group-specific z-score) and (c) the different measurement moments (represented by the amount of minutes after intubation). These three covariates were considered as fixed effects. Additionally an interaction possibility between these covariates and the type of drug received was added to the model. As random effects we selected the variable 'mean blood pressures' and the variable expressing the moments of measurement.

Covid-19 adaptations

As a result of the global health crisis, certain adaptations needed to be made during the course of this trial. The most important implications were the sudden lack of trial participants, alterations in the clinical workload of the investigators, and a change in the intubation process. An extension of the trial inclusion period was approved by the Ghent University Hospital Ethics Committee. With regard to the safety of the health care personnel, a rapid sequence intubation protocol was implemented, with a necessary switch to rocuronium as the used muscle relaxant.

Adverse event reporting and quality control

Adverse (AE) and Serious Adverse Events (SAE) were reported according to hospital wide policy, as

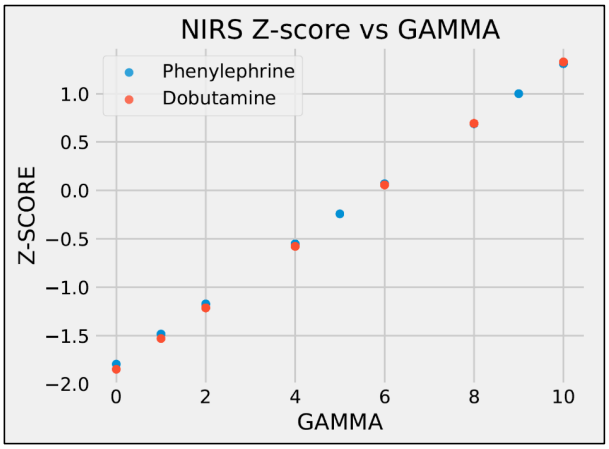

Fig. 1 — Illustration of the group-specific z-score values. Group-specific z-scores (y-axis) were calculated for the administered dosages for each interventional drug (gamma, x-axis). The respective groups are represented by colour (red = dobutamine, blue = phenylephrine). By this adaptation, a comparison between the two vasoactive drugs could be made.

