MAP, cerebral oxygenation and TES-MEP variability's in scoliosis surgery

Variations in cerebral oxygenation measured with NIRS related to differences in MAP and contribution to TES-MEP monitoring during scoliosis surgery in neural healthy patients.

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Abstract

Objective: At this moment, a wake-up test needs to be done when amplitudes of TES-MEP monitoring decrease irreversible during scoliosis surgery, what mostly turns out to be a false-positive. To make TES-MEP measurements more reliable, we need to know what causes variability in TES-MEP amplitudes and how to diminish this variability. There is an indication that MAP is related to these variability's. The aim of this study was to improve IONM during scoliosis surgery by examining change in blood pressure in relation to cerebral oxygenation, measured with NIRS, as a possible cause of change in cortical excitability and therefore, variability in TES-MEP amplitudes.

Methods: Seven healthy subjects participated in a pilot study. MAP and NIRS were measured during this. Four interventions were executed to vary MAP of each subject: 1) valsalva manoeuvre, 2) handgrip exercise, 3) hip anteversion and 4) tilttable test. $EtCO_2$ is also measured to monitor its influence on cerebral oxygenation. Data of MAP, oxygenation and EtCO2 were analysed by Microsoft Excel, Matlab 2014a and IBM SPSS Statistics 21.

Results: The results of the handgrip exercise show a significant correlation between MAP and oxygenation (r_s = 0.893, P<0.01). There was no significant differ in MAP and oxygenation. Hip anteversion shows no significant correlation between MAP and oxygenation (r_s = -0.107, P<0.05). There was also no significant differ in MAP and oxygenation. The tilttable test and valsalva manoeuvre were excluded.

Conclusion: Blood pressure is related to cerebral oxygenation, but further research needs to be done to correlate oxygenation to the variability in TES-MEP.

Keywords: IONM, TES, MEP, NIRS, cerebral oxygenation, MAP, scoliosis surgery

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1 Introduction

1.1 Scoliosis

Scoliosis is a sideways curvature of the spine that most often occurs during the growth spurt just before puberty. While scoliosis can be caused by conditions such as cerebral palsy and muscular dystrophy, the cause of scoliosis is idiopathic in 80% of the patients. Most cases of scoliosis are not severe and therefore monitored on decline, usually with X-rays. Severe scoliosis can be disabling because of reduction in the amount of space within the chest, also induced by additional rotation of the spine in scoliosis. Braces are used for children with curvatures between 25 and 40 degrees who still will be growing significantly. In the Netherlands, about 60,000 people are known with scoliosis. Each year, this amount increases with approximately 6,000 patients, mostly girls between 10 and 18 years old. About 10% of these patients undergo scoliosis surgery, mainly for a curvature over 40 degrees. During this surgery, the spine is straightened as much as possible in a safe manner. Thereby, vertebrae along the curve are fused and supported by instrumentation like steel rods attached to the spine with screws.

1.2 Complications of scoliosis surgery

Besides general complications of surgery, like infections, a rare but feared complication during scoliosis surgery is damage of the spinal cord. Reported prevalence of spinal cord injury (SCI) following scoliosis surgery varies from 0.3% to 1.4%.[1][2][3] Types of potential SCI causes during scoliosis surgery involve: a) direct trauma from placement of wires, hooks, pedicle screws or from an expanding postoperative epidural hematoma; b) compression of spinal cord following corrective manoeuvres for the curve; c) excessive tension on the local vasculature, leading to decreased blood flow and cord ischemia. Spinal cord ischemia may also result from prolonged extreme hypotension (mean arterial pressure (MAP) <55 mmHg) or hypoxia secondary to decreased haemoglobin level.[2] [4]

Essential for spinal cord perfusion is maintaining adequate blood pressure. MAP is maintained at 65 to 70 mmHg during exposure and placement of instrumentation[5]. According to earlier literature, the anaesthesiologist should gradually elevate MAP to >70 mmHg approximately 30 minutes before performing corrective manoeuvres, to maintain cord perfusion during spinal manipulation and correction. [2][5][6][7]

1.3 Intraoperative neuromonitoring

Intraoperative neuromonitoring (IONM) is used to prevent SCI during surgical scoliosis procedures. Neuromonitoring must be sensitive to the feared pathophysiological process (i.e. ischemia, mechanical damage), taken account of all other factors liable to interfere with the recordings like anaesthesia, previous pathologies and body temperature.[8] Intraoperative monitoring can warn the

surgeon in time to correct problems and prevent postoperative deficits. Most used methods for IONM are described below.

1.4 Stagnara wake-up test

Before the use of electrophysiological methods, the only available method of observing spinal cord function was the Stagnara wake-up test.[9] The Stagnara wake-up test is 100% accurate in detecting gross motor movements, when properly administered. However, the main disadvantage of this test is that the patient has to become adequately awake during surgery. Therefore, this wake-up test involves a temporary reduction in anaesthesia, after which the patient is asked to move upper and lower extremities. The test carries risk, discomfort and provides only information regarding motor function.[2][10] For this reason, a need came for electrophysiological methods used for IONM.

1.5 Somatosensory evoked potential (SEP) monitoring

The first electrophysiological method used for IONM was recording of somatosensory-evoked potentials (SEPs)[11], which was first reported in 1977 by Nash et al[2][12]. The introduction of SEP monitoring to spinal surgery reduced the rate of intraoperative injury significantly. According to the Scoliosis Research Society and the European Spinal Deformities Society, the injury rate reduced from 0.7 to 4.0% before SEP monitoring to less than 0.55% with SEP monitoring[13][14]. SEP monitoring became widely used, but was significantly affected by the operating room environment, especially the presence of anaesthesia[15]. High concentrations of inhalation agents may cause false reductions in recorded amplitude and increased latencies[16]. However, there has been found that the use of propofol as anaesthetics causes reduced rate of false depression in SEP signals[2][12][17]. Also, patient's core temperature must be maintained close to normal range, because low body temperature may cause difficulties with reliable SEP monitoring[6].

SEP data can be obtained reliable in 98% of the patients without pre-existing neurologic disorders and in 75% of those with neuromuscular scoliosis, for example caused by cerebral palsy[6][7]. Warning criteria for SEP monitoring are a (more than) 50% drop in amplitude and/or 5-10% increase in latency[2][8][18][19]. Unfortunately, several cases of significant SCI have not been detected by SEP monitoring[13][20][21][22]. Since the SEPs were unchanged from baseline recordings, these cases are described as false-negatives[13]. Wiedemayer et al (2004) classified 4.1% of 658 neurosurgical cases using SEP monitoring as false negatives[22]. The pathophysiology of such cases is probably related to vascular injury to the spinal cord[13].

SEPs only assess the dorsal columns of the spinal cord and not the descending motor pathways[8][16]. Blood supply differs for dorsal columns from that of the anterior two-thirds of the spinal cord, which derives its blood supply from the anterior spinal artery. In theory, the anterior spinal cord would be at risk in case of a loss of adequate blood flow through the anterior spinal artery, but the dorsal columns remain intact. In that case, SEP recordings might not be affected[13]. According to Schwartz et al. (2007), the specificity of SEPs for qualifying sensory and motor loss are each 100%. However, sensitivity of SEPs for identifying motor loss is only 43%[5].

1.6 Motor evoked potential (MEP) monitoring

Previous described false-negative findings with the use of SEPs alone for surgical monitoring suggest the need for usable methods to monitor the motor tracts of the spinal cord during surgery[11]. Since the late 1980s, transcranial electrical stimulated motor evoked potential monitoring (TES-MEP) is introduced and proved capable of providing direct monitoring of the spinal cord motor tract function[7][17]. During surgery, TES-MEPs are elicited by transcranial electrical stimulation of the motor cortex. Resulting EMG responses are recorded at peripheral muscles below the level of surgery. Various limb muscles can be used simultaneously for recording, usually including the bilateral anterior tibial muscle[17]. Earlier, no strict warning criteria for detection of neurologic damage were defined. As TES-MEP became more popular, the use of explicit response warning criteria became more desirable.

1.7 Warning criteria of TES-MEP monitoring

Despite the desire for explicit warning criteria, most hospitals do not use consequent warning criteria in practice. Clinicians interpret TES-MEP monitoring outcomes on the basis of surgical and clinical information[17]. Examples of several criteria used are briefly discussed below.

First, some studies define the same warning criteria as in SEP are used for MEP monitoring: decrease of amplitude by 50 or increased latency response of 10%[2][23]. Despite using these criteria, Modi et al. (2009) reported a case of false-negative intraoperative MEP that developed paraplegia after surgery. They believe that intraoperative blood loss and hypotension could have caused the cord injury. However, those changes should have been noticed on MEP monitoring by decreased amplitude.[23]

Second, Schwartz et al. (2007) defined warning of TES-MEP at 65% decrease in amplitude and used the Stagnara wake-up test to confirm neurologic injury identified by MEP and SEP based on these criteria. They reported 100% sensitivity with TES-MEP for identifying true-positive neurologic damage in 1121 patients treated for scoliosis.[5] Pastorelli et al. (2011) also defined warning criteria as a reduction in amplitude of at least 65% for TES-MEPs compared with baseline. In five of the 66 cases in their study, a transient reduction in the amplitudes of SEPs (two patients) and/or MEPs (five patients) was recorded intraoperative without postoperative neurologic deficits. In two cases, the alert was related to hypotension and two cases to surgical manoeuvres.[19] These five cases are called true positives.

Finally, Langeloo et al. (2003) concluded that at least one recording, satisfying the warning criteria of amplitude decrease of at least 80%, is sufficiently strict to prevent occurrence of false-negatives for TES-MEP recordings in 142 patients. This warning criterion is also sufficiently stringent to ensure that no neurologic event goes undetected. Severe amplitude decreases (80% or more) caused by systemic problems, such as hypotension, occurred in 7 of the patients.[17] The University Medical Centre Groningen (UMCG), where the current study is executed, handles a warning criterion of at least 80% decrease in TES-MEP amplitudes as well.

1.8 False-positives

Combining SEP and TES-MEP monitoring enables prediction of the postoperative neurologic status with 98.6% sensitivity and 100% specificity[19]. Nevertheless, as previously mentioned, false-positives occur during TES-MEP monitoring. Probably, a significant number of false-positive findings in IONM are attributable to the used anaesthetics[14][24]. In 2011, Pastorelli et al. described a total intravenous anaesthetic regimen with controlled delivery rates of propofol and remifentanil. This regimen together with combined SEP and TES-MEP monitoring resulted in a sensitivity and specificity of IONM for sensory motor impairment of 100% and 98% respectively.[19] Tiecks et al. (1995) described propofol and remifentanil in total intravenous anaesthesia adequate for intraoperative MEP monitoring as well[25]. During surgery, significant decreases in TES-MEP amplitudes also occur when nothing is changed in anaesthetic regimen.

Some other reports, including IONM in spinal cord monitoring, mentioned an association of decline in evoked potentials (false-positives) with a drop in systemic blood pressure[2][12][24][26][27]. Wiedemayer et al. (2002) describe 17 of 93 cases of change in intraoperative evoked potentials in which evoked potentials returned to normal during surgery (false-positives). In 11 of those 17 cases interventions were directed to tissue perfusion pressure. In only two cases, systolic blood pressure was below 90 mmHg when evoked potentials started to decline. This indicates that in individual cases, perfusion of nervous tissue may be affected even at normal systemic blood pressures, for example during exerted additional mechanical stress on nervous tissue.[24]

It has been shown that TES-MEP data may show changes in activity before SEP monitoring does, because TES-MEP responses reflect neural transmission through corticospinal motor tracts[2]. Also, mechanical injury, vascular injury or hypotensive anaesthetics can result in MEP changes without SEP changes in neuromonitoring. Since motor pathways are more supplied with blood than sensory pathways and most neurologic injuries during scoliosis surgery appear to be related to ischemia, TES-MEPs are more likely to change under conditions of decreased blood pressure than SEPs.[5] [19]

Besides this, decline in amplitude and blood pressure are not always related to surgical interventions[19]. When significant decline in TES-MEP amplitude occurs and does not restore after incremented blood pressure, a wake-up test is executed to check for neurological damage.

1.9 Aim of the study

In the current situation, a wake-up test needs to be done when amplitudes of TES-MEP monitoring decrease irreversible during surgery, what mostly turns out to be a false-positive. To make TES-MEP measurements more reliable, we need to know what causes variability in TES-MEP amplitudes and how to diminish this variability. As previously mentioned, possible causes for false-positive monitoring are decreased blood pressure, surgical interventions and anaesthetics. Because of the occurrence of false-positive monitoring during surgery without intervention or change in anaesthetics, this study will concentrate on the influences of blood pressure on TES-MEP measurements. Taking into account the relatively stable conditions under which false-positives may occur, the ori-

gin of the amplitude variability might be deriving from the location where the stimulus is provided: the motor cortex. Therefore, this study will be focused in particular to the influence of MAP on the excitability of the neurons in the motor cortex. Excitability of neurons depends on the amount of available oxygen in the brain. This could be measured with near-infrared spectrometry (NIRS).

1.10 Research question

Do variations in cerebral oxygenation measured with NIRS relate to differences in MAP and how could this relation contribute to TES-MEP monitoring during scoliosis surgery in neural healthy patients?

The examination of the research question is based on literature and a pilot study on healthy subjects. Literature provides insight in the current situation and shows the potential contribution of this study to the future. This will be reviewed later, in the discussion. At first, the principles of TES-MEP and NIRS are clarified below. The relation between cortex oxygenation and MAP will be considered combining literature and the results of the pilot study. Subsequently, examining the findings from the pilot study and earlier research in literature on the correlation between blood pressure, NIRS and TES-MEP monitoring will lead to a recommendation for the orthopaedic, anaesthetic and/or neurosurgical department in the UMCG. But primarily, the suspicion between MAP and oxygenation will be described. Autoregulation is mainly preserved during anaesthesia with propofol[25] and is therefore taken in account. This mechanism will be discussed later.

1.11 Expected results

Based on what is published on the subject, protocol and results of our pilot study, we expect to find an answer to the research question. We hope to explain the changes in TES-MEP amplitudes by using NIRS, during scoliosis surgery in neural healthy patients. This could confirm our hypothesis.

If the hypothesis below is confirmed, the final product of the multidisciplinary assignment will contain a research proposal for a subsequent study. The following study could confirm our results and will give an explanation for the variability in MEP amplitudes. If we have to reject the hypothesis below, we will write a recommendation for a subsequent research proposal with reference to other variables, e.g. temperature, position of the patient etc.

1.12 Hypothesis

The outcome of this study will contribute to the knowledge of the relation between differences in blood pressure and associated change in cortex oxygenation measured with NIRS. If a decrease in blood pressure and a decrease in oxygen concentration in the motor cortex are present, this could indicate that MAP influences the excitability of the brain. Therefore our hypothesis is: When mean arterial pressure decreases, cerebral oxygenation also decrease, which results in a decrease of excitability of the cortex. This could help answering the question if blood pressure influences TES-MEP amplitudes during scoliosis surgery. Be-

fore we start answering this last question, we need to know if there is a relation between blood pressure and excitability.

