Pressure on Perfusion
- Mean Arterial Pressure in Relation to Cerebral Ischemia and Kidney Injury

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Abstract

Objective
The objective of this randomized clinical trial of elective coronary artery bypass grafting (CABG) patients was to investigate, whether mean arterial perfusion pressure (MAPP) below 60 mmHg could lead to cerebral ischemia and impaired kidney function postoperatively. The trial compared the impact of two strategies during cardiopulmonary bypass on outcome. Patients were randomized to a low MAPP group (LP), 40-60 mmHg or a high MAPP group (HP), 60-80 mmHg.

Methods
A total of 11 low risk patients (age>60 years) undergoing primary, nonemergency CABG were randomized to either the LP group (n = 5) or the HP group (n = 6). The impact of the two MAPP strategies in regard to cerebral and kidney outcome was assessed by measuring rSO$_2$, S100Beta and creatinine. Results were analysed using simple comparison with t-test and Fisher´s exact test. A p-value of <0.05 was considered statistical significant.

Results
The LP and HP group were comparable in relation to demographical and clinical factors. A borderline statistical difference was observed regarding weight (p=0.06), body surface area (p=0.06) and baseline rSO$_2$ right (p=0.07) and left side (p=0.06).

Significant differences were observed regarding MAPP (p=0.000006), use of norepinephrine (p=0.047), rSO$_2$ left side (p=0.045), lowest haematocrit (p=0.02) and creatinine 24 hours postoperative (p=0.022). Further on, borderline significant differences were obtained regarding use of Metaoxidrine (p=0.07), rSO$_2$ right side (p=0.09) and fluid balance (p=0.14). No significant difference was seen regarding S100Beta (p=0.98).

Conclusion
We were not able to conclude that conduct of CPB at MAPP below 60 mmHg leads to cerebral ischemia and impaired kidney function. However, we discovered a trend towards patients with a large difference from their normal mean arterial pressure and pressure received during CPB, is at higher risk of cerebral ischemia.
Introduction

Cardiac surgery on cardiopulmonary bypass (CPB) is a safe and effective procedure performed routinely at hospitals throughout the world, but is still associated with complications. Because of these complications, focus has been on conducting CPB more safely; to reduce morbidity and mortality and enhance patient outcome.

During CPB, patients are maintained in a non-physiological condition for a number of reasons: The flow generated by the heart-lung machine (HLM) is laminar, and especially the kidneys are dependent on pulsatile flow generated by the heart, according to creatinine clearance and urine output (Sirvinskas 2012). The perfusion pressure from the HLM is lower than the physiological mean arterial pressure. Patients are hemodiluted because of priming volume in the HLM system resulting in lower haematocrit and their immune system is activated, because of the foreign surfaces from the circuit. Remaining debris from production can, despite of filtration in the circuit, be forced into the patient, where especially the brain is at concern. The blood may also experience temperature alterations because of the tradition for cooling during CPB, which induces alterations in the blood gasses of a non-physiological manner. During CPB pharmacological drugs are administered in the HLM and blood samples are withdrawn through a small shunt. This, along with other components in the system, will induce micro bubbles undetectable for the bubble sensor. How all these alterations affect the human physiology is not completely understood (Schell 1993; Murphy 2009). This indicates that multiple factors influence patient outcome during the conduct of CPB.

In order to improve patient outcome, there is still a need for investigating safe ways to conduct CPB, even though morbidity and mortality rates have been reduced significantly during the last decade (Bartels 2002). Studies have been investigating factors influencing patient outcome, these factors include: Age, emboli, comorbidity, hemodilution, low haematocrit, bleeding, transfusion, perfusion time, hypoperfusion and cross clamp time (Brassard 2013; Sirvinskas 2012). Morbidities related to CPB are impaired kidney function or kidney damage, cerebral injuries, stroke, impaired cognitive function, ischemic injuries (to the heart, abdominal organs, kidneys, brain and lungs), embolic incidents and systemic inflammatory response syndrome (Baehner 2012).