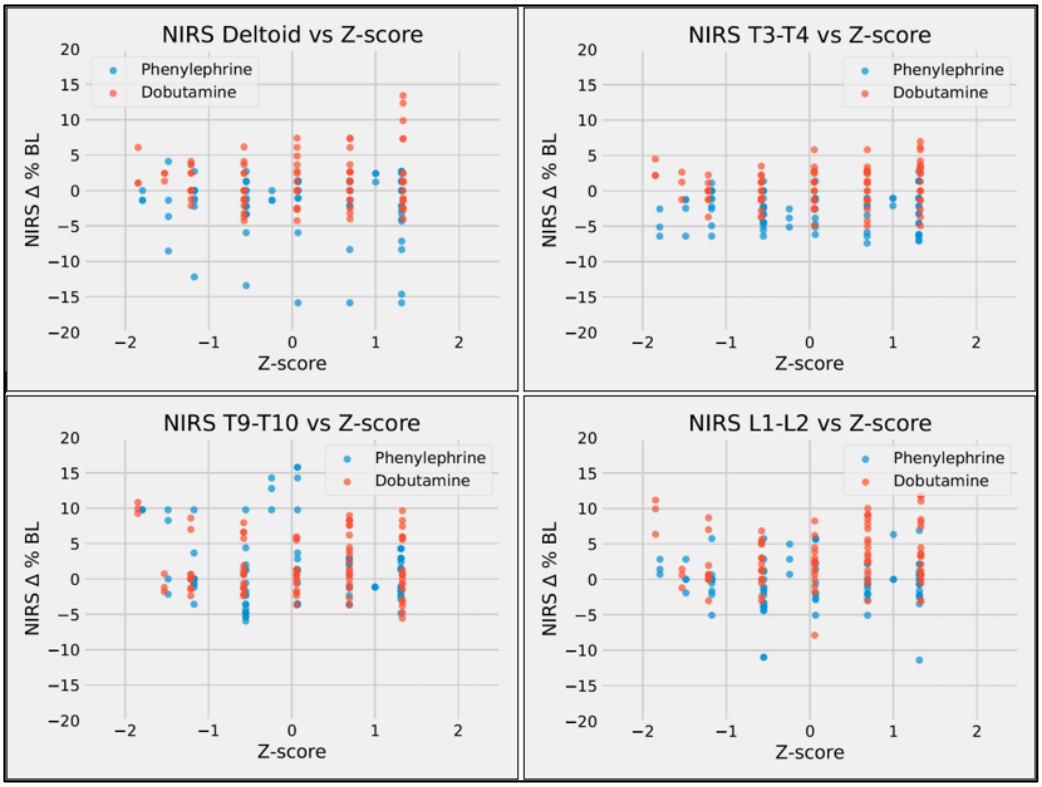

Fig. 2 — IIllustration of the observed relative NIRS-values (y-axis) with their respective z-scores (x-axis). Illustration for each of the four measurement locations. The respective groups are represented by colour (red = dobutamine, blue = phenylephrine).

described in the trial's protocol (see Attachments). Adverse events were reported between the first dose administration of trial medication and 24 hours after last administration.

Results

Patients demographic and descriptive analysis

In Table I essential patient characteristics are represented. No significant differences were observed between the two interventional groups, except for patient's Body Mass Index (BMI), with a significant higher BMI in the dobutamine group (26.8 vs 24.3 $kg.m^{-2}$). Occurrence of preoperative therapy with ACE-I differed as well (70 vs 20 %), but this therapy was interrupted well in advance, as required by trial inclusion. For each group, an equal number of patients are treated by beta-adrenergic blocking agents.

In Table II the most essential baseline measurements are shown, illustrating the clinical

Table I. — Patient characteristics.

		Phenylephrine N = 10	**Dobutamine** N = 10	**Total** N = 20	**Alpha**
Sex = Female	N (%)	5 (50%)	4 (40%)	9 (45%)	1,00
Smoking	N (%)	7 (70%)	6 (60%)	13 (65%)	1,00
Bètablocker	N (%)	6 (60%)	6 (60%)	12 (60%)	1,00
CCB	N (%)	4 (40%)	3 (30%)	7 (35%)	1,00
ACE-I	N (%)	7 (70%)	2 (20%)	9 (45%)	0,07
Length (cm)	Mean (SD)	167,6 (4,32)	164,6 (9,83)	166,1 (7,55)	0,39
Body weight (kg)	Mean (SD)	68,3 (8,45)	73,2 (9,93)	70,8 (9,32)	0,24
BMI (kg/m^2)	Mean (SD)	24,3 (2,53)	26,8 (2,36)	25,6 (2,75)	0,02
Age (years)	Mean (SD)	70,3 (11,85)	73 (6,27)	71,7 (9,33)	0,53

Essential patient characteristics are represented for each interventional group, and additionally for all the patients included. Respective mean values, standard error values and alpha-values are represented. Legend Table I: N : absolute amount of patients; % : respective percentage relative to the total amount of patients included; ACE-I : angiotensin converting enzyme inhibitor; CCB : calcium channel blocker; Mean : group-specific mean values; SD : group-specific standard deviation values; BMI : body mass index; Alpha : respective alpha-values, resulting from unpaired two-sided t-test analysis.

Table II. — Baseline measurement statistics.

	Phenylephrine (N = 10)			tamine 10)			Total (N = 20)			
		SD	Max	Mean	SD	Min		SD	Max	
		11,67	118	100,5	16,74	86		10,81	118	0,66
MAP baseline T2 CS	84,0	57				107	81,2	54		
		18,05	127	95,9	59			23,45	134	0,66
		8,43	89	78,9	69			7,49	94	0,80
NIRS T3T4	80,4	63			7,77	92	80,1	63		
		8,86	89	75,4	65			7,77	89	0,85
		9,86	92	80,1	71			7,78	92	0,99
BASELINE T2										
		7,66	93	80,8	73			6,71	94	0,42
		9,17	95	81,6	71			7,83	95	0,49
		8,29	87	77,2	63			7,94	91	0,98
		8,64	92	81,1	70			7,47	95	0,79