1.13 Mean arterial pressure

Literature shows that cerebral blood flow (CBF) and cerebral oxygen consumption ($CMRO_2$) are linearly correlated[28]. Furthermore, MAP and blood flow are correlated positively[29], which indicates a relation between MAP and cerebral oxygenation. Harper (1966) shows that blood flow remains practically constant when MAP value is between 90 and 180 mmHg[30]. During scoliosis surgery, MAP is maintained at 65 to 70 mmHg as mentioned before. A change in MAP in this range results in a major change in cortical blood flow and therefore also in cerebral oxygenation. For that reason, it is likely that a change in MAP results in a change in cerebral oxygenation, and therefore in NIRS signal.

1.14 Autoregulation

Autoregulation is preserved during scoliosis surgery[25]. This mechanism influences cerebral blood flow and is affected by metabolism, $PaCO_2$ and PaO_2[31]. The CBF in grey matter is five to six times higher than in white matter. This can be explained by higher metabolic activity in or near cell bodies of neurons in the grey matter. The brain uses 20% of the total oxygen consumption of the body and besides that, it uses aerobically oxygen, storage of glucose and oxygen is minimal. Hence, sufficient cerebral blood flow is necessary for adequate oxygen delivery in the brain. Autoregulation ensures that cerebral blood pressure remains between 50 mmHg and 150 mmHg despite changes in perfusion pressure by means of vasoconstriction and vasodilatation. When the pressure is beyond this range, autoregulation is not able to keep the blood flow sufficient. This results in irreversible injury of the brain. When CBF decreases, release of vasoactive substances from the brain is stimulated and will cause arterial dilatation. Increase of pCO_2 and decrease in pH level also leads to vasodilatation due to change in acidity of cerebrospinal fluid. When the pressure raises, the cerebral smooth muscle will constrict and will dilate when the pressure decreases. Next to that, increase of pO_2 leads to vasoconstriction.

The blood flow can be explained by two laws, Ohm's law and Poisseuille's law. Ohm's law describes the following function: $Flow = \Delta P/R$. In which ΔP is the difference between intra-arterial pressure and venous pressure, the cerebral perfusion pressure (CPP)[32]. Blood flow can also be described by Poisseuille's law. This law assumes that flow is directly linked to ΔP, (η) blood viscosity, (L) length of the vessel and (R) the radius of the vessel.[33]

$$Flow = (\pi \times R^4 \times \Delta P)/(8 \times \eta \times L)$$

This formula shows that the radius of the vessel has the most influence on blood flow. Even small changes in radius can cause a significant change in flow.

1.15 TES-MEP

Transcranial electrostimulation (TES) using muscle motor evoked potentials (MEPs) is used to monitor the motor pathway in the spinal cord. Significant

changes in MEP are correlated with spinal cord injury. Monitoring with TES-MEP is currently used in many surgeries in which the spinal tract is at risk to be damaged[34].

The principle of TES involves the use of stimulation of the brain with an electrical current. This causes stimulation of the pyramidal tract, motor neurons, nerves, neuromuscular junction and finally produces a muscle contraction. MEP is the compound muscle (motor) action potential recorded by surface electrodes at different muscles, including the anterior tibial muscle. Two electrodes, a cathode and anode, are placed at C3 and C4 on the head, according to the 10-20 system. Maximal stimulation occurs in the white matter deeper inside the brain, presumably the corona radiate.[35][36]

The duration of TES pulses used in scoliosis surgery is very short, about 0.05 ms. A train of five pulses with an interval of 2 ms is provided during one stimulation. The voltage range of this stimulation lies between 75 and 900 V, with maximal currents up to 0.9 A. A higher current is needed when using EEG cup electrodes compared to the minimal current that is necessary when using subdermal needle electrodes or corkscrew electrodes.[34] This last type of electrodes is used for TES-MEP monitoring during scoliosis surgery in the UMCG.

Transcranial stimulation could cause metabolic activation changes depending on whether it is transcranial electrical stimulation or transcranial magnetic stimulation (resp. TES or TMS). TMS causes a local increase in oxygenated hemoglobin (HbO_2) and a decrease in cytochrome aa3 concentrations. A decrease in cytochrome aa3 concentration indicates a transformation from oxidized state of cytochrome to reduced state. In this way, a decrease in cytochrome aa3 provides direct information about increased intracellular utilization of oxygen. Data of Oliviero et al.(1999) showed that repetitive TMS induces metabolic activation of the cerebral cortex together with an increase in cerebral blood flow. In contrast, TES activates axons in the underlying white matter, but does not cause a change in metabolic activation of the underlying tissue. Consequently, TES induces no change in CBF.[37]

Signal recording is possible at the spinal cord or at muscle level. At the spinal cord, the first wave that can be recorded by an epidural electrode placed over the upper thoracic spinal cord, is the direct or D-wave. This is the orthodromic action potential that origins from direct stimulation of the white matter and involves no synaptic activity. Therefore, D-waves are relatively insensitive to the effects of anaesthetics. The succeeding waves at the spinal cord are indirect or I-waves and are produced by a current induced by the cortical neurons, excited by the same stimulus. I-waves contain synaptic activity and therefore, are strongly suppressed by general anaesthetics. This is because during general anaesthesia, there is a reduction in spontaneous activity in the interneurons of the spinal cord, reducing the overall level of excitation reaching the anterior horn cells. In normal awake patients, D- and I-waves reach the anterior horn cells from where a muscle contraction is produced. Without anaesthetics, either D-waves, I-waves and MEP's are obtainable using just one pulse. In addition, with the use of anaesthetics, only a train of five cortical stimulation pulses enables recording of D-waves and MEPs. Under very mild anaesthetics I-waves could sometimes be recorded, but this does not apply to scoliosis surgery. With certain (non muscle relaxant) anaesthetics muscle MEPs can be measured. In the UMCG, total intravenous anaesthesia (TIVA) with propofol is used during

scoliosis surgery, which is preferred when monitoring muscle MEP, because it suppresses the responses less than inhalational agents (Figure 1).[34]

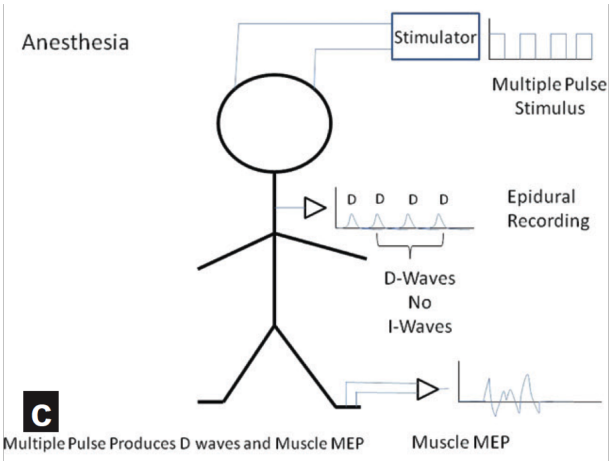

Figure 1: D-waves and MEPs recording during scoliosis surgery.[34]

Baseline responses of muscle MEP to multipulse TES are obtained prior to incision. To establish initial (baseline) thresholds, IONM during scoliosis surgery starts by looking for a response for a single trial using a stimulus intensity of 100 V for a given configuration (for example, C3-C4; anode-cathode;5 $\times$ 2 ms protocol). If there is no response to stimulation in any muscle, intensity will be increased by 25-50V increments and stimulation is repeated. Once a muscle responds to stimulation, the voltage needed to elicit that response is noted and becomes the threshold value for that particular muscle. This value serves the basis for amplitude comparisons. Stimulus intensity is increased until all muscles being monitored were recruited or until a maximum intensity is reached.[38]

As mentioned before, when significant decline in TES-MEP amplitudes during IONM does not restore, a wake-up test is executed to check for neurological damage. This decline is not always related to surgical interventions[19]. Some reports mentioned an association of decline in evoked potentials (false-positives) with a drop in systemic blood pressure[2][12][24][26][27]. A change in MAP results in a change in cortical blood flow and therefore also in cerebral oxygenation[28][29]. For that reason, it is likely that a change in MAP results in a change in cerebral oxygenation, and therefore in NIRS signal.

1.16 Near Infrared Spectroscopy

NIRS is a technique that measures cerebral oxygenation and hemodynamics continuously in a non-invasive way. It is based on the principle that near infrared light, with a range from 700 to 1000 nm, penetrates skin, soft tissue and bone easily[39][40]. The Near Infrared Light is absorbed by two chromophores: hemoglobin and cytochrome aa3. These chromophores absorb the near infrared light, depending on oxygen. Due to this, NIRS measures the absolute change in HbO_2, deoxygenated hemoglobin (HHb) and total concentration hemoglobin

(THb). Changes in intracellular cytochrome aa3 are also measured[41]. Cytochrome aa3 is the final enzyme in the mitochondrial respiratory electron transport chain. This enzyme catalyses 90% of the intracellular oxygen consumption. Therefore, hemoglobin is an indicator for blood oxygenation and cytochrome aa3 is indicator for tissue oxygenation[42]. Hence, NIRS gives information about the balance between oxygen supply and demand in the brain[43]. It is possible to measure changes in intravascular and intracellular oxygenation conditions and hemodynamics, constantly and rapidly.

1.16.1 Principles

The algorithm of NIRS is based on the modified Lambert Beer law[42][44]:

$$OD_\lambda = Log(I_0/I) = \varepsilon_\lambda \times c \times L \times B + OD_{R,\lambda}$$

Where OD_λ is a dimensionless factor known as the optical density of the medium, I_0 is the incident radiation, I the transmitted radiation, ε_λ the extinction coefficient of the chromophore ($\mu M^{-1} \times cm^{-1}$), c the concentration ($\mu M$) of the chromophore, L is the distance (cm) between light entry and light exit point, B the pathlength correction factor to correct scattering and $OD_{R,\lambda}$ gives the oxygen independent light losses due to scattering in the tissue. The modified Lambert-Beer law describes the correlation between the absorption of near infrared light by a chromophore and the concentration chromophore in tissue.

The modified Lambert-Beer law can be used only for medium with one chromophore. NIRS measures three chromophores. The sum of the contributions of each compound give the solution and this is most used algorithm in NIRS systems.

1.16.2 Pathlength correction factor B

The factor B can be approached by "time-of-flight" measurements (Artinis). During these measurements, a very short pulse is released in the tissue. The pulse is received by an ultrafast camera. This gives the time of flight t. The travelled distance d is given by:

$$d = (c \times t)/n$$

Where c is the velocity of light and n the refractive index of the tissue.Factor B is given by:

$$B = d/L$$

1.16.3 PortaLite

The NIRS system PortaLite is used during this research. This is a continuous wave system with two wavelengths (around 760 nm and 850 nm) of emitting light. 2 MB data can be stored. The PortaLite weighs 84 grams including battery. The size of the device is 84 ×54×20 mm. The wire to the probe (58×26×6 mm) is about 1.3 meter. The device is wireless and utilizes a Bluetooth connection. It is allowed to use the PortaLite for monitoring during surgery[45].

The PortaLite contains three LD's (optodes) which each sending two wavelengths ($\pm$ 760 nm and $\pm$ 850 nm). If the probe is attached to the skin, the near infrared light emits through the skin and diffuses back. The recipient recieves the final signal. The source-detector distance is the distance between the receiver and the LED's. The source-detector distance of the first LED is 30 mm, second is 35 mm and third is 40 mm. The depth of measurement is 2 to 2.5 cm[45].

1.17 Correlation between MAP and NIRS

Literature shows that NIRS has the potential to reduce postoperative dysfunctions in patients during lumbar spine surgery in prone position [46]. There is an indication, as mentioned before, that a positive correlation exists between blood pressure and cerebral oxygenation. When MAP increases, there is also an increase in cerebral tissue oxygen saturation ($SctO_2$) [47][48]. However, according to Lahaye (2014), MAP is inconsistently related to $SctO_2$[49].Van Noord (2014) shows a negative correlation between MAP and NIRS[50]. A positive correlation means that a decrease in MAP leads to a decline in cerebral oxygenation and this will result in lower excitability of the brain. This correlation could be an explanation for changes in MEP potentials during spine surgery. To examine this correlation a pilot study was performed.

2 Methods

2.1 Methods of data collecting

All quantitative data were collected during the pilot study on healthy subjects. The structure and essence of pilot are based on the literature listed. Data were collected from primary sources in high and low frequencies.

2.2 Healthy subjects

We studied seven healthy subjects, six women and one man with a mean age of 21 years (range, 20 to 25 years). Subjects were included as healthy, i.e. neurological healthy, ambulatory, no former history of cardiovascular diseases, respiratory diseases or head or arm injuries. The study was approved by the Medical Ethics Committee of the UMCG and all healthy subjects gave their informed consent prior to the study.

2.3 Interventions

To vary blood pressure of the subject, four interventions were executed during this study according to the written protocol in this order: 1) the valsalva manoeuvre , 2) the handgrip exercise, 3) hip anteversion and 4) the tilttable test. The complete protocol of the pilot study is attached in Appendix II including a detailed description of the influence of each manoeuvre on blood pressure.

For the valsalva manoeuvre a manometer was used to keep the pressure up to 40 mmHg. The handgrip test was executed with a manometer to measure the maximum voluntary contraction (MVC) and to control a minimum of 37.5% of the MVC during the test.

2.4 Pilot protocol

A schematic representation of the protocol is shown in Figure 10 in Appendix II.The study consists of four short exercises and took a total time of 45 minutes. The valsalva manoeuvre was executed twice while the other three tests were executed once. To determine a baseline, the study started with a rest measurement maintaining for five minutes. Two minutes of rest preceded each measurement to recover to the baseline. The participant was in supine position during all exercises.

2.4.1 Valsalva manoeuvre

Subject exhaled forcibly at the maximum of the effort during 15 seconds. A period of increased blood pressure started and recovered to the baseline in a few minutes. This test was repeated once when blood pressure returned to baseline.

2.4.2 Handgrip exercise

Subjects maximal voluntary contraction (MVC) was obtained before exercise and should at least be kept at 37.5% of the personal MVC during the test. Isometric contraction was performed during at least two minutes. Blood pressure returned to baseline.

2.4.3 Hip anteversion

The researchers were holding both legs in a 90-degrees hip anteversion, sustained for five minutes. The legs were lowered to the original position followed by a short time of rest to observe the effect. Blood pressure returned to baseline.

2.4.4 Tilttable

The tilttable was electrically rotated from original horizontal position to 70 degrees. This position was hold for 5 minutes, where after the tilttable was returned to original horizontal position. To ensure capturing the complete effect, it was necessary to wait for recovery of blood pressure.

2.5 Measurement of blood pressure and oxygenated hemoglobin of the frontal cortex

Blood pressure is varied by performing the aforementioned interventions. Therefore, the subjects lied in supine position on the tilttable with their feet supported on a footrest. A continuous sphygmomanometer was fixated on the right or left index finger while the hand was held on heart level. The NIRS probe was placed on the right side of the forehead of the subject. CO_2 measurement was performed with a face mask fixed over mouth and nose and was given in $EtCO_2$; the level of CO_2 released at the end of expiration. The CO_2 measurer (sphygmomanometer) and the NIRS device were connected to the computer and visualized on a PC monitor in a program written by dr. J.W. Elting in Labview. Raw data were digitally stored on the laptop and extracted in Excel-format for analysis.

