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Research paper

Neurophysiological and paraspinal oximetry monitoring to detect spinal cord ischemia in patients during and after descending aortic repair: An international multicenter explorative study

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ABSTRACT

Background: During descending aortic repair, critically decreased blood flow to the myelum can result in ischemic spinal cord injury and transient or permanent paraplegia. Assessment of motor evoked potentials (MEPs) has been shown to be a valuable tool which allows to detect spinal cord ischemia (SCI) intraoperatively within a therapeutic window suitable to prevent progression to paraparesis or paraplegia. MEP monitoring is not feasible during postoperative care in the awakening patient. Therefore, ancillary techniques to monitor integrity of spinal cord function are needed to detect delayed spinal cord ischemia.

Objective: The purpose of this study is to evaluate whether assessment of long loop reflexes (LLR; F-waves) and paraspinal muscle oximetry using Near-Infrared Spectroscopy (NIRS) are feasible and valid in detecting delayed SCI.

Methods: We aim to include patients from three tertiary referral centers undergoing aortic repair with MEP monitoring in this study.

F-wave measurements and paraspinal NIRS oximetry will be operated intra- and postoperatively. Measurement characteristics and feasibility will be assessed in the first 25 patients. Subsequently, a second cohort of 75 patients will be investigated to determine the sensitivity and specificity of F-waves and NIRS in detecting perioperative SCI. In this context for the MEP group SCI is defined intraoperatively as significant MEP changes and postoperatively as newly developed paraplegia.

Conclusions: A clinical study design and protocol is proposed to assess if F-waves and/or NIRS-based paraspinal oximetry are feasible and valid in detecting and monitoring for occurrences of delayed SCI.

1. Introduction

During descending aortic repair interruption of blood flow leads to a significant decrease of spinal cord perfusion in up to 50% of procedures [2]. If the ensuing ischemia exceeds a critical level and duration, spinal cord function will be impaired either transiently or permanently. If the spinal cord perfusion is not restored, postoperative paraparesis or paraplegia will result, in up to 25% of descending aortic repair patients [5].

Eliciting motor evoked potentials (MEPs) is a reliable means of testing the functional integrity of the spinal cord during the procedure. The absence or presence of MEPs at the end of the intervention predicts with nearly a 100% sensitivity and specificity whether acute paraplegia will occur [1,2]. MEPs react within a few minutes to spinal cord ischemia but also show improvement within a similar time frame after implementation of a bundle of therapeutic countermeasures. Therefore,

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the deduction of MEPs during descending aortic repair fulfills all demands for a reliable and valid ancillary test. Consequently, with the use of MEP monitoring and MEP-guided acute countermeasures, the incidence of postoperative paraplegia can be reduced to a level of 5% or less.

Notwithstanding the above, a number of patients develop paraplegia not *during* but *after* the surgical or endovascular procedure, the so-called delayed paraplegia [3,4]. Its incidence is higher than that of immediate paraplegia. An occurrence rate of 5–10% has been reported from patients monitored intraoperatively [2]. Unfortunately, when the level of sedation is reduced postoperatively and the patient becomes more conscious, it is not feasible to monitor for impending SCI with electrical MEPs. MEPs are elicited by means of a strong electrical stimulus, which is unacceptably painful for the recovering patient.

Therefore, alternative tests are needed for the early postoperative period. Two candidate techniques might qualify. First, the so-called F-waves as quantifiers of the integrity of Long Loop Reflexes (LLR), and second, paraspinal transcutaneous hemoglobin oximetry (rSO_2) determined by Near-Infrared spectroscopy (NIRS), as a quantifier of the balance between oxygen delivery and demand in paraspinal muscle tissue.

F-waves are triggered by stimulating a peripheral nerve. The test is performed by stimulation of the tibial nerve and recording the motoric answer from the abductor hallucis brevis muscle. A normal late response indicates a proper function of the α-motor neuron at the lower lumbar or upper sacral spinal cord level. These neurons are most susceptible for ischemia due to their high metabolic need. As a reference value, the F-waves of the ulnar nerve are recorded.

F-waves have sporadically been used for intraoperative monitoring of peripheral nerve function [9]. This is the first trial in which F-waves are studied as a potential monitoring tool for detection of spinal cord ischemia.

Paravertebral NIRS noninvasively measures the oxygenation of paraspinal muscular tissue. A large collateral vascular network supplies both the spinal cord as well as other structures in its vicinity, such the paraspinal muscles [6–8]. Therefore, NIRS monitoring of the paraspinal muscular tissue has been suggested to reflect the oxygen supply/demand balance of the spinal cord [6]. This technique has already been applied clinically and shown to be feasible. However, more studies are needed to establish its validity, and whether it is a useful surrogate measure of spinal cord perfusion [6,8,10].