Studies have focused on injuries to the kidneys and the brain as the main concern in the conduct of CPB, but there is no consensus on which of the CPB related factors, that leads to damage in the
kidneys and brain (Kanji 2010; Tan 2008). It looks like perfusion pressure is important, because the kidneys need a pressure between 80-180 mmHg for maintenance of the autoregulation (Sorensen 2000). The lower limit of renal autoregulation may be as low as 60 mmHg (Fischer 2002). The autoregulation of the brain is incapacitated at pressures below 50 mmHg (Haugen 2006; Ono 2013).

Generally, at the Department of Cardiac Thoracic Surgery, University Hospital Odense, mean arterial perfusion pressure (MAPP) is maintained about 40 mmHg. Only occasionally CPB is performed at pressures above 50 mmHg, and if MAPP exceeds 60 mmHg, we aim to lower the pressure. These relatively low perfusion pressures in relation to pressures necessary for autoregulation in the kidneys and the brain could be reason for concern.

We investigated available research literature, to elucidate this concern, using the databases PubMed, Cinahl and The Cochrane Library. The search was conducted with an aim to retrieve meta-analysis, systemic reviews and randomized controlled trials. If only few hits were acquired, other types of trials were included. Title and abstracts were evaluated for relevance and potential studies were obtained for full text analysis. References in obtained literature were used to find further relevant literature. Key words for search strategy were: Cardiopulmonary bypass, conduct of cardiopulmonary bypass, low perfusion pressure, morbidity, kidney failure and cerebral ischemia.

In the databases, advanced search methods were used. Search criteria were: Available full text, English, German, Scandinavian language and research published within the last 5 years, but because of scarcity of relevant literature, we accepted older research.

Investigated literature concerning conduct of CPB agree, that not enough clinical trials have been made with high enough quality to recommend an evidence based practice (Bartels 2002; Murphy 2009). Furthermore the investigated literature does not agree, whether or not MAPP is related to kidney impairment and brain ischemia. In the following acquired literature will be presented.

Fischer et al. (2002) made a retrospective study looking at patients with normal se-creatinine preoperatively, undergoing cardiac surgery. They divided the patients into three groups: An ARF-group, who developed acute renal failure after CPB requiring hemofiltration/dialysis, a Crea-group with patients having elevated se-creatinine not requiring treatment and a control group constituting
the remaining patients with normal se-cretinine postoperatively. In the ARF-group CPB duration was significantly longer and CPB flow was lower compared to the Crea-group and the control group. CPB duration at a MAPP below 60 mmHg was longer in both the ARF-group and the Crea-group compared to the control group. Fischer et al. concluded that the only significant different variable between the Crea-group and the control group was duration of CPB at MAPP below 60 mmHg, which points to MAPP as an important variable in CPB management with impact on renal function.

This finding is confirmed by Ono et al. (2013), suggesting that the definition of an optimal MAPP should be decided from physiological endpoints rather than using an empirical MAPP management during CPB to optimize organ perfusion. This has also been investigated in a small single centered prospective trial by Kanji et al. (2010). They looked at the relationship between mean arterial pressure (MAP) and mean arterial perfusion pressure (MAPP) in 157 patients with high risk of acute kidney injury. They introduced delta-MAP as a measure of the difference between the perfusion pressure during CPB and the preoperative mean arterial pressure. It was indicated that a large delta-MAP and low CPB flow was associated with early postoperative acute kidney injury. In contrast to Kanji and Ono, Sirvinskas et al. (2012), looked at the influence of MAPP during CPB on postoperative renal dysfunction in 122 patients with normal preoperative renal function, and found no significant relation between renal dysfunction and MAPP at pressures in the range of 48-80 mmHg.