2.6 Data analysis

First, all data were imported into Microsoft Excel and data of each test for each participant were plotted to visualize effects. Values were marked as artefact when one value differed more than 25% from the last and the following value. Artefacts were removed. Values of the NIRS signal measured by the third LED, were referred to as oxygenation. This value gives the amount of oxygenated blood in micromolar. Oxygenation data were corrected to a zero baseline by subtracting the first measured value of oxygenation from all other values. In this way, all measured oxygenation values are relative. All aforementioned analyses were executed in Microsoft Excel (2010-2013).

2.7 Cross correlation and lag difference

As mentioned before, there is a discussion if blood pressure and oxygenation of the cortex are positively correlated. Data were analysed with a cross correlation to calculate the correlation between MAP and oxygenation measured with NIRS. Trendlines were added to each graph. To correct for a delay of NIRS signal with respect to MAP, a lag difference between MAP and oxygenation was calculated and was taken into account with the formation of scatter plots. This lag difference is a shift in time between an event in MAP and in oxygenation. If there was a lag difference, effects of events would not occur at the same time and therefore distort the effect in the scatter plot.

2.8 Graphs

To examine smaller drifts, which are more likely to occur during scoliosis surgery in the UMCG, averages per 30 seconds were determined. Between two events (E1 and E2), e.g. tilt of the table/leg raise/etc., a slow drift in MAP was identified. Change in MAP between these events was calculated over two different periods as shown in Figure 2. Therefore, in period 1 (P1), the mean of MAP after E1 and the mean of MAP before E2 were calculated. After that, the mean increase or decrease was calculated. The same was done for period 2 (P2). Important was that MAP formed a plateau with no high peaks in it. These peaks could indicate an additional event, such as movement. Since the interest lies in a slight drift, peaks were excluded by the chosen periods. A second set of 30 seconds was chosen in the higher and lower plateau to examine differences between these periods. Cross correlations and mean differences, in percentage, were executed in Matlab 2014a. To include only relevant data in further analysis, some inclusion criteria were applied to the data. Mean change of MAP of each manoeuvre had to exceed 5 mmHg. Besides, a test will be included if the two periods of MAP and Oxy not differed significantly from each other.

For the included tests, graphs showing MAP, oxygenation and CO_2 during the different manoeuvres of each participant were included in the results. The two chosen periods are visible in the graphs and differ for each manoeuvre. The first period is visible as the black horizontal bars in the graphs. Second period are visible as the grey horizontal bars in the graphs (Figure 2). Change between these periods were plotted in a bar graph where MAP is shown as a percentage and oxygenation as the absolute change of the relative data. Differences in CO_2 were calculated and plotted in a second bar graph for each of the seven

participants for the two periods, CO_2 in P1(CO_2-1) and CO2 in P2 (CO_2-2).

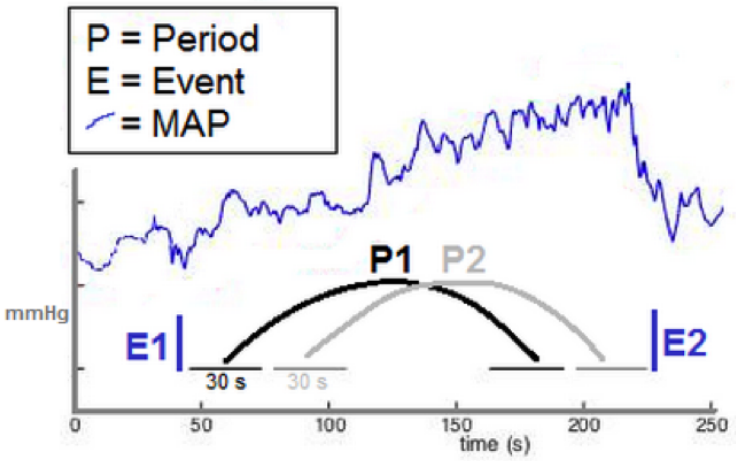

Figure 2: Methods of data collecting of the pilot study.

2.9 Statistics

A Wilcoxon signed-rank test was executed to find a possible difference between the change in MAP of P1 (MAP-1) and the change in MAP of P2 (MAP-2). If there was no significant difference between those two periods, the periods were assumed to be representative for the rest of the time. If there was a significant difference found between the two periods, it was not possible to assume that these periods were representative for this manoeuvre and were excluded for further data analysis. This test was also executed between the change in oxygenation of P1 (Oxy-1) and oxygenation of P2 (Oxy-2). Spearman's test was performed to find a correlation between all four variables: 1) MAP-1 and MAP-2, 2) MAP-1 and Oxy-1, 3) MAP-2 and Oxy-2, 4) Oxy-1 and Oxy-2, 5) MAP-1 and Oxy-2.

3 Results of pilot study

3.1 Handgrip

Figure 3 shows a cross correlation of MAP and oxygenation during the handgrip test. During this test the highest correlation found, is ($r_s = 0.772$).

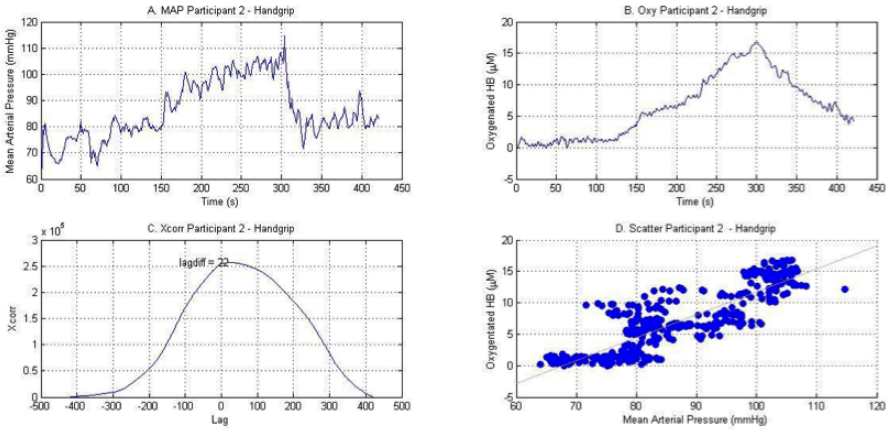

Figure 3: (A) Mean arterial pressure of participant #2 plotted against the time. (B) Oxygenation of participant #2 plotted against the time. (C) Lag difference of the cross correlation of the oxygenation plotted against the MAP of participant #2. (D) Scatterplot corrected by lag difference of oxygenated HB plotted against MAP.

The mean MVC measured was 63 kg (range, 40 to 92 kg). The mean of 37.5 % of the MVC was therefore 23 kg (range, 15 to 35). This 37.5% of MVC was hold for a mean of 2.4 minutes (range, 2 to 3.06 minutes). In Figure 3 panel (D) a trend is shown to visualize an effect. Since there was a loop in the figure, the plot was corrected by a lag difference. The mean lag difference of six of the seven participants was 36.7 seconds (range, 1 to 64). The lag difference of participant #7 was 302 seconds and was excluded in the mean. The lag difference was not incorporated in the plots in Figure 4. In Figure 4, the oxygenation increases with the time until the handgrip manometer was released.

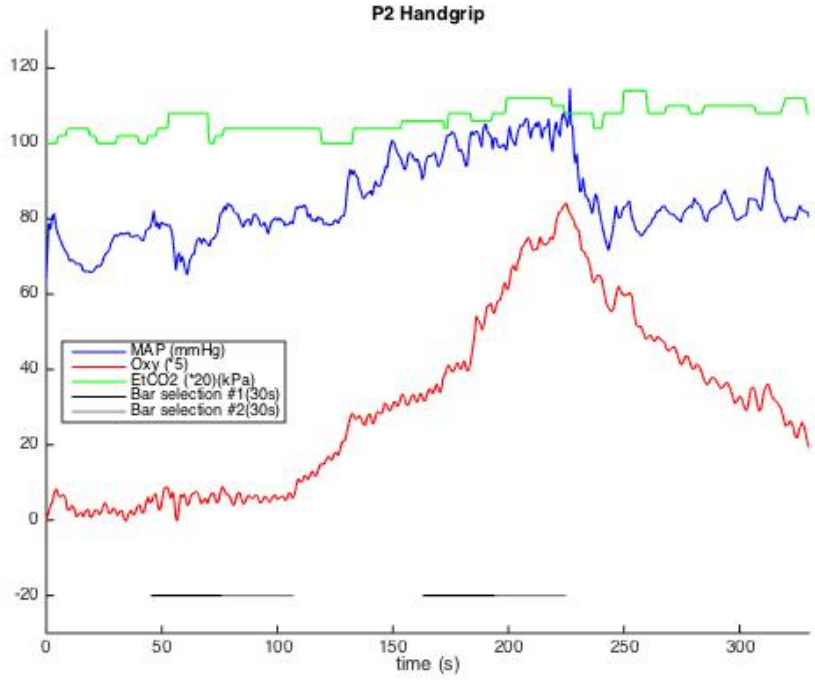

Figure 4: A plot of the handgrip manoeuvre of participant #2. MAP, Oxygenation and $EtCO_2$ are showed. The dark grey and light grey bars show the selection over which the mean of the variables is calculated.

The mean difference of CO_2 in P1 and P2 CO_2-1/2 difference is 0.29 kPa (range 0.14 to 0.42 kPa) and per participant are shown in Figure 5 (5B shows only CO_2 and given in Figure 6 (table overview participant information).

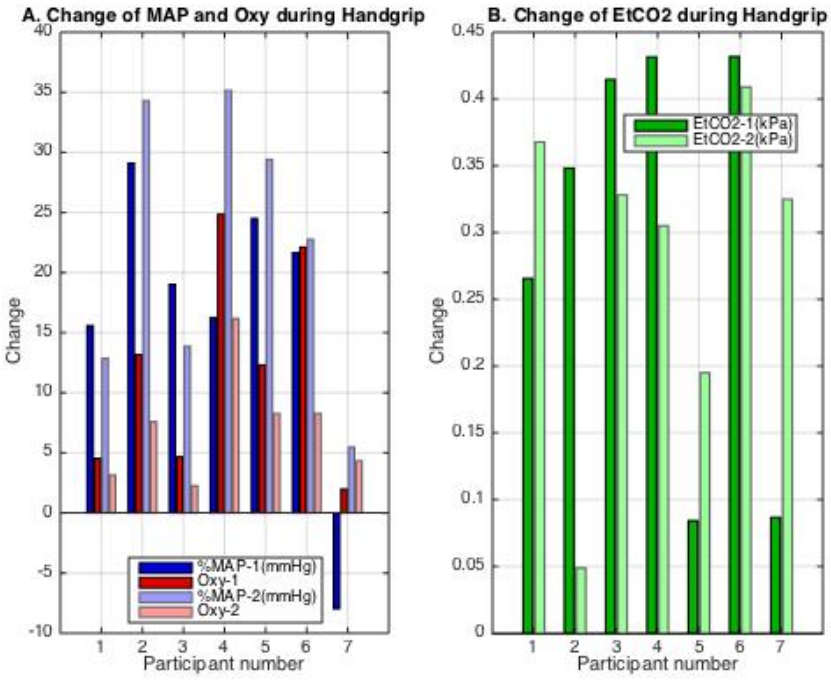

Figure 5: A. The change in MAP and Oxygenation of the two different periods is shown for all participants, #1 to #7. B. The mean change in CO_2 is given for each participant during the two periods.

In the Table 1 is shown that the absolute average of the change in the mean MAP for the handgrip is 16.14 mmHg. It is the largest of all changes per manoeuvre. The change in mean $EtCO_2$ for the handgrip is the second largest of all manoeuvres with a value of 0.29 kPa.

Table 1: An overview of information of the participants and the independent variables MAP and $EtCO_2$. Remarkable values of the table given in red. The overall means are given as an absolute average over all periods per participant and in total.

Abbreviations: V, valsalva manoeuvre test; HG, handgrip exercise; HA, hip anteversion; TT, tilttable test

P	M/F	Length (m)	Weight (kg)	Mean MAP (mmHg)				Mean change MAP (mmHg)			
				V	HG	HA	TT	V	HG	HA	TT
1	F	1.77	56	85.2	91.8	91.1	90.5	-0.52	12.18	1.16	-6.91
2	F	1.74	72	66.6	89.2	86.1	68.8	-1.07	24.35	8.14	5.06
3	F	1.70	68	81.0	108.0	96.5	76.9	-1.15	16.43	-4.80	-2.68
4	F	1.72	65	72.7	85.2	66.5	67.5	-4.34	18.81	-4.12	-0.37
5	F	1.72	58	84.6	88.2	65.4	99.7	0.38	20.94	-11.8	-7.09
6	F	1.75	63	81.3	93.2	83.4	65.7	1.58	18.61	3.38	-2.50
7	M	1.93	78	104.2	103.3	103.3	101.1	-1.01	-1.67	-4.28	-7.85
ABS. AVERAGE		**1.76**	**65.7**	**82.2**	**94.1**	**84.7**	**81.8**	**1.58**	**16.14**	**5.38**	**4.64**

P	Mean $EtCO_2$ (kPa)				Mean change $EtCO_2$ (kPa)			
	V	HG	HA	TT	V	HG	HA	TT
1	4.88	5.45	5.81	5.16	-0.63	0.32	0.15	-0.18
2	5.42	5.34	5.57	4.89	-0.21	0.20	0.16	-0.10
3	5.39	5.45	5.40	5.13	-0.19	0.37	-0.17	-0.06
4	5.23	5.34	5.00	4.65	-0.58	0.37	0.06	0.36
5	5.29	4.71	4.45	4.61	-0.22	0.14	-0.08	-0.06
6	5.07	5.09	4.93	4.91	-0.28	0.42	0.03	0.01
7	5.24	5.09	4.94	5.01	-0.14	0.21	0.25	0.06
ABS. AVERAGE	**5.22**	**5.21**	**5.16**	**4.91**	**0.32**	**0.29**	**0.13**	**0.12**

The content of Table 2 shows that the mean change of MAP in case of the handgrip is 22.0% in the first period and 16.0% in the second period. As result to the Wilcoxson signed-rank test, MAP in P1 and P2 and Oxy in P1 and P2 did not significantly differ, $p < 0.05$. Oxy-1 did significant correlate to the Oxy-2($r_s = 0.786$, $p < 0.05$). The pairs of MAP/Oxy in P1 and MAP/Oxy in P2 did not correlate significantly (MAP/Oxy in P1 $r_s = 0.643$, $p > 0.05$, MAP/Oxy P2 $r_s = 0.536$, $p < 0.05$). Although MAP-1 did correlate strongly to Oxy-2 ($r_s = 0.893$, $P < 0.01$) .

Table 2: This figure shows the mean and standard deviation of all variables during handgrip exercise, MAP-1, MAP-2, Oxy-1 and Oxy-2. The outcome of the Wilcoxon Signed-Rank Test between MAP-1 and MAP-2, Oxy-1 and Oxy-2 are showed. The outcome of the Spearman's correlation test between 1). MAP-1 and MAP-2, 2). MAP-1 and Oxy-1, 3). MAP-1 and Oxy 2, 4). MAP-2 and Oxy-2, 5). Oxy-1 and Oxy-2 are listed.