To be able to investigate whether these new monitoring techniques can be introduced to monitor the spinal cord in the postoperative phase, we first have to know to what extent these techniques are able to demonstrate the same events of spinal cord ischemia as the intraoperative MEP monitoring.

Therefore, the purpose of this study is to evaluate whether F-waves and rSO_2 by NIRS correlate with spinal cord function and are feasible, valid and reliable monitoring parameters.

2. Hypothesis

The pilot part of the study is a feasibility test of F-wave and rSO2 monitoring during and after descending aortic repair as well as a descriptive study of the baseline characteristics of these parameters. The hypothesis of the main study is that combined monitoring of F-waves and rSO2 is able to detect significant intraoperative MEP loss. The pilot phase will be used to define the definitive protocol and cut-off values.

3. Materials and methods

3.1. Study design

This study is an international multi-center prospective observational cohort study, in first instance evaluating the feasibility of two potentially useful non-invasive monitoring techniques for postoperative SCI. If feasibility has been demonstrated in a pilot sub-study, then in the subsequent main study part the validity and diagnostic accuracy of these diagnostic tests will be determined.

3.2. Study population

Patients will be included from the Maastricht University Medical Center (the Netherlands), the Inselspital Bern (Switzerland) and the University Hospital RWTH Aachen (Germany), all tertiary referral centers for aortic surgery.

3.3. Inclusion and exclusion criteria

The following inclusion criteria apply:

- Adult ($\geq$ 18 years).
- Patients undergoing a descending aortic repair (open or endovascular) with standard procedure MEP monitoring in Maastricht UMC+, Inselspital Bern or the University Hospital RWTH Aachen.
- Written informed consent prior to inclusion to the study (National regulatory guidelines will be adhered to as per study center).

3.4. Study rationale/objectives

Ancillary tests are needed which can detect spinal cord ischemia postoperatively at an early, i.e. potentially reversible stage, thus preceding the phase with clinically overt paraplegia. The purpose of this study is to evaluate long loop reflexes (LLR) - consisting of F-waves - and paraspinal muscle oxygenation using NIRS-based oximetry for the detection of SCI. In particular, to find a diagnostic test which is not painful for the recovering or partially sedated patient and therefore can also be performed postoperatively. The test should be valid, reliable, non-invasive and easy to operate for an extended period of time, up to several days.

These tests will be made in the fully sedated as well as partially sedated and recovering patient. The following candidate tests will be evaluated, and compared to routine monitoring by motor evoked potentials (MEPs):

1. F-waves.
2. Transcutaneous oximetry of the paraspinal muscles using Near-infrared spectroscopy (NIRS).

3.5. Surgery and anesthesia protocols

All centers use their own standard operating procedure for surgery and anesthesia, as reported previously [2]. Briefly, centers agree on use of non-volatile anesthetics, low-dose propofol and minimizing the use of muscle relaxants in order to optimize MEP monitoring.

To optimize spinal cord perfusion, target cerebrospinal fluid (CSF) pressure is up to 7.4 mmHg. Also, distal aortic perfusion is applied with target mean arterial pressure (MAP) of at least $>$ 60 mm Hg. When a significant decrease of MEP signals is observed, interventions are applied to increase spinal cord perfusion [2].

3.6. Stimulation protocols

3.6.1. Routine monitoring using motor evoked potentials (MEPs)

During surgery the spinal cord is monitored using MEPs as the gold standard. (Digitimer 185, Digitimer Ltd, Welwyn Garden City, Hertfortshire, UK), The anode is placed in the Cz position. The cathode consists of three interconnected electrodes placed on both mastoids (TP9 and TP10) and Fpz. A train of five stimuli with an interstimuli interval of 2 ms is applied. The voltage is constant (500V), the current depends on the skin resistance and is on the order of 1–1.5A. MEPs are recorded with surface electrodes from the abductor pollicis brevis muscle (APB), the tibialis anterior muscle (TA) and the rectus femoris muscle (RF) on both

sides (R and L; Oxford Synergy; IOM software). Filter settings are 3–5 KHz and sweep duration 100 ms. The amplitude is defined as peak-to-peak. These measurements are performed at least every 5 min and every minute during critical stages of the procedure.