Essential baseline measurements are shown for each interventional group, and additionally for all the patients included. Analysis is made of awake and baseline mean systemic blood pressure values, and additionally of awake and baseline mean NIRS-values (at the four measurement sites). Respective alpha-values, resulting from unpaired two-sided t-test analysis, are depicted as well. Legend Table II: N : absolute amount of patients; Mean : group-specific mean values; SD : group-specific standard deviation values; Alpha : respective alpha-values, resulting from unpaired two-sided t-test analysis; MAP : mean arterial pressure; NIBP : non-invasive blood pressure; MAP preop NIBP : preoperative measured NIPB-values; CS : clearsight blood pressure; MAP baseline T2 CS : clearsight-measured systemic blood pressure at the artificial baseline moment, e.g. two minutes after intubation; MAP baseline T2 NIBP : NIBP-measured systemic blood pressure at the artificial baseline moment, e.g. two minutes after intubation; Baseline T2 : the artificial baseline moment, e.g. two minutes after intubation; NIRS : respective NIRS-values at each of the outcome locations; Min : minimum observed value; Max : maximum observed value.

setting before drug administration. Mean systemic blood pressure values and mean NIRS-values (at the four measurement sites) were calculated, this both in the awake patient and at the artificial baseline moment (T2). No significant differences in patient baseline values were observed between the two interventional groups. The NIRS-values at levels T9-T10 and L1-L2 are mean values for the left and right optode measurements.

Graphs

To give the reader an illustration of the collected data, all of the observed relative NIRS-values are plotted against their respective z-score, and this for each of the 4 locations (Figure 2). Additionally, the relative NIRS-values (and a group-specific mean) are represented in time (Figure 3). These relative values are the measurements compared to their respective baseline values (at T2). Therefore, all of these measurements are after the start of drug administration. It is important to realise that these relative NIRS-values in the graphs are the observed values, and not the estimated (predicted) mean values after modelling statistics.

Preliminary analysis by means of linear mixed

Application of the constructed model on the preliminary data resulted in estimated (or predicted) outcome values, this at the four different locations, and this for each intervention group (phenylephrine versus dobutamine). These outcome values are estimated mean values for the changes in NIRS values (i.e. relative values) at the paraspinal level ($rS_{ps}O_2$) and at the deltoid muscle (rS_dO_2). This output was calculated while modifying the covariates (i.e. MAP-values or z-score-values) (Table III). The differences of these estimated mean relative values (and their respective alpha-values) were calculated as well.

In Table III the results of forementioned strategy are depicted. In light of a correct interpretation, the chosen covariate values are of importance. For uniformity of the results, the covariate indicating the time of measurement was invariably chosen at 10 minutes, therefore after a sufficient amount of time after laryngoscopy and thus after start of the vasoactive drugs. Additionally, we would like to express the importance of the z-score scaling value, since the 'standard' model used a z-score of zero, i.e. an administered dosage of approximately 0.6 $\mu g.kg^{-1}.min^{-1}$ for phenylephrine, and 6 µg.kg-1.min-1 for dobutamine, both of which are considerable dosages. Made adaptations of the covariates (z-score and MAP) are depicted as well.

As Table III depicts, there is a noticeable difference in estimated mean relative NIRS-values between the two interventional groups. We observed overall positive values of the estimated mean relative $rS_{ps}O_2$ and rS_dO_2 in the dobutamine