		MAP-1	MAP-2	Oxy-1	Oxy-2
DESCRIPTIVES		(change in %)		(change in µM)	
Mean		22.0	16.9	8.933	11.946
Std. deviation		11.6	11.9	7.053	8.927
WILCOXON SIGNED-RANK TEST					
Sig.		0.176		0.063	
SPEARMAN'S CORRELATION					
MAP-1	r_s	-	0.643	0.607	0.893 **
	Sig.		0.119	0.148	0.007
Oxy-2	r_s	-	0.536	0.786 *	-
	Sig.		0.215	0.036	

* Correlation is significant at the 0.01 level (2-tailed).
** Correlation is significant at the 0.05 level (2-tailed).

3.2 Hip anteversion

During the hip anteversion there are two events initiated: 1) the legs are raised to 90 degrees 2) the legs are lowered to original position. As an example, MAP, Oxy and $EtCO_2$ of participant 2 during hip anteversion are showed in Figure 6, which also provides a clear picture of the (reactions to the) events.

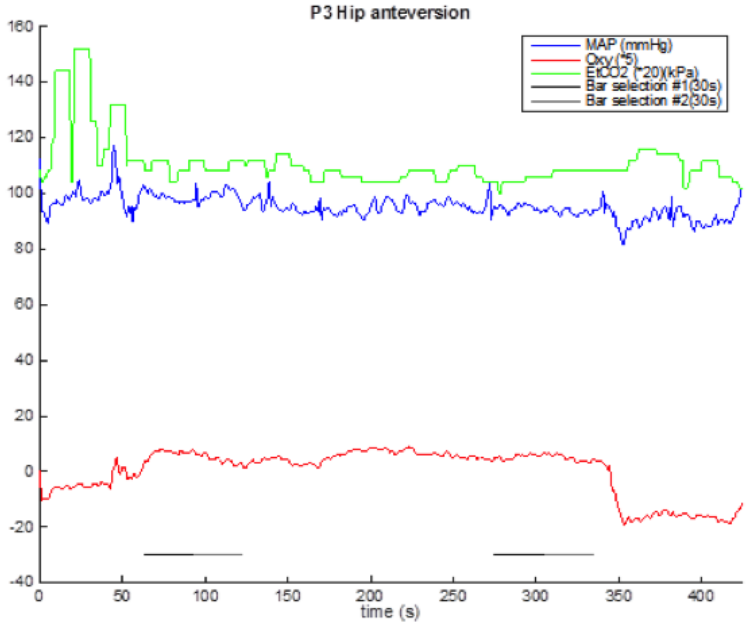

Figure 6: This figure shows a plot of the handgrip manoeuvre of participant #2. MAP, Oxygenation and $EtCO_2$ are showed. The dark grey and light grey bars show the selection over which the mean of the variables is calculated.

Panel A of Figure 7 shows that the change in MAP and Oxygenation differs in orientation between all participants. As shown in panel B of figure 9 the $EtCO_2$ differs in orientation similar to the MAP and Oxygenation although the orientation is not similar in some participants and periods.

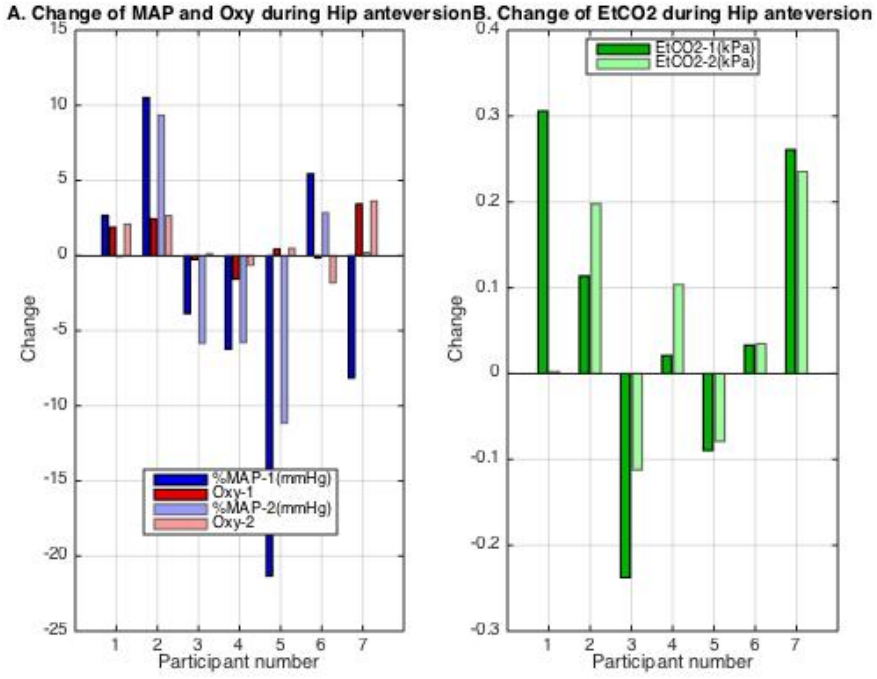

Figure 7: Hip anteversion A. The change in MAP and Oxygenation of the two different periods is shown for all participants, #1 to #7. B. The mean change in CO_2 is given for each participant during the two periods.

The absolute mean change in MAP for the hip anteversion is 5.38 mmHg as shown in Table 1. The absolute mean change in $EtCO_2$ for the hip anteversion is 0.13 kPa.

The content of Table 3 shows that the mean change of MAP is -2.99% in the first period and -1.49% in the second period in case of the hip anteversion. As result to the Wilcoxson signed-rank test, MAP-1/2 and Oxy-1/2 did not significantly differ, $p > 0.05$. Oxy-1 did significant correlate to the Oxy-2($r_s = 0.893$, $p < 0.01$). The pairs of MAP-/Oxy- 1 and MAP-/Oxy-2 did not correlate significantly (MAP-/Oxy-1 $r_s = 0.071$, $p > 0.05$, MAP-/Oxy-2 $r_s = 0.500$, $p > 0.05$). MAP-1 did not correlate to Oxy-2 ($r_s = -0.107$, $P < 0.05$).

Table 3: This figure shows the mean and standard deviation of all variables during hip anteversion, MAP-1, MAP-2, Oxy-1 and Oxy-2. The outcome of the Wilcoxon Signed-Rank Test between MAP-1 and MAP-2, Oxy-1 and Oxy-2 are showed. The outcome of the Spearman's correlation test between 1). MAP-1 and MAP-2, 2). MAP-1 and Oxy-1, 3). MAP-1 and Oxy 2, 4). MAP-2 and Oxy-2, 5). Oxy-1 and Oxy-2 are listed.

		MAP-1	MAP-2	Oxy-1	Oxy-2
DESCRIPTIVES		(change in %)		(change in µM)	
	Mean	-2.99	-1.49	0.89	0.93
	Std. deviation	10.48	6.73	1.76	1.93
WILCOXON SIGNED-RANK TEST					
	Sig.	1.000		0.237	
SPEARMAN'S CORRELATION					
MAP-1	r_s	-	0.750	0.071	-0.107
	Sig.		0.052	0.879	0.819
Oxy-2	r_s	-	0.500	0.893 **	-
	Sig.		0.252	0.001	

** Correlation is significant at the 0.01 level (2-tailed).

4 Discussion

In our pilot study we tested the correlation between change in MAP and cortical oxygenated Hb over relatively stable phases during four different tests. The results of the handgrip test reveal that these variables are correlated, which is consistent with our hypothesis that if MAP increases, oxygen saturation level in the cortex also increases. In our findings, the hip anteversion test showed less convincing results to confirm our hypothesis. The two other tests were excluded on grounds of inclusion criteria.

4.1 Interventions

4.1.1 Handgrip test

The handgrip test results are most consistent with our hypothesis, in comparison to the other tests. The trendline as shown in the scatterplot (Figure 3) implies a higher blood pressure leads to a higher oxygenation. The lag difference for the subjects was determined. As previously mentioned, the mean of the lag difference was 36.7 seconds for 6 out of 7 participants. However, subject #7 showed a lag difference of 302 seconds. Assuming that it is not physiologically

possible that the healthy body cortical oxygen response takes 302 seconds to react on rise in blood pressure, subject #7 was excluded in the calculation of the mean lag difference. The script, to calculate the lag difference, written in MATLAB, by our best knowledge, did not work sufficiently for subject #7, thence the large lag difference was given. Statistically, there is a strong correlation found (r_s=0.893, p<0.01) between MAP-1 and Oxy-2, which differed round 30 seconds. This could attribute to the assumption of the delay, earlier found with the lag difference. According to this test, blood pressure and oxygenation are associated, which is supportive for our explanation of differences in TES-MEP amplitudes.

4.1.2 Hip anteversion

The hip anteversion test gave neither fast response nor distinct visible change in MAP. Only a very slight slope was noticed. Overall, there was a sufficient response to determine MAP changes. Because of the slight slope and the fluctuations in MAP, it was not possible to determine a delay of Oxy relative to MAP. We found that the overall change in MAP was 5.38 mmHg, while the lower limit lies at 5 mmHg. We have showed that the mean change in CO_2 was very low (0.13), this concludes that the outcome could not be influenced by the CO_2 response. It is possible that it points out that there was not much alteration in all of the variables. Statistically, there are no significant differences in Oxy-1 and Oxy-2, but there is a high correlation between these two parameters (r_s=0.893, p<0.01). Besides, MAP and Oxy were not correlated, according Spearman's correlation. This can be explained by the fact that however differences in MAP values were too small, we conclude that the test was not completely suitable for the expected response.

4.1.3 Tilttable test

According to the Wilcoxon signed-rank test, the two measurement periods differ significantly for MAP (p<0.05). Therefore, the tilttable test is not included for further analysis, because apparently both measurement periods are not representative for the complete stable phase during the tilttable test. A table with the statistical analysis of the tilttable test and the corresponding graphs are displayed in the appendix.

4.1.4 Valsalva

We found that the Wilcoxon signed-rank test, which is used to calculate if there are significant differences between the two chosen measurement periods, showed no significant difference for the valsalva manoeuvre. There was no significant correlation between MAP-1 and MAP-2, Oxy-1 and Oxy-2 and MAP-1 and Oxy-2 either according to Spearman's correlation. The valsalva manoeuvre showed an absolute average in mean change of MAP of 1.58 mmHg (table met alle waarden). This alteration is too low to generate a difference in oxygenation. The valsalva manoeuvre is excluded for this reason. Besides, the absolute average in mean change $EtCO_2$ was highest during this test, namely 0.32 kPa(table). This influences the results possibly, but we do not know the role of CO_2 exactly. We cannot conclude anything owing to carbon dioxide therefore.

4.2 Protocol

To answer the research question regarding the relation between MAP and cortical oxygenation, four different tests to influence blood pressure are used in the pilot study. Effects of these tests differed and gave us the opportunity to select data we could use for analysis. We have explicitly chosen to analyse the stable phases of the tests between the events, because this was the most comparable period with surgery setting. Of this stable phase, two periods of 30 seconds were chosen right after the first event and two periods of 30 seconds just before a second event. We chose a duration of 30 seconds for the periods to 1) examine largest differences in blood pressure in the stable phase while 2) ensuring that enough data is captured to calculate referable values for the rest of the period. However, this resulted in a loss of data in two out of four tests, in which the period between the events lasted at least five minutes. In these cases, we have not used three minutes for analysis with potentially valuable information.

As we expected prior to the pilot study, during valsalva and handgrip exercise a greater amount of change in CO_2 was measured compared to the other tests. The amount carbon dioxide (CO_2) in blood could have been a possible confounding factor during the research. By means of a high CO_2 rate, blood pressure (and therefore also MAP) will increase. This effect will be nullified by vasodilatation due to autoregulation. This is established at the Valsalva manoeuvre for instance. Because of exhaling forcibly during 15 sec., the CO_2 rate in the blood will increase. It is necessary to eliminate this excess of CO_2 by the respiratory system. Therefore, $EtCO_2$ decreases fast in slow-drift phase, after the manoeuvre. There is barely any change in blood pressure as a result of autoregulation.

Even though autoregulation remains intact using intravenous anaesthetics [25], the setting of the pilot differed a lot from the OR setting. For example, the participant being awake caused uncontrolled movements and changes in the measured variables. In OR setting a lot of variables are controlled by anaesthetics, while we just tried to influence MAP.

Because of a thorough background research and description of each manoeuvre, we knew precisely what we had to do during the measurements, allowing us to work as efficiently as possible. Besides that, our time schedule was not very realistic. We could not finish our four times seven participants measurements in just one day, but we finished it in three. Likewise we did not describe some basic principles in detail in the patient information letter, for example that participants are not allowed to move or talk during the measurements. This interrupted our measurements once in a while and we had to do it over or measure for a longer period. Another point to discuss is to think beforehand about how, in which format, we would have preferred our output of data. During our pilot we used 'time per heartbeat' instead of the usual 'seconds' to plot the time. When the heartbeat frequency would have differed strongly, this could have had influence on our data analysis. Since the time in all graphs is per heartbeat, an examination was executed to calculate a possible variation in heartbeat frequency. Therefore, the X value (heartbeat) was differentiated and plotted to check the frequency differences. In our case, it turned out all right. We worked with the variable oxygenated Hb and deoxygenated Hb although we could think of using the total Hb. It is possible that the ratio of oxy- and deoxygenated Hb influences the excitability of the motor cortex, besides the

amount of oxygenated Hb. Furthermore, we did not take a possible delay into account between the change in MAP and the change in oxygenation. To determine whether there was a delay, we should have done all measurements twice to compare these and to exclude any coincidence and artefacts. The duration of our measurements was small compared to a normal duration of a scoliosis surgery, which is around eight hours. We would like to assume that our ratio of time analysed to our total time is representative for the ratio of time analysed of the scoliosis surgery to the total time a scoliosis surgery takes. We calculated the correlation and differences between different time periods to make a hopeful assumption about the representation, although a longer duration could give more insight or information. At last, the periods are chosen by eye, it could be improved to do this programmed in Matlab. The gradient of MAP should be taken as small as possible and a minimal drift could be set. This way it will be more precise and more reliable.

4.3 Results in context of literature

As mentioned in the introduction, literature showed no consequent correlation between MAP and cerebral oxygenation. Variability of TES-MEP amplitudes could be related to confounding factors of their study. Our pilot study showed a positive correlation between MAP and cerebral oxygenation for the included (handgrip) test. During scoliosis surgery, MAP is maintained between 65 to 70 mmHg to minimize (the effect of) blood loss. Literature shows that MAP has to be maintained high (>80 mmHg or 20% above baseline) to counteract the decrease of perfusion of the spinal cord. If MAP decreases below 60 mmHg, alerts may occur and if MAP increases, amplitudes of TES-MEP often return without spinal cord injury.[2][4][5][7][51] Important is to find an explanation for the loss in TES-MEP amplitudes at the moments when no surgical intervention takes place, whereby waking up patients during scoliosis surgery is not necessary. Despite some literature attributes the loss of TES-MEP amplitudes to a decrease in perfusion of the spinal cord[2][4], no evidence has proven this assumption. To find an explanation for the variability of TES-MEP amplitudes, it could be helpful to discriminate different parts of the TES-MEP pathway that could influence MEP amplitudes. One of these parts is the motor cortex, where the TES-MEP pathway starts and where we started a study to examine the influence of MAP on its amplitude variability. The next step in discriminating the influence of the motor cortex on TES-MEP amplitude variability needs further research during spinal surgery.