A MEP decrease is considered significant if the amplitudes over the TA or RF muscles fall below a level of 50% in comparison to the pre-existing response. It is noteworthy that MEP changes are not absolutely determined but as the ratio between lower and upper extremity MEPs. In other words: the APB-MEPs serve as a reference in order to correct for, e.g., changes in the degree of muscle relaxation.

3.6.2. Routine monitoring of neuromuscular transmission

For a proper assessment of the MEP signals neuromuscular transmission is monitored concomitantly. A stimulus is given directly to the peripheral nerves in arm (ulnar nerve) and legs (peroneal nerves). Surface electrodes record the potential over the abductor digitus minimi muscle (ADM) and the tibialis anterior muscles (TA). This measurement is used to determine the degree of muscle relaxation, which influences the amplitude of MEP potentials.

3.6.3. Monitoring using F-waves

During surgery F-waves are measured along with electrical MEP stimuli simultaneous with the standard peripheral nerve stimulation. The tibial nerve is supramaximally stimulated at the ankle to record an F-wave from the abductor hallucis brevis (AHB) muscle. These stimuli are applied to the leg which is not used for cannulation of the iliac artery for distal perfusion during extracorporal circulation. A normal late response indicates a proper function of the α-motorneuron at the lower lumbar or upper sacral spinal cord level.

As a reference, F-waves are recorded from the ADM muscle. The ulnar nerve will be supra-maximally stimulated in order to record an F-wave.

After surgery, F-waves are measured once every 6 min. Measurements are performed when the patient is (fully to partially) sedated. The surface electrodes are left in place. The tests are continued until the patient is awake (or 24 h postoperatively, if the patient is not awake yet and the device is needed for clinical purposes).

3.6.4. Monitoring using NIRS

During surgery, bilateral regional tissue oxygenation (rSO_2) in the thoracic and lumbar paraspinal region is continuously measured (INVOS 5100C system, Medtronic, Minneapolis, Minnesota, United States). The optode emits a near-infrared light that is absorbed, depending on emitted wave-lengths, differently by oxygenated (O_2Hb) and deoxygenated hemoglobin (HHb). The light reflected back to the optode is analyzed to calculate the oxygen saturation ($O_2Hb/(O_2Hb + HHb)$) of the hemoglobin contained in subcutaneous and muscle tissue.

Self-adhesive optodes are placed on the skin above the collateral network of the spinal cord at the thoracic levels (Th 5–7) and lumbar levels (L 1–3). However, during surgery (and afterwards), the position of the optodes and its cables can interfere with access sites, catheters and other procedures. This usually involves the left side. In this case, the thoracic optode (reference) is placed more cranially before the intervention starts.

Postoperatively, rSO_2 ratio is recorded quasi-continuously until the patient is awake (or 24 h postoperatively, if the patient is not awake yet and the device is needed for clinical purposes).

3.6.5. Safety aspects

Minimal risk is anticipated with participating in the study. During the intervention and in the first postoperative phase, the patient is fully sedated and the burden is comparable to the standard care (intra-operative neuromonitoring). As soon as sedation is decreased and patients are recovering, the demand for the exams will be at most comparable to routine outpatient neurophysiological studies (F-waves are performed in the outpatient clinic without sedation). However, should any discomfort be noticed, the procedures will be discontinued.

Discomfort may also arise due to the permanent attachment of the electrodes to the skin, covering the leg muscles and of optodes adhering to the skin and overlying the paraspinal muscles. The patient's skin is inspected for pressure marks (due to cables) to prevent ulcers. In case of significant findings that should, in the judgment of the investigator, prevent further treatment, patients can be excluded from further monitoring for significant medical reasons. Clinical and neurological examination is performed as in standard patient care.

Serious adverse events (SAEs) are defined as a serious untoward medical occurrence or affect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability to a subject during the study, whether or not considered related to the clinometric evaluation of measurement tools. The precise definition will be adjusted according to the federal laws of the individual country recruiting. Serious adverse events reported spontaneously by the subject or observed by the investigator or his staff are recorded and reported according to national regulatory guidelines. Before hospital discharge, a member of the study team visits the patient and inquires about any possible problems or discomfort during the study period. The patient file is also checked. In addition, the treating physicians are asked to report all SAEs to the study team.

In accordance to section 10, subsection 4, of the WMO, the sponsor can suspend the study if there is sufficient reason that continuation of the study will jeopardize subject health or safety [11]. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

3.7. Eligibility process/recruitment

All adults (age >18 years), undergoing descending aortic repair (open or endovascular) are eligible for inclusion. When the procedure is planned, the patient's attending physician or case manager is contacted to ask for permission to approach the patient in person or by telephone. An investigator or his/her delegate will contact the patient by phone and ask if they would like to receive an information letter concerning the study. If they are interested, the letter will be sent to their home address or handed over in person if the patient is already in hospital.