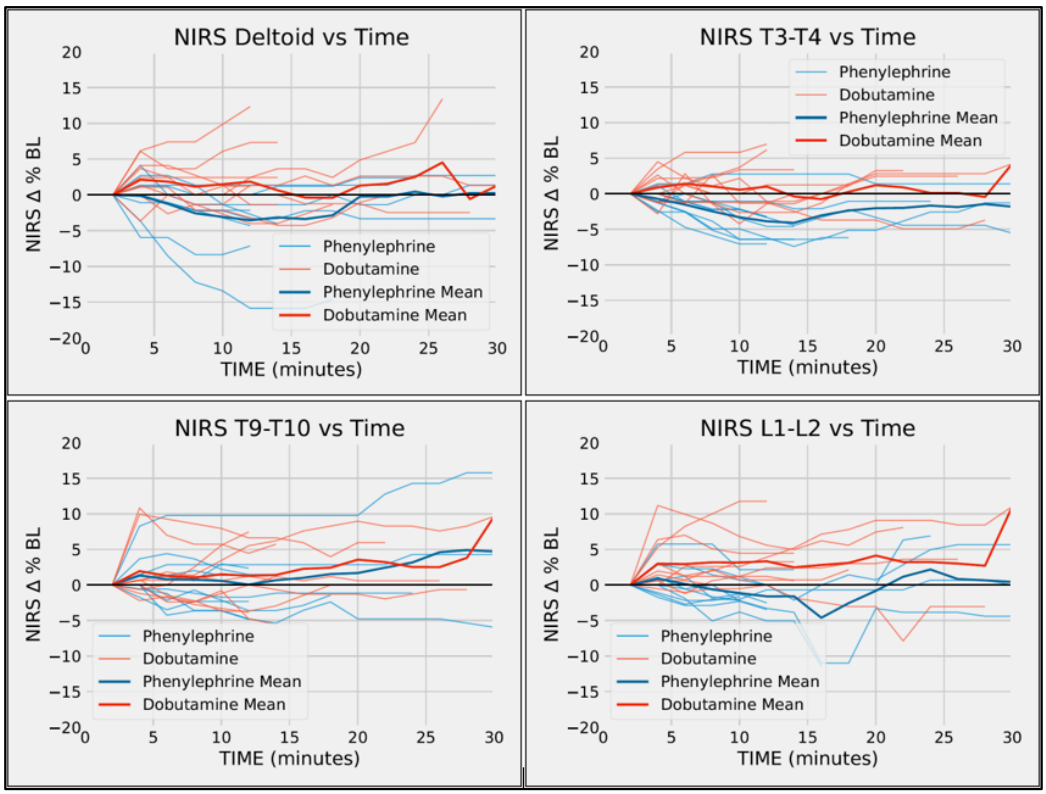

Fig. 3 — Illustration of the observed relative NIRS-values (y-axis) in time (minutes, x-axis). Additionally, a group-specific mean is added to the graphs. Illustration for each of the four measurement locations. The respective groups are represented by colour (red = dobutamine, blue = phenylephrine).

administered group. This in remarkable contrast with the overall negative relative values in the phenylephrine administered group. This overall trend is seen after application of the 'standard' model (with covariates z-score = 0 and MAP-value = 72.2 mmHg), but just as well after modifying the covariates (see Adaptations). The detailed results for each respective location are not discussed here, since the added Table III is more illustrative.

It is important to differentiate between on the one hand these 'modelled' estimated relative values (with the baseline values in mind) for each interventional group, and on the other hand the calculated differences between the two groups. The first are considered group-specific, the latter are comparative calculations between the two groups. When we compare these two interventional groups by applying the 'standard' model, significant differences between the estimated mean relative $rS_{ps}O_2$ and rS_dO_2 - values were observed at the deltoid muscle (-2.63% vs 2.01%), and at the lumbar level (-0.67% vs 2.97%). For both these locations, further significant differences were observed after adaptation of certain covariates (see Table III). At the high thoracic level, calculated alpha-values were on the verge of significance. Adaptations with rising blood pressure (MAPs of 90 or 100 mmHg) reduced the overall difference in mean estimated NIRS-values. Adaptations with rising dosage administration (z-score of 0.25) exert no apparent change on the observed differences in mean estimated NIRS-values between the two groups. Estimated mean values seem to be marginally lower for both groups when adapting for rising dosage administration.

Adverse event reporting

In this analysis we would like to report 3 adverse events, without occurrence of any serious adverse events. All of these events occurred in the dobutamine-administered group. In two of these cases a limited femoral haemorrhage was noticed postoperatively. No additional interventions were needed. In the third case, the patient complained postoperatively of angor thoracalis. Postoperative ECG and cardiac specific troponin testing were negative. No additional treatment was needed. Symptoms in this patient disappeared within minutes.

Discussion and conclusion

This master's dissertation is a preliminary data analysis of the research conducted. The objective was to investigate the influence of the continuous administration of phenylephrine or dobutamine on NIRS-measured paraspinal regional tissue oxygenation ($rS_{ps}O_2$).