5 Future research recommendations

Our research indicated a correlation between changes in cerebral oxygenation due to changes in MAP. Based on this indication, we recommend to examine correlation between cerebral oxygenation and TES-MEP in further research. Future research will hopefully give more insight into influences of MAP on the excitability of the (motor)cortex and may give an explanation for the variability in TES-MEP amplitudes during scoliosis surgery. Possibly, fluctuations in TES-MEP amplitudes could be explained by NIRS. With these outcomes, false-positives could be controlled with NIRS and more assurance during IONM in

scoliosis surgery.

This further research has to be performed during a complete scoliosis surgery. Practically, we advise to include MAP, NIRS and MEP in future research during scoliosis surgery, including annotations of 1) surgical interventions and 2) manual changes in anaesthetics that could influence either MAP or MEP. For example, in case of a surgery takes eight hours, it is important to choose the periods for analysing real specific. We described a delay in oxygenation with respect to MAP of about 30 seconds. For this reason, we recommend to analyse a slight drift in MAP (at least 5 mmHg) with a time frame longer than 1 minute. Regarding to our study, we recommend choosing at least two periods. The amount of periods depends on the available time frame, allowing the whole time frame being filled with periods. Changes over these periods in MAP should be compared to the annotations, i.e. if there is a logical explanation for the change or that no surgical intervention was performed. Subsequently, we suggest that changes in MAP and cortical oxygenation are compared to the TES-MEP amplitudes measured during the same time frame. Finally, which part of the data is chosen during analysis of the results is dependent of the following criteria: 1) the period of 30 seconds must have the lowest gradient, this could be programmed in Matlab, 2) there has to be a slow drift between the two periods. The reason why is described in the discussion.

As described in the introduction, different kinds of spinal surgeries struggle with false-positive results[52]. In the case that a future research confirms a positive correlation between change in MAP, oxygenation and differences in TES-MEP amplitudes during scoliosis surgery, this method could also be introduced in other areas of spinal surgery. In those areas, for example spinal tumour dissections, MEP is already used resulting from TES or TMS and, if proven valuable, using NIRS could provide more well-founded information.

Future research could also focus on combining NIRS with SEP measurements. Compared to TES-MEPs, SEP responses are very low in amplitude and require prolonged averaging. Therefore, depending on the ambient level of noise, the time required to determine if a significant change has occurred may be 3-5 minutes or more.[2][34] SEP responses are more easy to quantify than muscle MEPs, because of a simple waveform. SEPS can be sensitive to anaesthesia, since some of the potentials recorded are 2-3 synapses away from the stimulus (Figure 8). SEPs have high specificity but low sensitivity. Nevertheless, SEPs are most critical during placement of wires during spinal surgery, because of the direct damage to the dorsal columns during this manoeuvre, which may not be detected using MEPs. For this reason, SEP could provide more insight in discriminating different levels to which a change in blood pressure could have an influence. For example, when both MEP and SEP show a decrease in amplitude following a decrease in cerebral blood flow, it could be possible that MAP influences the perfusion of the spinal cord more than that cerebral oxygenation influences cortical excitability. Prior to the future research, including SEP amplitude analysis should receive attention in order to determine the value added.

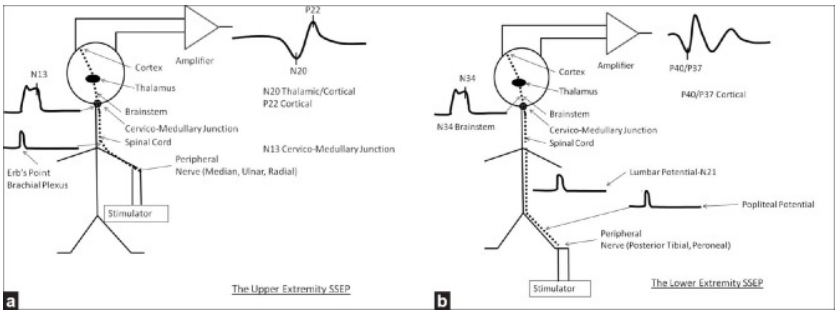

Figure 8: Illustrations of the anatomy underlying the upper (a) and lower (b) somatosensory evoked potentials by Stecker et al. (2012)

Moreover, further research should take the latency into account. This latency is presumably related to the amount of voltage used during surgery and therefore to the excitability of the brain (Figure 9)[38]. As mentioned before, some studies define an increased latency response of 10% as warning criteria for MEP monitoring[2][23]. Jellinek et al. (1991) concluded that changes in latency as well as amplitude are useful evaluation criteria of intraoperative motor evoked potentials[53].

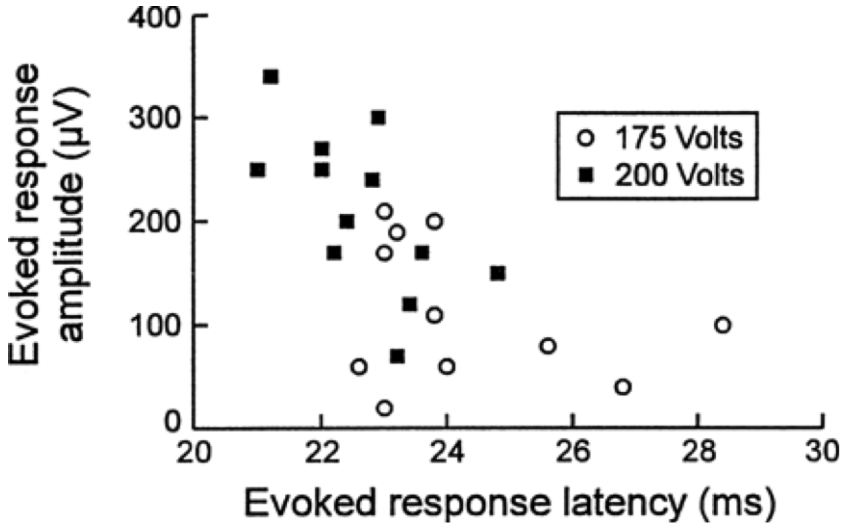

Figure 9: Relation between evoked response amplitude and latency depending on the voltage of the stimulus according to Calancie et al. (1998)

It could also be beneficial to measure total Hb with NIRS during the complete surgery. The ratio between oxygenated and deoxygenated Hb can be determined by NIRS. Storage of oxygen is minimal in the brain, so this ratio is a measure for brain activity[37]. A higher ratio, and therefore more oxygenated Hb, results in an increase in brain activity. Tissue saturation index (TSI), given by NIRS, is also a measure for brain activity. Most of the energy used in the human brain comes from the mitochondria[37], where cytochrome aa3 catalyzes

90% of the intracellular oxygen consumption[42]. Therefore, this could be an indicator for tissue saturation index.

6 Conclusion

The aim of this study was to improve IONM during scoliosis surgery by examining change in blood pressure in relation to cerebral oxygenation, measured with NIRS, as a cause of the variability in TES-MEP amplitudes and thereby the excitability. Blood pressure is related to cerebral oxygenation, but further research needs to be done to correlate oxygenation to the variability in TES-MEP.

7 Dankwoord

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8 Abbreviations

CBF	Cerbral Blood Flow
$CMRO_2$	Cerebral oxygen consumption
CO_2	Carbon dioxide
CPP	Cerebral Perfusion Pressure
$EtCO_2$	End Tidal CO2
HbO_2	Oxygenated Hemoglobin
HHb	Deoxygenated Hemoglobin
IONM	Intraoperative Neuromonitoring
MAP	Mean Arterial Pressure
MAP-1	Change in mean arterial pressure of period 1
MAP-2	Change in mean arterial pressure of period 2
MEP	Motor Evoked Potential
MVC	Maximal Voluntary Contraction
NIRS	Near Infrared Spectroscopy
OR	Operation Room
Oxy-1	Change in Oxygenation of period 1
Oxy-2	Change in Oxygenation of period 2
$PaCO_2$	Partial pressure of arterial CO2
PaO_2	Partial pressure of arterial O2
SCI	Spinal Cord Injury
$SctO_2$	Cerebral tissue oxygen saturation
SEP	Somatosensory Evoked Potential
TES	Transcranial Evoked Stimulation
THb	Total concentration Hemoglobin
TIVA	Total Intravenous Anaesthesia
TMS	Transcranial Magnetic Stimulation
UMCG	University Medical Centre Groningen

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I Appendix I - working method

I.1 Short summary

In the Netherlands, about 600 people with a scoliosis undergo surgery of the vertebral column each year. A rare but feared complication during scoliosis surgery is damage of the spinal cord, which can lead to paraplegia in the worst case. To prevent this, intraoperative neurophysiological monitoring (IONM) is used during surgery. The function of the spinal cord is 'monitored' by, among others, trans cranial electrical stimulation (TES) of the brain. This electrical stimulation of the brain results in a contraction of the muscles trough the pyramid tracts. The potentials arising in the muscles, called 'motor evoked potentials' (MEP) are registered with needles or with electrode pads. TES-MEP measurement can predict when motoric problems will or will not arise. (Pastorelli et al., 2011) Before the surgeon starts the surgery, the amplitude of the TES-MEP potentials are measured in different muscles after anesthesia is given to create a baseline measurement. If the potentials decrease over 80 percent in amplitude during scoliosis surgery, motoric failure is expected. (Pastorelli et al., 2011) A problem of TES-MEP is the variability of the amplitudes in some patients during surgery. The cause of this variability is unknown, although, partly from experience, we know that blood pressure and anesthesia depth could play a part in this. Motor evoked potentials are (partly) affected by excitability of neurons in the motor cortex. Variations in excitability might occur because of differences in the oxygen supply of the brain, in response to changed blood pressure in the body. To investigate this, near infrared spectroscopy (NIRS) could be used. This is a safe, non-invasive technique based on light radiation that detects differences in light, which may indicate local changes in the amount of oxygenation in the brain. However, there are a few disadvantages of this relatively easy technique. For example, NIRS showed high rate of intra variability in absolute values (Madsen and Secher, 1999). Thereby is shown that body posture or the rotation of the head in patients that are anesthetized during spinal cord surgery influences NIRS measurements. (Andersen et al., 2014) (Fuchs, Schwarz, Kulier, and Litscher, 2000) Overall, in the current study, we would like to investigate the reaction of NIRS signal on blood pressure changes and if NIRS is correlated to TES-MEP amplitudes during scoliosis surgery. In the University Medical Center Groningen (UMCG), a pilot study can help in order to examine the relationship between blood pressure and NIRS signal and in the influence of body posture on NIRS measurement. This all may result in a clinical applicable protocol for a pilot study in the operation room.

I.2 Purposes of research

I.2.1 Clinical, social and scientific interest

Clinical we would like to find an explanation for the variability in amplitude in the TES-MEP measurements. At this moment, a 'wake-up test' needs to be done when TES-MEP amplitudes decrease irreversible during surgery, what mostly turns out to be false-negative. To make TES-MEP measurements more reliable, we need to know what causes the variability in TES-MEP amplitudes. In this case we will firstly focus on if there is a relationship between TES-MEP

amplitude changes and changes in cortical oxygenation and metabolism. Consequently, the clinical relevance is that monitoring the patient during scoliosis surgery will be improved. The biggest interests are blood perfusion of the brain, excitability of the neurons in the motor cortex, the way that TES stimulates the brain and what influences the NIRS signals.

During scoliosis surgery, it could be that the spinal cord is damaged by stretch forces. If there is an indication for this, like persistent decrease of TES-MEP amplitudes, the patient should be taken out of narcosis to test if there is any damage. This wake-up test can be a traumatically experience for the patient. Besides, it takes a while to wake the patient and the staff can not do anything during this time: surgery is temporarily stopped. This is a financial loss and the staff could use this time for other proceedings what relates to a social interest. Another important social interest of the research is to minimize the chance of taking out the patient of the narcosis according to the protocol, for example at low amplitude of the TES-MEP measurements. Surgery will unnecessarily prolongs and causes an increased chance on complications and stress for the patient.

To use a NIRS device along with TES-MEP measurements, it is important to know what the technical possibilities of the device are . Besides, it is important to know how the NIRS system can be implemented in the devices that are already being used. The reliability of the results of TES-MEP will increase when NIRS can explain the variability's present in the amplitudes. There is also a scientific interest to find if the results are significant better when NIRS is used. Will the use of it lower the amount of false-negative cases? What are the disadvantages and do the benefits compensate the drawbacks?

I.2.2 Research question

Do variations in NIRS signal relate to differences in blood pressure and do they correlate to TES-MEP amplitude changes during scoliosis surgery in neural healthy patients?

I.3 Subquestions

1. How does TES influences the neurons of the motor cortex?
2. What is the effect of TES on the distribution of intracranial effective depolarized fields?
3. How can properties like latency, amplitude and variations of MEP's be described?
4. What is the warning criteria during surgery of TES-MEP?
5. Do TES-MEP and blood pressure relate to each other?
6. What is known about the relationship between blood pressure and oxygenation of the cortex?
7. What is known about the relationship between variations in blood pressure and cortex excitation?
8. How do anesthetics influence excitability of the cortex?

9. Is NIRS applicable in the OR considering the usage of bluetooth and with the position of the patients head resting in a headrest?

10. How do oxyhemoglobin, desoxyhemoglobin and TSI relate to the amplitudes of the TES-MEP and autoregulation?

11. What is the influence of variation in blood pressure on NIRS assuming that other variables will remain constant?

I.4 Methods

Firstly to draw a conclusion from our research question we will have to take a few steps during this study. We use data from patients who have had cardiac surgery from the UMCG. This data gives us an indication that there is a correlation between NIRS data and blood pressure during surgery. We will start the research with a literature study. This way we want to find answers to some of the subquestion.

Secondly, we will make an appointment with the medical supervisor, Gea Drost, for a mid-term evaluation. The intention is to discuss our progress.

Thirdly, we will develop a protocol intended for the pilot study below. We are going to analyze and process data we get from the pilot study and we will evaluate all results with our medical, technical and process supervisor. After that, an option is to process the data with Matlab or to do a statistic data analysis. We will draw a conclusion after the literature study and pilot study.

At all times, we will keep the OR, NIRS and TES-MEP protocols as a guideline to be sure that our ideas and conclusions will be realistic and executable.

Eventually, we will develop a protocol for a pilot study using NIRS on the operating room in the UMCG and we will write the final paper. We will finish the multidisciplinary assignment with a presentation at the University of Twente and at the University Mecial Center Groningen.

I.4.1 Pilot study

During our pilot study, we would like to find answers to our subquestions regarding NIRS. Our aim is to find a relation between blood pressure and NIRS signal. Therefore, we will examine different variables such as NIRS values, CO2 and blood pressure. Examples of other variables that could influence MEP amplitude could be anesthetics in terms of depth and duration, stress-reaction of the body, blood volume and saturation or respiratory rate. However if this pilot will be in an OR these variables will be kept as stable as possible so we will leave those out of our pilot.