Patients are informed in due time by a member of the local study team to ask if they are interested in participating in the study. If the patient indicates they had enough time for consideration and wants to participate, an informed consent is signed by the participant and researcher.

3.8. Description of the study protocol

Fig. 1 depicts an overview of the study measurement protocol.

3.9. Physical assessments, measurements/interventions

3.9.1. Preoperative

One day prior to the surgical procedure the patient is neurologically assessed by grading the functioning of the m. flexor digitorum superficialis, m. iliopsoas and m. tibialis anterior with the medical research council (MRC)-scale. For the m. flexor digitorum, the participant is asked to flex their hand and the researcher will use moderate force to pull the hand in the opposite direction. For the m. iliopsoas, the participant is requested to lie down on bed and lift their leg while the researcher creates resistance by pushing the leg down. For the assessment of the m. tibialis anterior the participant is asked to sit or lie down on bed and flex their foot while the researcher pushes the foot back. The assessment is done bilaterally.

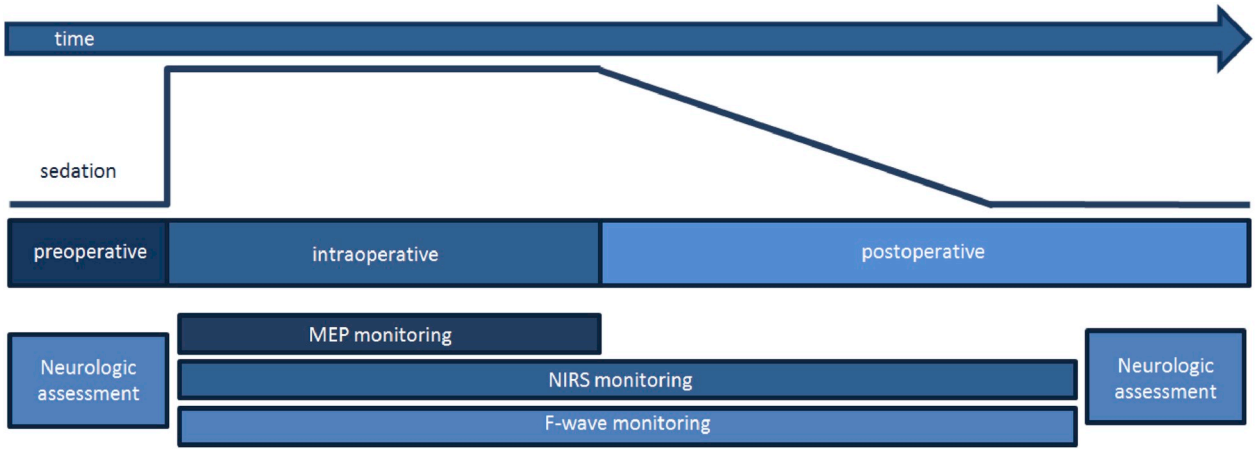

Fig. 1. Overview of study protocol.

3.9.2. Intraoperative

3.9.2.1. Routine monitoring using motor evoked potentials (MEP). During surgery the spinal cord is being monitored as a standard procedure using MEPs, as described under "stimulation protocols".

3.9.2.2. Routine monitoring using conduction studies of the nerves. For a proper judgment of the MEP signals peripheral nerve conduction of the ulnar nerve and peroneal nerves is performed, as described under "stimulation protocols".

3.9.2.3. F-waves. During surgery, F-waves of ulnar and tibial nerves are measured simultaneously with the standard peripheral nerve conduction measurements, as described under "stimulation protocols".

3.9.2.4. rSO_2 by NIRS. During surgery, tissue oxygenation rSO_2 ratio is measured and recorded continuously, as described under 'stimulation protocols'.

3.9.3. Postoperative when patient is (partially) sedated

3.9.3.1. F-waves. After surgery, the F-waves of the ulnar and tibial nerves are measured as described under 'stimulation protocols'.

3.9.3.2. NIRS. After surgery, tissue oxygenation rSO_2 ratio is also measured continuously.

3.9.3.3. Hemodynamic monitoring. After surgery, mean arterial pressure (MAP) is measured continuously.

3.9.4. Postoperative when patient is awake

The patient is neurologically assessed in the same manner as preoperative.