Table III. — Linear mixed modelling results.

	Phenylephrine (N = 10)		Dobutamine (N = 10)		Alpha	Delta
	%	SE	%	SE		
DELTA NIRS DELTOID						
Standard model	-2,63	1,26	2,01	1,26	0,02	-4,64
Adaptations						
MAP 80mmHg	-2,17	1,27	2,12	1,3	**0,03**	-4,29
MAP 90mmHg	-1,58	1,31	2,26	1,37	0,06	-3,84
MAP 100mmHg	-0,99	1,37	2,40	1,47	0,10	-3,39
Z-score = 0,25	-2,70	1,26	1,89	1,26	**0,02**	-4,59
DELTA NIRS T3-T4						
Standard model	-1,62	0,98	1,18	0,99	0,06	-2,80
Adaptations						
MAP 80mmHg	-1,02	1,02	1,15	1,06	0,15	-2,17
MAP 90mmHg	-0,25	1,10	1,10	1,19	0,41	-1,35
MAP 100mmHg	0,53	1,20	1,06	1,34	0,77	-0,53
Z-score = 0,25	-1,69	0,98	1,13	0,99	0,06	-2,82
DELTA NIRS T9-10						
Standard model	0,70	1,01	1,34	1,02	0,66	-0,64
Adaptations						
MAP 80mmHg	0,72	1,04	1,30	1,09	0,70	-0,58
MAP 90mmHg	0,73	1,11	1,24	1,21	0,75	-0,51
MAP 100mmHg	0,75	1,22	1,18	1,37	0,81	-0,43
Z-score = 0,25	0,40	1,01	1,04	1,02	0,66	-0,64
DELTA NIRS L1-L2						
Standard model	-0,67	0,99	2,97	1,00	**0,02**	-3,64
Adaptations						
MAP 80mmHg	-0,54	1,01	2,85	1,06	**0,03**	-3,39
MAP 90mmHg	-0,38	1,07	2,71	1,18	0,06	-3,09
MAP 100mmHg	-0,21	1,17	2,58	1,34	0,12	-2,79
Z-score = 0,25	-1,05	0,99	2,81	0,99	**0,01**	-3,86

In Table III the results of the linear mixed modelling statistics are depicted. The constructed model was applied for the different outcome locations, and additionally for some covariate adaptations. See the Methods section for more information.
Legend Table III: N : absolute amount of patients; % : relative difference in mean estimated NIRS-values, in percentage; SE : standard error values for the modelled mean estimated NIRS-values; Alpha : respective alpha-values for the calculated differences between the mean estimated NIRS-values of the two interventional groups, for each of the different outcome locations, and different models applied; Delta : difference of mean estimated values of phenylephrine administered group minus mean estimated values of dobutamine administered group ('phenylephrine' minus 'dobutamine'); MAP: mean arterial pressure; Z-score : group-specific z-score, applied to the model as covariate.

By means of a linear mixed modelling approach, noticeable differences in estimated mean relative NIRS-values between the two groups were observed at the four different locations. We observed overall positive values of estimated mean relative $rS_{ps}O_2$ and rS_dO_2 in the dobutamine administered group. This in remarkable contrast with the overall negative relative values in the phenylephrine administered group. Besides an overall positive influence in the dobutamine administered group, significantly higher values were observed at the lumbar and deltoid level, this in comparison to the phenylephrine administered group. At the high thoracic level, the calculated differences were on the verge of significance. These modelled mean estimated relative NIRS-value differences are as high as 2.97% compared to baseline values (at the lumbar level), and as high as 4.6% for calculated differences between the two interventional groups (at the deltoid level). Furthermore, these differences in mean estimated NIRS-values tend to diminish (but not disappear) after implementing higher blood pressure values in the model.

To summarize, despite meticulous drug titration following a predetermined drug administration protocol, and statistical correction for differences in systemic blood pressure, noticeable differences in relative NIRS-values between the two interventional

groups were observed, and seem to favour the administration of dobutamine. Presumably, the vasodilating properties of dobutamine and concomitant rise in cardiac output are major confounding factors concerning these findings. Interestingly, the observed (and modelled) overall negative relative NIRS-values in the phenylephrine administered group are in contrast to previously conducted research at the paraspinal level[20,21]. A possible explanation for this contradiction is a less pronounced venous recruitment effect given the continuous drug administration, opposed to bolus administration. Furthermore, since administration of phenylephrine was started right after intubation, the anaesthetic-induced vasodilation was countered gradually and immediately.