The set-up of the pilot will be described in a protocol and will be defined later on. During this pilot study, we will measure the NIRS signal, CO2 and blood pressure in different conditions: in rest, with a tilt-table (to increase and decrease blood pressure), with the handgrip maneuver, with the valsalva method and with the legs in anteversion whereupon we will lower our legs quickly.In some of these tests the CO2 will differ and in some of them they will not. Therefor we can see how CO2 influences the signal of NIRS or not to control if it is a confounding factor. We will not be able to lower our blood pressure to extremely low levels without medication. Thereupon, we have to make some assumptions about the lower blood pressure levels. This could give us an insight in the

situation of the patient in the OR. We will also try out different positions of the head in combination with the NIRS equipment. We will examine if there is an influence of the position of the head on the NIRS outcome and if the pressure of the head on the NIRS has an influence on the signal. Firstly, we will focus on the difference in blood pressure and position of the head. After that, we will write a research proposal for a second pilot study in the OR.

I.5 Planning

I.5.1 Timetable and distribution of tasks

	Step/Phase	Deadline	Hours
1	Initiation setup working method	6 May 2015	15
2	Meeting in UMCG	30 May 2015	5
3	Midterm evaluation medical mentor UMCG	11 or 12 May 2015	2
4	Midterm evaluation Process mentor UT	5 June	2
5	Midterm evaluation Technical mentor UT	Week 7 (to define)	2
6	Pilot study	13 May if we have a "GO"	8
7	Final paper	24 June 2015	50
8	Proces paper	26 June 2015	20
9	Paper presentation UMCG	29 or 30 June or 1 July 2015	20
10	Paper presentation UT	2 July 2015	8

I.5.2 Expected results

Based on the results of the literature study, protocol and results of our pilot study, we expect to find answers on the subquestions. These results will hopefully lead us towards the final answer of the research question. We hope, to explain the changes in TES-MEP amplitudes by using NIRS, during scoliosis surgery in neural healthy patients. This could confirm our hypothesis.

The final product of the multidisciplinary assignment will contain a research proposal for a subsequent study if the hypothesis below is confirmed. The following research could confirm our results and will give an explanation for the variability in MEP amplitudes. When we have to reject the hypothesis below, we will write a recommendation for a subsequent research with reference to other variables, e.g. temperature, position of the patient etc.

Hypothesis When the blood pressure is low and autoregulation can not counteract the decreased blood supply to the brain, the motor cortex will have a lower oxygenation. This could lead to lesser excitation of the motor cortex, which could explain the lower TES-MEP amplitudes showing on the EMG. This could explain the differentiation of the amplitudes.

II Appendix II - Protocol of Pilot Study

II.1 Project summery

The aim of this pilot study is to find a relationship between blood pressure and NIRS signal. Therefore, we will examine different variables such as NIRS values, CO2 and blood pressure in eight healthy participants (range, 20-25 years). During this pilot study, we will measure NIRS signal, CO2 and blood pressure in different conditions: rest, during valsalva maneuver, hip anteversion, handgrip maneuver and with a tilt-table test. Blood pressure may increase or decrease during these conditions. In some of these tests also CO2 concentrations will differ. By measuring CO2, we could examine if and how this influences the signal of NIRS if it is a confounding factor. We will not be able to lower our blood pressure to extremely low levels without medication so we examine the effect of difference in blood pressure. Data will be processed by using statistical analysis.

II.2 Goal

The aim of the pilot study is to find out if there is any relationship between differences in blood pressure and variations in NIRS signal. Therefore, we will examine different variables such as NIRS values, blood pressure and CO2. The reason to know if there is any relation, is to find an answer to the second part of the research question: does this connection correlates with changes in TES-MEP amplitudes during scoliosis surgery in patients without any other neurological problems?

II.3 Study design

The study is an experimental study on a group of six people. Young adults with a mean age of 22 are more sensitive to raise their blood pressure then children. [54] To investigate if there is a relation between blood pressure and oxygenation it is the most suitable population. The research population will consist of six women with an age between 20 and 23 years. The conditions of the test persons has to be as constant as possible, except for the condition being tested. They all have to be sober and in good health state. Beforehand the panel has to fill in a questionnaire about their physical terms. In that way it is possible to take the remaining differences in account. The expected duration of the study is three days from 10.00 AM till 17.00 PM. In those days all the measurements will take place. One week is scheduled to process the results of the measurements.

The whole test on one participant takes about 45 minutes. In **figure 1** is the time division shown.

10

Inclusion criteria:

1. Age between 20 and 25
2. Neurological healthy
3. Ambulatory

Exclusion criteria:

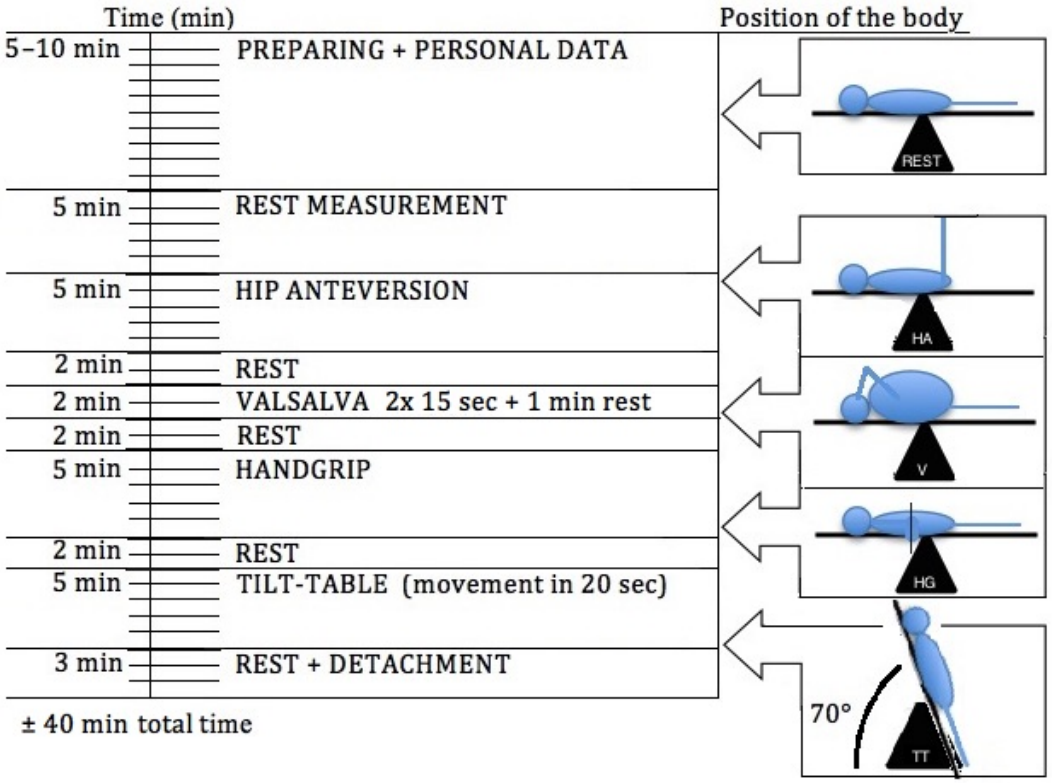


Figure 10: Schematic overview of pilot study protocol.

1. Known with cardiovascular diseases
2. Known with respiratory diseases
3. Injured hand/arms

II.3.1 Interventions

Tilttable Head-up tilttable test (HUTT) is the primary diagnostic test for neurocardiogenic syncope (NCS). NCS occurs secondary to cerebral hypotension because of bradycardia, hypotension, or both. Placing a NIRS probe over the temporal region allows an indirect measurement of cerebral perfusion. A study showed that patients with a positive HUTT test had a sudden, significant decrease in regional tissue oxygen saturations. Regional tissue oxygen saturation levels remained stable in patients with a negative test or psychogenic syncope due to the patient's intact auto-regulation (Ayers and Lawrence (2014)).

Goal: For this reason, HUTT is used in this pilot study to examine influences of auto-regulation and blood pressure on oxygen saturation of the brain.

Protocol: HUTT starts with the participant lying on a tilt-table in supine position while sensors for blood pressure; CO2 concentration and brain oxygen

saturation are attached. One strip is placed over the thighs to secure the body to the tilt table. After a period of rest for the participant, the tilt-table is electrically rotated to 70 degrees.

Usually, upright position time during HUTT is about 20 minutes. When no dizziness occurres during that time, some nitroglycerin is sprayed beneath the patients tongue and the patient remains in upright position for another 15 minutes. During this pilot study, the upright position will be about 5 minutes and no nitroglycerin spray will be used. Data from study of Roa et al. (2010) showed that most drops in oxygen saturation occurred within 10 minutes (Figure 13).

11

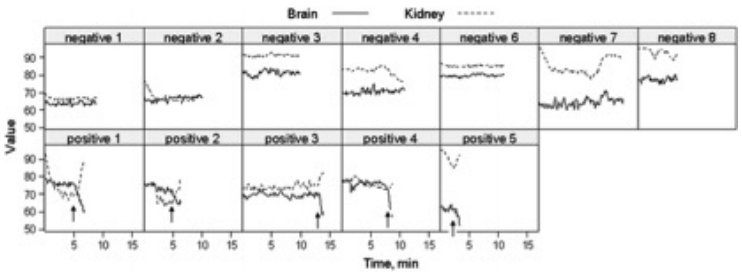


Figure 11: The rSO2C (continuous line) trends remain stable, which is suggestive of intact cerebral autoregulation. In contrast, in the patients with syncope, the initial rSO2 trends behave identically as the controls, but in the midst of the tilted positioning, the rSO2C shows an abrupt onset of a decreasing trend of regional desaturation, soon followed by clinical symptoms (arrows) Roa et al. (2010)

Effect: Due to this passive upward rotation, gravity and the absence of muscular influences on blood pressure from the lower extremities, blood pressure in the brain decreases. During long passive standing, muscles in the lower extremities do not contribute to a normal blood pressure anymore. Auto-regulation normally reacts on this change. In patients with NCS, this process takes too long. To compensate for this, auto-regulation increases the blood pressure above the normal levels. Another neural regulation system reacts on the increase by decreasing blood pressure and pulse. This results in fainting.

Risks: A tilt-table test is generally safe, and complications are rare. Potential complications include: low blood pressure, asystole and symptoms of dizziness or fainting. Complications usually go away when the table is returned to a horizontal position.

Participant information: During the tilt-table test you are lying in supine position on the tilt-table with strips placed over the chest and thighs to secure the body to the table. After a period of rest, the tilt-table is electrically rotated to almost upright position (70 degrees). You need to relax. If you feel uncomfortable dizzy, the table is brought back to the horizontal position. Otherwise, you stay in the upward position for about 10 minutes before the table returns horizontal.

Hip anteversion Blood pressure in the brain raises when somebody lies in supine position down with his legs up. The body gets "used to" the hard work and keeps the pressure in the legs high so that the blood can keep reaching the toes. When suddenly the legs lower down, the body still tries to push the blood to the toes until it registres that it is not necessary anymore. For one moment the blood pressure in the brain decreases.

Goal: The measurements will be conducted during the complete test, but the main goal is to see what happens when the blood pressure suddenly decreases.

Protocol: The participant needs to lie in supine position and put his feet in the air, in such a way that the angle of the leg to the trunk will be 90 degrees. The legs will be held up by two another persons. In that way the participant does not need to tighten his muscles, because that will also influence the blood pressure, and it will not get too heavy for the subject.This position needs to be hold for five minutes. After five minutes the participant may put his legs down and then the blood pressure in the brain will decrease.

Effect: The blood pressure in the brain will increase when the subject has his feet up and it will decrease when he puts his feet down.

Risks: There is an off-chance of passing out, because of the decreasing blood pressure in the brain. However because the subject lies in supine position, the body shall recover within a few seconds. Besides there is a chance of dizziness and getting dinged.

Participant information: You lie in supine position with your feet in the air, in such a way that the angle of the legs to the trunk will be 90 degrees. One of the researchers will hold your legs for five minutes. You feel the blood stream downwards and get blushes. After five minutes you can put your legs down.

Valsalva maneuver Information: The valsalva maneuver is normally used to evaluate the cardiac function. The intrathoracic pressure changes by forcefully exhaling against a closed glottis. This causes variations in blood pressure and heart rate.

Goal: The aim of the valsalva maneuver is to change the blood pressure and to examine the infuence of this change on oxygen saturation of the brain.

Protocol: The participant keeps his mouth and nose closed while exhaling forcibly for 15 seconds.This maneuver will be performed once. The blood pressure is measured before starting the valsalve maneuver. This measurement in rest shows the baseline of the blood pressure.

Effect: The increase of blood pressure is caused by four distinct phases during the valsalva maneuver (figure 3). The first phase consist of an increase of the intrathoracic pressure and rise of the systolic blood pressure. This is a result of compression of the aorta. The second phase can be divided in two phases, the early and late phase. There is a decrease in systolic and diastolic blood pressure caused by a decline in venous return during the early phase. This is followed by a secondary increase of the systolic and diastolic blood pressure due to enhanced activity of the adrenergic system in the late phase. The third phase consist of an acute reduction of the blood pressure. The reduction is caused by the acute loss of the pressure on the aorta. A lot blood is stored in the large veins beyond the thorax during the valsalva maneuver. This blood is suddenly available to the heart during the fourth phase. The hart will pump the blood around quickly as a response resulting in an increase of the blood pressure.

12

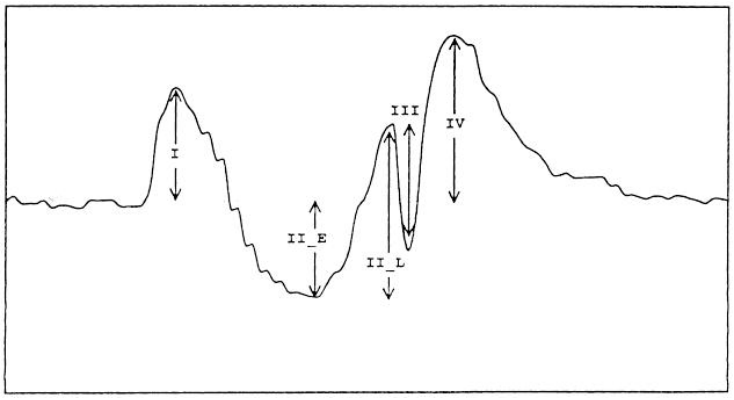


Figure 12: Four phases in blood pressure variations during valsalva maneuver.

Risks: Serious consequences are uncommon due to the valsalva maneuver. The participant may feel dizzy during the valsalva maneuver. Rare consequences are bleeding, abnormal rhythms originating in the ventricle, blood clots and cardiac arrest.

Participant information: You keep your mouth and nose closed while exhaling forcibly for 15 seconds. You can breathe normally after this. The maneuver will be performed twice.

Handgrip exercise Information: When it comes to the handgrip test we are dealing with isometric effort. With isometric effort does the length of the muscle not change. The mechanisms are probably autonomous, the increase of the sympathetic activity and the descent of the vagal tone. In the beginning of the exercise the blood pressure increases mainly because of the increase of heart rate by the vagal tone, meanwhile with persisting isometric effort the increase of blood pressure can be explained by the raise in sympathetic activity.[55]

Protocol: To execute the handgrip exercise the participant has to squeeze the dynamometer at its maximum power. This is his or her personal Maximal Voluntary Contraction (MVC). Within 0.4 to 0.6 seconds after the initiation of the effort will the heart rate rise. The heart rate will rise continuously as the time passes. The peak heart frequency will get higher the longer the exercise is executed.[**?**] The participant will hold the grip as long as possible until the force falls below the 20 percent of its MVC. The participant must hold at least the grip for 2 minutes and is has to let go at a maximum of 6 minutes. We expect that our participant will not be able to hold the force above the 20 percent of its MVC after the 6 minutes and we expect to have enough information collected by then.