3.10. Statistical methods, sample size and (interim) data analyses

MEPs as the intraoperative reference modality will be recorded and analyzed intraoperatively, whereas both the F-waves and NIRS will be examined and analyzed in the intraoperative and postoperative phase. *Physicians are blinded for the values of the measurements both intraoperative and postoperative.* Postoperatively, during the phase the candidate monitoring modalities will finally be evaluated, the focus will be on feasibility first, and second on validity.

The incidence of defined SCI events (defined as postoperatively observed transient or permanent paraplegia) is estimated relatively low due to a bundle of interventions triggered by intraoperative MEP monitoring. Therefore, data from the intraoperative period is used for exploring the statistical association of pathological MEP signaling with decreases of lumbar/thoracic ratios of NIRS-based rSO_2 or tibial versus ulnar versus F-wave data. Intraoperatively, a significant decrease of MEP signals, as a valid surrogate parameter for paraplegia occurs *in up to 50%* of patients undergoing open descending aortic repair [1]. Therefore, this high event rate will enable us to determine the relationship between MEPs, rSO_2 and F-waves.

3.10.1. Primary and secondary endpoints

The primary aim is to evaluate the reliability and feasibility of NIRS and F-waves in the intraoperative and postoperative period. The second aim is to describe characteristics of the data gathered from the monitoring tools. Special attention will be paid to any changes and if present whether they are an indicator of SCI. Because the current data on the incidence of signal changes in patients undergoing descending aortic repair of 1) F-waves and 2) rSO_2 is scarce, analysis of descriptive data using Statistical Package for the Social Sciences (SPSS) version 23 after this pilot phase ($n = 25$) is needed to fine-tune the definitive study protocol and calculate definitive sample size [12]. The third and last aim is to study whether there is an association between rSO_2 values and F-wave and (surrogates of) SCI. SCI will be defined as 1) a significant intraoperative decrease in MEP amplitude, and/or as 2) new postoperative paraplegia. In a post-hoc and descriptive analysis, correlations with hemodynamic characteristics, especially MAP will be explored.

3.11. The third and last aim is to study whether there is an association between rSO_2 values and F-waves and (surrogates of) SCI

SCI will be defined as 1) a significant intraoperative decrease in MEP amplitude, and/or as 2) new postoperative paraplegia.

In a post-hoc and descriptive analysis, correlations with hemodynamic characteristics, especially MAP will be explored.

3.12. Withdrawal and premature termination of the study

Subjects can leave the study at any time for any reason without any consequences. The investigator can decide to withdraw a subject from the study for significant medical reasons, with reasons documented accordingly. Individual subjects will not be replaced after withdrawal from study. Patients who are withdrawn from the study will receive standard patient care only (no study specific measures).

Measurements will be discontinued in patients if measurements are technically difficult or cause the patients discomfort (e.g. in the postoperative phase). According to the investigator, subjects will be withdrawn from the study in case of significant medical reasons.

3.13. Safety evaluation

The safety and tolerability of NIRS and F-waves as a postoperative monitoring tool for SCI will be evaluated for each individual patient. Patients which have been weaned from sedation after monitoring will be asked when possible, if they experienced any discomfort due to the monitoring devices.

3.14. Data management, data storage

All data are entered in the eCRF in a coded format. A consecutive study-specific number is assigned to included individuals. The key (subject identification code list) is held by the local principle investigator. For audits and inspections, the competent Ethics committees on human research and oversight authorities will be granted access to all study data. The research data will be destroyed according to federal law.

3.15. Ethical considerations

The study is conducted according to the principles of the Declaration of Helsinki (adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013) in accordance with the Medical Research Involving Human Subjects Act (WMO) and registered at www.clinicaltrials.gov. The study will be approved by the Competent local Ethical committees on Human Research and will be performed as per national regulations.

4. Discussion and conclusion

Intraoperative MEP monitoring detects SCI reliably, often at a reversible stage, which contributes to reducing the occurrence of paraplegia after descending aortic repair. However, the patient is still at risk to develop delayed SCI during the postoperative phase, particularly in the first 24 h after the intervention. Currently, there is no reliable technique available to monitor spinal cord function in the post-operative phase as long as the patient is still unresponsive from sedation. This study in patients undergoing surgical or endovascular descending aortic repair will determine, first, if perioperative non-invasive monitoring of F-waves and rSO_2 by NIRS is feasible, and second, whether both are valid monitoring tools for detecting SCI not only in the intraoperative but also during the early postoperative period.

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