We have to keep in mind some important remarks concerning the interpretation of these results. Firstly, it is important to differentiate between on the one hand these 'modelled' estimated relative values, and on the other hand the observed values during the execution of the trial. These estimated (predicted) values are entirely dependent on the quality of the available data and the used model. By means of this constructed model, we could calculate estimated mean NIRS-values for (a) each interventional group, and (b) the four different locations. Additionally, we could create an uniform assumption (i.e. prerequisite) for all these calculations. Therefore, we could correct for any heterogeneity within variables (e.g. the changes in mean arterial pressures), any heterogeneity between patients and any interindividual variation over time (e.g. the different administered dosages at each moment). Furthermore, by implementing the use of pre-determined baseline values, z-scores and relative changes in $rS_{ps}O_2$ values, we have constructed a very realistic and clinically relevant model. On the other hand, given the fact this is a preliminary data analysis concerning twenty patients, and the application of a rather complex modelling approach, we cannot exclude overfitting of the constructed model, and therefore a potential loss of quality of the available data. This is a first limitation of the analysis.

Secondly, needless to say, the physiologic properties of dobutamine and phenylephrine are entirely different. As mentioned before, their different resulting effect on the patient's cardiac output is possibly a major confounding factor concerning the observed regional tissue oxygenation values. Cardiac output values and other hemodynamic parameters were registered during the trial, but not used in this preliminary analysis. Therefore, the effect of any changes of the patient's cardiac output on the regional tissue oxygenation could not be determined. Inclusion of these hemodynamic variables (e.g. heart rate, cardiac index, etc.) made the used model too complex for the available data. Therefore, this strategy was abandoned to preserve the intrinsic quality of the statistical approach. This is a second important limitation of the analysis. Future research should focus on investigating the impact of changes in the patient's cardiac output on the paraspinal regional tissue oxygenation.

Lastly, we want to mention the pronounced differences in mean estimated NIRS-values between the two interventional groups specifically at the lumbar level. According to previous research conducted, it is primarily at the lumbar levels that significant changes in $rS_{ps}O_2$ are detected during ischemia and reperfusion[1,5]. We have to keep in mind that the spinal vasculature and perfusion in the included patients never was compromised, therefore local autonomic and regulatory mechanisms are presumed to be intact. Still, the observation of these remarkable differences at the lumbar level is an important finding of this preliminary analysis, and should be the focus of future research.

Conclusions

One of the more promising ways to evaluate spinal oxygenation during extensive aortic repair perioperatively is NIRS-based evaluation of the paraspinal collateral network. This technique allows us to evaluate the spinal oxygenation in an indirect, continuous, real-time and non-invasive manner. However, to date, validation for the detection of spinal cord ischemia in both open and endovascular repair of thoracoabdominal aneurysms is lacking. Likewise, the impact of different vasopressors on the paraspinal regional tissue oxygenation is still unknown. To our knowledge, this is the first randomized controlled trial that investigates the influence of continuous administration of phenylephrine and dobutamine on $rS_{ps}O_2$ in human participants.

By means of a linear mixed modelling approach, noticeable differences in estimated mean NIRS-values between the two groups were observed at the four different locations. These modelling results seem to favour the use of dobutamine. Besides an overall positive influence in the dobutamine administered group, significantly higher NIRS-values were observed at the lumbar level, in comparison to the phenylephrine administered group.

The clinical significance of these findings is unclear. Future research should focus on investigating (a) the impact of changes in the patient's cardiac output on the paraspinal regional tissue oxygenation and (b) the effect of different

vasoactive drugs at the lumbar paraspinal level.

Further research is warranted to establish more evidence with regard to the underlying pathophysiology and the clinical use of the vasoactive properties of these drugs during spinal cord ischemia, since a conclusive hemodynamic management is an important neuroprotective adjunct during major aortic repair.

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