Conditions: upward of the 20 percent of its MVC are we able to observe a response in adults. With some participants there could be observed a significant increase after 2 minutes, so that is our minimum time to hold the grip.

Risks: We expect no risks during this exercise.

Effect: Because of contraction during isometric effort, vessels will constrict. Due to constriction the ejection of blood out of the heart will be opposed. This

will result in afterload. Afterload develops a higher heart rate and aortic pressure, pulmonic pressure or pulmonary artery pressure. Cardiac output decreases when afterload increases. This all together will result in a decreased blood pressure. Participant information: During the handgrip exercise you will have to squeeze the dynamometer for at least 2 minutes at your maximum power. You will release your grip after 6 minutes or after your power has decreased below 20 percent of your maximum power. During the test your blood pressure will be measured every 30 seconds.

II.4 Data management and statistical analysis

Data management will be done by using MatLab. NIRS signal is plotted against blood pressure for all measurements. SPSS will be used to determine if there is any correlation between NIRS signal and blood pressure.

II.5 Quality assurance

To assure quality of this study, we try to keep intra-observer differences as small as possible. Despite the pilot character of this study, we try to use equipment equally during all data-analysis. Data will be processed anonymously.

II.6 Expected outcome of the study

The outcome of this study will contribute to the knowledge about the relationship between differences in blood pressure and variations in NIRS signal. If there is a linear relationship between these variables, it could be possible that this relates to excitability of the neurons in the motor cortex. For example, if we know that blood pressure decreases and therefore oxygen concentration in the motor cortex decreases, this could help us to answer the question if blood pressure influences TES-MEP amplitudes during scoliosis surgery. Before we start answering this last question, we need to know if a relationship between blood pressure and excitability does exist.

II.7 Problems anticipated

There could occur some difficulties such as too little time for the tests. We should test as many people as possible to have a lot of data to work with. To overcome the problem of to little time We should stick to the time schedule as earlier presented although we also have to keep the quality of the measurements in mind.

Also there could be a too small change in blood pressure that we are not able to measure any differences in NIRS signal, if there is any correlation between the two.

Since we use the newest software of Dr. JW. Elting, there still can be some start-up problems. We hope he can fix any problems. To overcome this problem we will firstly test the equipment on a test participant. If data is unusable we have to exclude this participant or we test this participant again in the hope this data set is usable.

When the blood pressure differs really quick our sample frequency could be too low to detect variation in the blood pressure or to explain the NIRS signal

changes. Therefor we might have to change the sample frequency. Although the higher the frequency gets the more data we have to analyse.

II.8 Project management

Each team-member is also participating in our study. Therefore, no defined function of each member is decided yet. Nevertheless, each team-member is responsible for a single intervention. This may result in a better overview and supervising of the process of the specific intervention.

II.9 Ethics

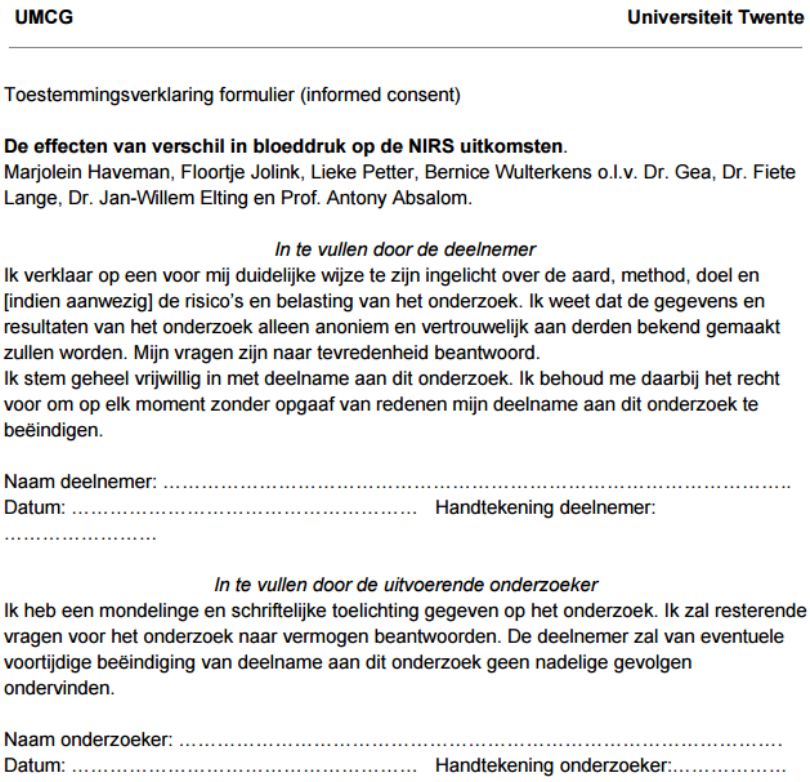
The participant receives an information letter and informed consent in advance. No serious complications are likely to occur during the measurements and participants declare to be aware of the risks by signing the informed consent. No METC request is needed for this pilot study, because we use healthy volunteers (including ourselves). Participants are allowed to withdraw from the study at any time during the measurements.

II.10 Informed consent forms

See Appendix I

II.11 Appendices

II.11.1 Appendix I - Informed consent pilot study



UMCG **Universiteit Twente**

Toestemmingsverklaring formulier (informed consent)

De effecten van verschil in bloeddruk op de NIRS uitkomsten.
Marjolein Haveman, Floortje Jolink, Lieke Petter, Bernice Wulterkens o.l.v. Dr. Gea, Dr. Fiete Lange, Dr. Jan-Willem Elting en Prof. Antony Absalom.

In te vullen door de deelnemer

Ik verklaar op een voor mij duidelijke wijze te zijn ingelicht over de aard, method, doel en [indien aanwezig] de risico's en belasting van het onderzoek. Ik weet dat de gegevens en resultaten van het onderzoek alleen anoniem en vertrouwelijk aan derden bekend gemaakt zullen worden. Mijn vragen zijn naar tevredenheid beantwoord.
Ik stem geheel vrijwillig in met deelname aan dit onderzoek. Ik behoud me daarbij het recht voor om op elk moment zonder opgaaf van redenen mijn deelname aan dit onderzoek te beëindigen.

Naam deelnemer: .....
Datum: ..... Handtekening deelnemer:
.....

In te vullen door de uitvoerende onderzoeker

Ik heb een mondelinge en schriftelijke toelichting gegeven op het onderzoek. Ik zal resterende vragen voor het onderzoek naar vermogen beantwoorden. De deelnemer zal van eventuele voortijdige beëindiging van deelname aan dit onderzoek geen nadelige gevolgen ondervinden.

Naam onderzoeker: .....
Datum: ..... Handtekening onderzoeker:.....

Figure 13: Informed consent

II.11.2 Appendix II - Biometrical information participant

Participant Number	Time (h)	M/F	Length (m)	Weight (kg)	Medication	Hours sports/week
1	-					
2	-					
3	-					
4	-					
5	-					
6	-					
7	-					
8	-					
9	-					
10	-					

III Appendix III - Handgrip exercise

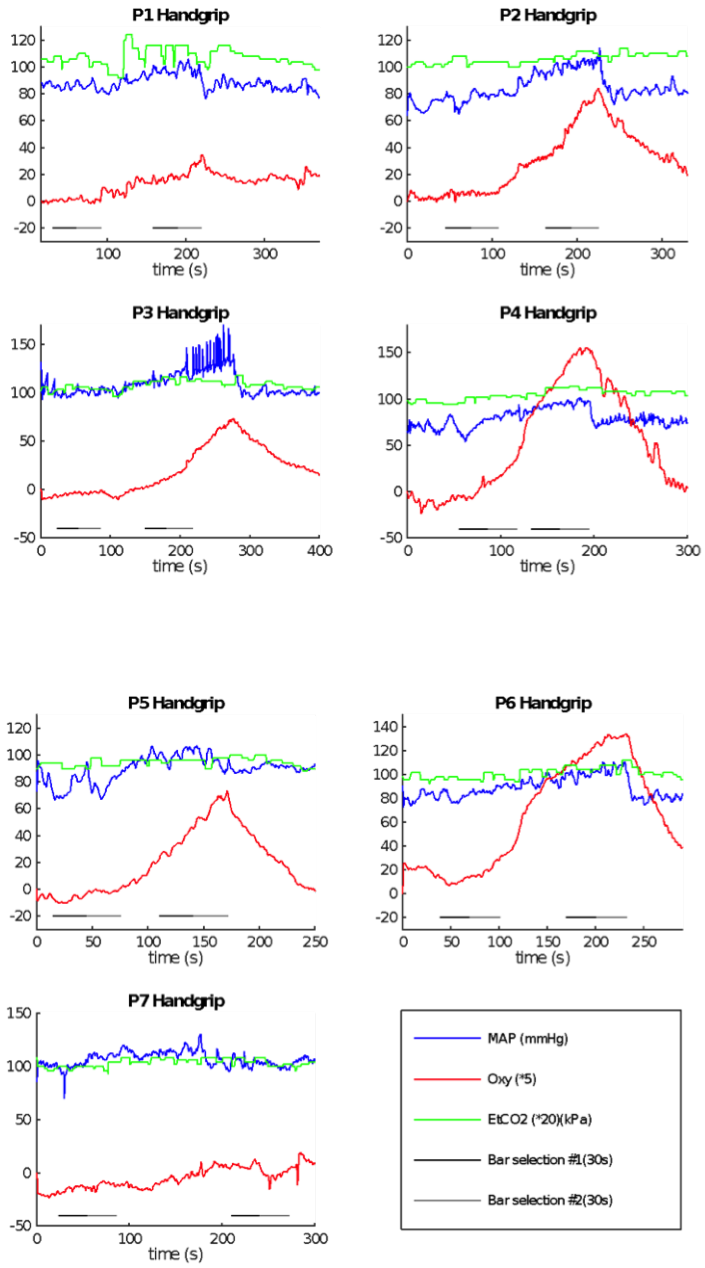


Figure 14: This figure shows a plot of the handgrip manoeuvre of all participants, #1 to #7. MAP, oxygenation and $EtCO_2$ are showed. The dark grey and light grey bars show the selection over which the mean of the variables is calculated.

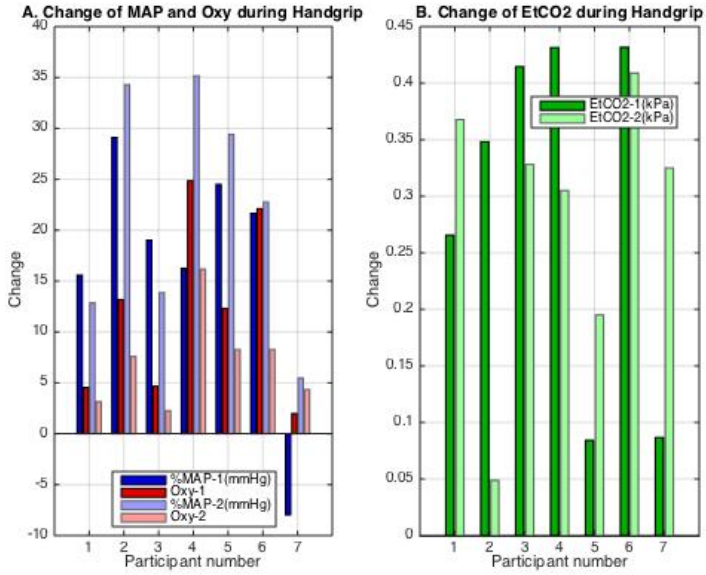


Figure 15: A. The change in MAP and Oxygenation during handgrip exercise of the two different periods is shown for all participants, #1 to #7. B. The mean change in CO_2 is given for each participant during the two periods.

Table 4: This figure shows the mean and standard deviation of all variables, MAP-1, MAP-2, Oxy-1 and Oxy-2, during handgrip exercise. The outcome of the Wilcoxon Signed-Rank Test between MAP-1 and MAP-2, Oxy-1 and Oxy-2 are showed. The outcome of the Spearman's correlation test between 1). MAP-1 and MAP-2, 2). MAP-1 and Oxy-1, 3). MAP-1 and Oxy 2, 4). MAP-2 and Oxy-2, 5). Oxy-1 and Oxy-2 are listed.

		MAP-1	MAP-2	Oxy-1	Oxy-2
DESCRIPTIVES		(change in %)		(change in µM)	
Mean		22.0	16.9	8.933	11.946
Std. deviation		11.6	11.9	7.053	8.927
WILCOXON SIGNED-RANK TEST					
Sig.		0.176		0.063	
SPEARMAN'S CORRELATION					
MAP-1	r_s	-	0.643	0.607	0.893 **
	Sig.		0.119	0.148	0.007
Oxy-2	r_s	-	0.536	0.786 *	-
	Sig.		0.215	0.036	

* Correlation is significant at the 0.01 level (2-tailed).
** Correlation is significant at the 0.05 level (2-tailed).

IV Appendix VI - Hip anteversion

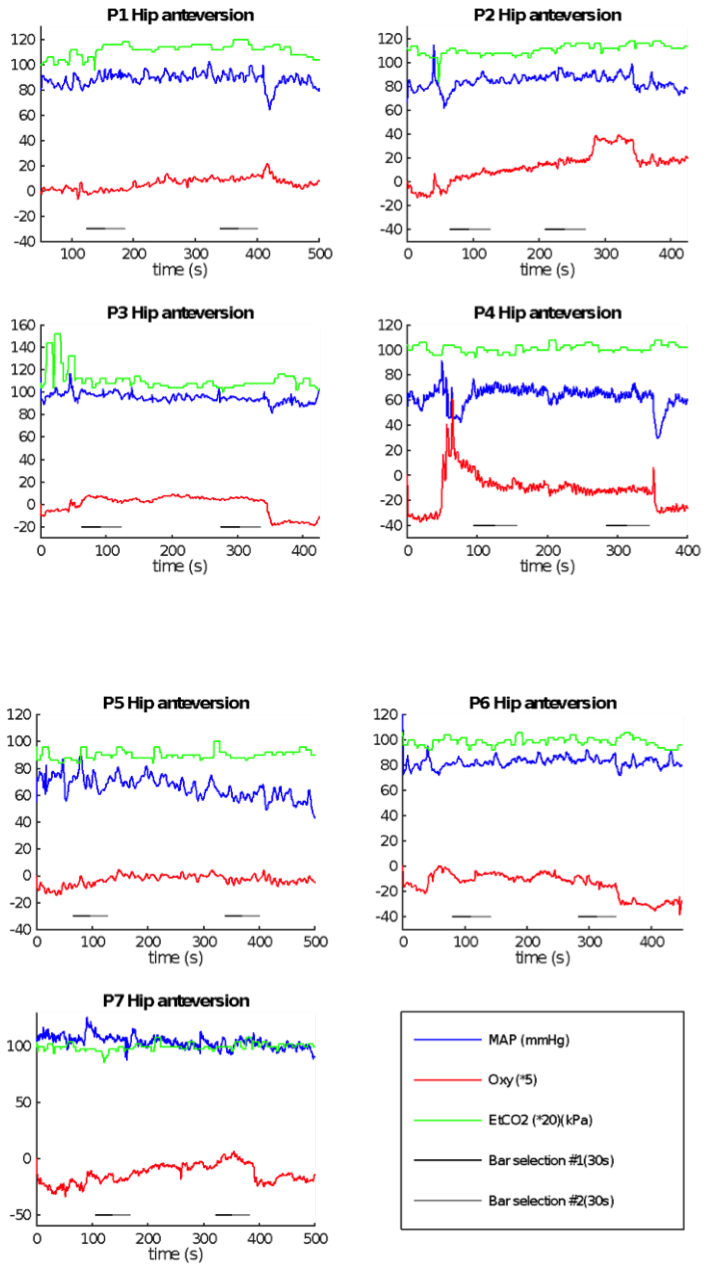


Figure 16: This figure shows a plot of the hip anteversion of all participants, #1 to #7. MAP, oxygenation and $EtCO_2$ are showed. The dark grey and light grey bars show the selection over which the mean of the variables is calculated.

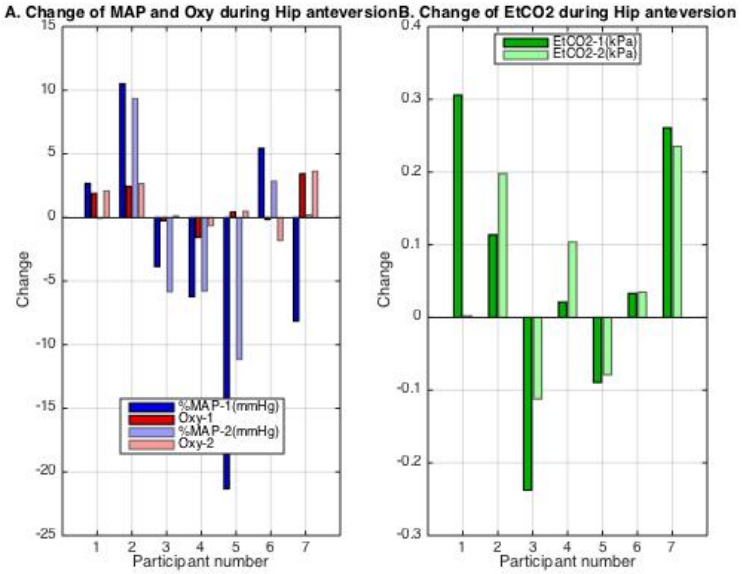


Figure 17: A. The change in MAP and Oxygenation during hip anteversion of the two different periods is shown for all participants, #1 to #7. B. The mean change in CO_2 is given for each participant during the two periods.

Table 5: This figure shows the mean and standard deviation of all variables, MAP-1, MAP-2, Oxy-1 and Oxy-2, during hip anteversion. The outcome of the Wilcoxon Signed-Rank Test between MAP-1 and MAP-2, Oxy-1 and Oxy-2 are showed. The outcome of the Spearman's correlation test between 1). MAP-1 and MAP-2, 2). MAP-1 and Oxy-1, 3). MAP-1 and Oxy 2, 4). MAP-2 and Oxy-2, 5). Oxy-1 and Oxy-2 are listed.

		MAP-1	MAP-2	Oxy-1	Oxy-2
DESCRIPTIVES		(change in %)		(change in µM)	
	Mean	-2.99	-1.49	0.89	0.93
	Std. deviation	10.48	6.73	1.76	1.93
WILCOXON SIGNED-RANK TEST					
	Sig.	1.000		0.237	
SPEARMAN'S CORRELATION					
	MAP-1 r_s	-	0.750	0.071	-0.107
	Sig.		0.052	0.879	0.819
	Oxy-2 r_s	-	0.500	0.893 **	-
	Sig.		0.252	0.001	

** Correlation is significant at the 0.01 level (2-tailed).

V Appendix V - Tilttable test

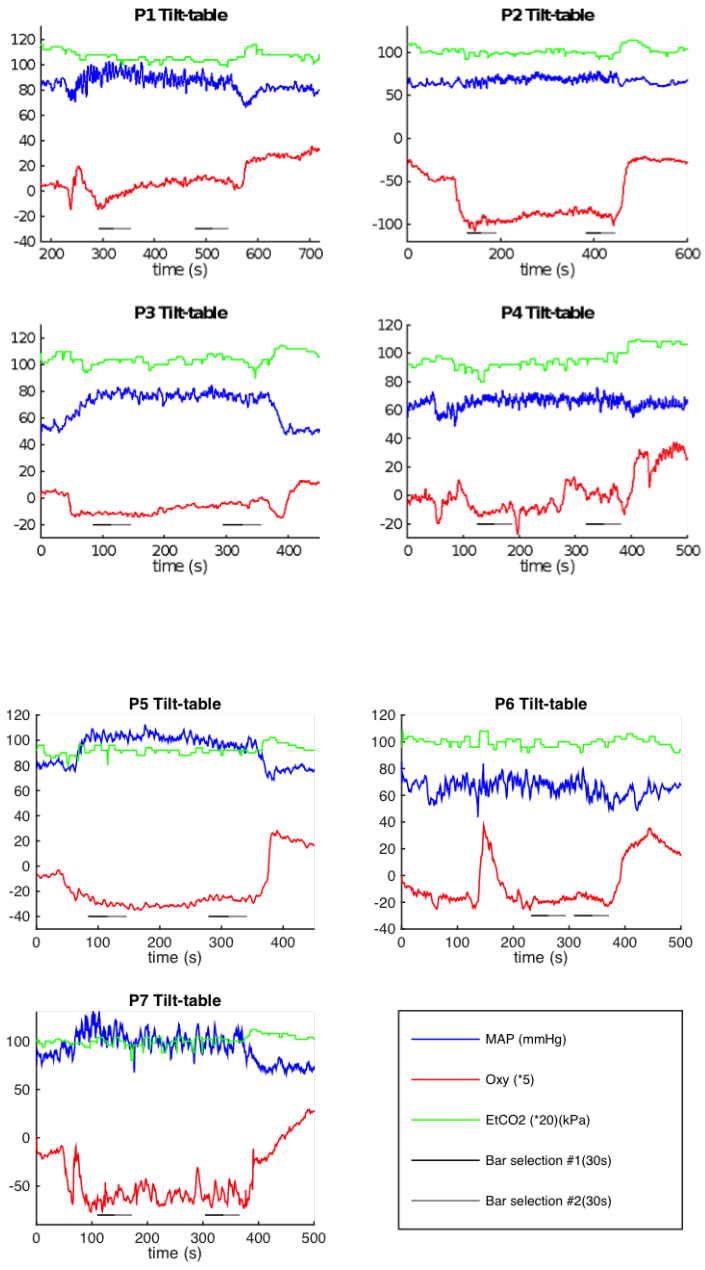


Figure 18: This figure shows a plot of the tilttable test of all participants, #1 to #7. MAP, oxygenation and $EtCO_2$ are showed. The dark grey and light grey bars show the selection over which the mean of the variables is calculated.

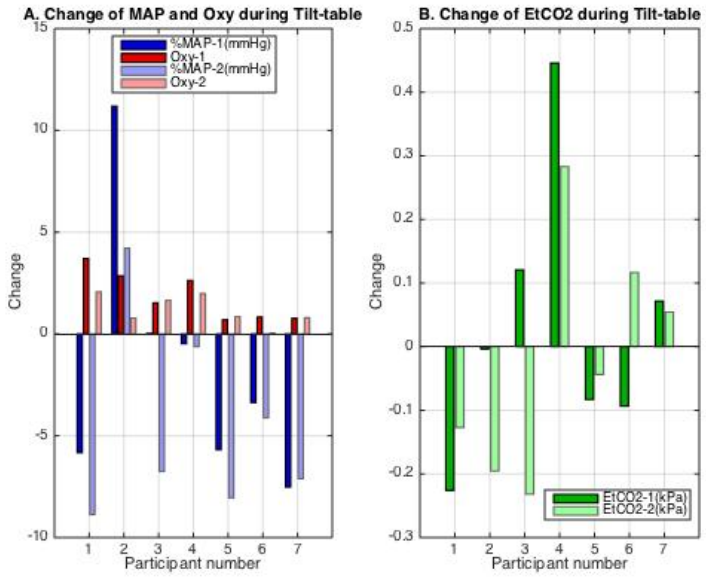


Figure 19: A. The change in MAP and Oxygenation during tilttable test of the two different periods is shown for all participants, #1 to #7. B. The mean change in CO_2 is given for each participant during the two periods.

Table 6: This figure shows the mean and standard deviation of all variables, MAP-1, MAP-2, Oxy-1 and Oxy-2, during tilttable test. The outcome of the Wilcoxon Signed-Rank Test between MAP-1 and MAP-2, Oxy-1 and Oxy-2 are showed. The outcome of the Spearman's correlation test between 1). MAP-1 and MAP-2, 2). MAP-1 and Oxy-1, 3). MAP-1 and Oxy 2, 4). MAP-2 and Oxy-2, 5). Oxy-1 and Oxy-2 are listed.

		MAP-1	MAP-2	Oxy-1	Oxy-2
DESCRIPTIVES		(change in %)		(change in μM)	
	Mean	-0.30	-3.97	1.87	1.16
	Std. deviation	7.66	4.64	1.20	0.74
WILCOXON SIGNED-RANK TEST					
	Sig.	0.043*		0.176	
SPEARMAN'S CORRELATION					
MAP-1	r_s	-	0.786 *	0.357	0.357
	Sig.		0.036	0.432	0.432
Oxy-2	r_s	-	-0.464	0.214	-
	Sig.		0.294	0.645	

* Correlation is significant at the 0.05 level (2-tailed).

VI Appendix VI - Valsalva manoeuvre

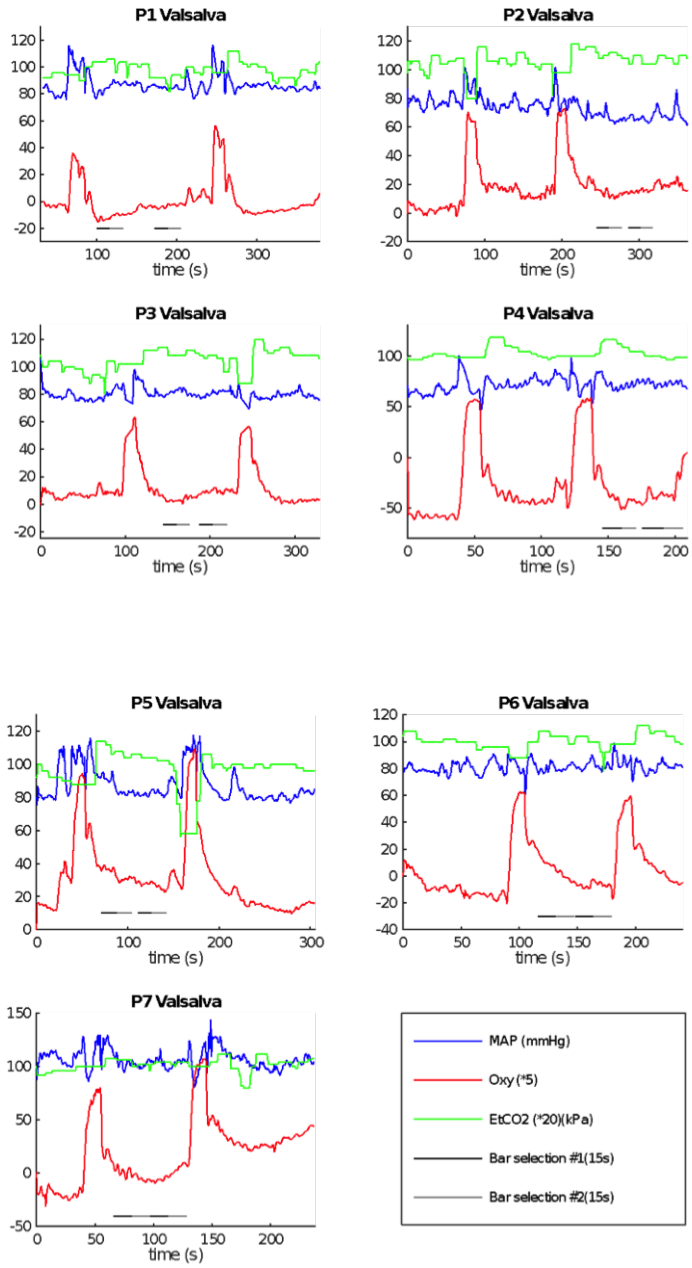


Figure 20: This figure shows a plot of the valsalva manoeuvre of all participants, #1 to #7. MAP, oxygenation and $EtCO_2$ are showed. The dark grey and light grey bars show the selection over which the mean of the variables is calculated.

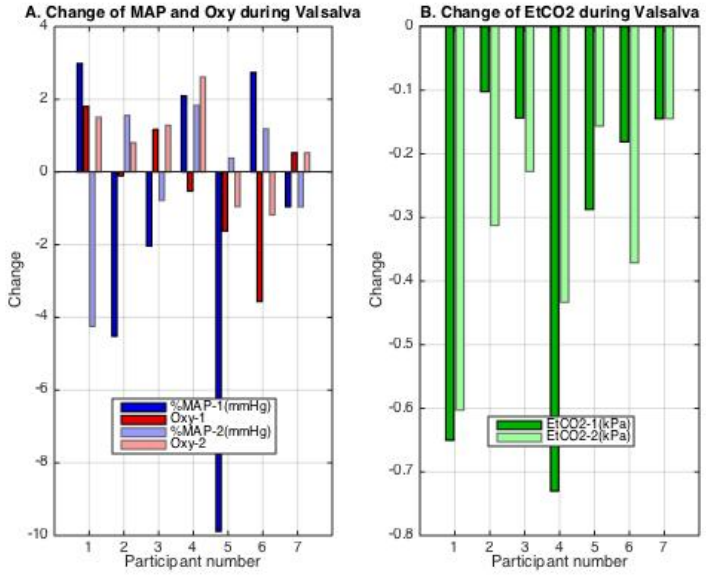


Figure 21: A. The change in MAP and Oxygenation during valsalva manoeuvre of the two different periods is shown for all participants, #1 to #7. B. The mean change in CO_2 is given for each participant during the two periods.

Table 7: This figure shows the mean and standard deviation of all variables, MAP-1, MAP-2, Oxy-1 and Oxy-2, during valsalva manoeuvre. The outcome of the Wilcoxon Signed-Rank Test between MAP-1 and MAP-2, Oxy-1 and Oxy-2 are showed. The outcome of the Spearman's correlation test between 1) MAP-1 and MAP-2, 2) MAP-1 and Oxy-1, 3) MAP-1 and Oxy 2, 4) MAP-2 and Oxy-2, 5) Oxy-1 and Oxy-2 are listed.

		MAP-1	MAP-2	Oxy-1	Oxy-2
DESCRIPTIVES		(change in %)		(change in μM)	
	Mean	-1.37	-0.15	-0.33	0.66
	Std. deviation	4.67	2.11	1.81	1.35
WILCOXON SIGNED-RANK TEST					
	Sig.	0.753		0.075	
SPEARMAN'S CORRELATION					
	MAP-1 r_s	-	-0.250	0.214	0.286
	Sig.		0.589	0.645	0.535
	Oxy-2 r_s	-	0.036	0.607	-
	Sig.		0.939	0.148	