Concerning the relation between MAPP and protecting the brain, an old study by Gold et al. (1995) concluded, that a higher MAPP (80-100 mmHg) can improve patients outcome, regarding functional status, cardiac and neurologic outcome, cognitive function and a pragmatic analysis -with a follow up of 6 month. The objective of the study was to compare the impact of two strategies of hemodynamic managements during CPB on outcome, where 248 patients were randomized into a low pressure group (50-60 mmHg) and a high pressure group (80-100 mmHg). The study also concluded that higher MAPPs can be achieved in a technically safe and reliable manner. Furthermore a study by Harilall et al. (2014) explored the use of interventions during CPB to improve cerebral oxygenation. They submit that MAPP affect cerebral oxygen saturation and can be used as an effective tool to prevent cerebral desaturation, which can result in brain injury.
In relation between MAPP and cerebral ischemia, Haugen et al. (2006, 2007) found significant coherence. They made 2 studies on piglets. In the first study, they investigated, with the aim to see if MAPP at the lower end of the commonly accepted range of 40-60 mmHg during CPB could lead to cerebral ischemia. They divided the piglets into three groups; a low pressure group (LP), a high pressure group (HP) and a control group (not receiving CPB). They found, that a MAPP about 40 mmHg may precipitate cerebral ischemia and cellular injury because cerebral perfusion pressure in the LP group was under the lower limit of autoregulation and cerebral markers of energy metabolism showed a pattern consistent with ischemia.

In the second study, they investigated if a MAPP of 40-45 mmHg could provoke the similar cerebral metabolic changes by a nitric oxide-independent intervention. In order to exclude nitric oxide used in the first study (nitroprusside), which can cause metabolic changes, they used phentolamine in the LP group as vasodilator. They made a similar set-up and identical protocol with a LP- and HP group. The HP group was used in both studies. In this study, the conclusion was that a MAP below 45 mmHg during CPB is associated with changes in cerebral metabolic markers and subcellular injuries.

In a literature study by Plestis and Gold (2001), investigating the effect of MAP during CPB on postoperative end-organ function, it is clear that maintaining a relatively high MAPP during CPB may have a significant impact in protecting the brain and the abdominal organs, particularly true in the subset of patients at high risk for embolization. In relation to the increasing age and vascular comorbidities of the cardiac surgical population, maintenance of an adequate cerebral perfusion pressure becomes of critical importance.

Regarding the maintenance of adequate pressure to ensure cerebral oxygenation, the brain is autoregulated. Cerebral autoregulation is a hemodynamic protective process, where changes in mean arterial pressure (MAP) results in low frequency diameter changes of cerebral arterioles. The change in cerebral vascular resistance (CVR) results in maintenance of cerebral blood flow (CBF), because $\text{CBF} = \frac{\text{CPP}}{\text{CVR}}$. CPP is the cerebral perfusion pressure defined as $\text{MAP} - \text{ICP}$ (intra cranial pressure). This means that in order to maintain CBF, CVR must be decreased when MAP is lowered. Because arterioles have limited ability to either dilate or constrict, there will be a plateau, where autoregulation can be maintained. Outside these limits CBF becomes pressure dependent (Zweifel 2014). In the study by Haugen et al. (2006), they also showed that CPB led to increased cerebral fluid levels. This means that ICP increases making drops in MAP even more profound on
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Cerebral blood flow. In this way, the curve for autoregulation is shifted to the left and the threshold for pressures, where CBF becomes pressure dependant is reached much earlier (Haugen 2006). The threshold for autoregulation is subjective and this makes it impossible to give a common interval for autoregulation for the brain and the kidneys in humans (Plestis 2001). Further on, it is influenced by a number of other factors, such as presence of vascular disease, hypertension and previous stroke. All these alterations of the circulatory system influence both the brain and other organs of the body (Ono 2013). Also CPB-related factors is believed to influence autoregulation, including hemodilution and non-pulsatile flow (Plestis 2001). For this reason, focus has been on development of a method for measuring autoregulation intraoperatively. In a study by Ono et al (2013), they hypothesized that MAPP below the limits of cerebral autoregulation during CPB, would be associated with major morbidity and operative mortality. The concern was that previous literature could not provide a MAPP range, where it was considered safe to perform CPB. The suggestions on safe MAPPs from previous studies ranged from 50 mmHg, perhaps even lower, and up to 80-100 mmHg. In a contemporary cohort of patients, they found that the lower level of cerebral autoregulation varied largely, between 40-90 mmHg. The main reason for conducting the study was, that the limits for cerebral autoregulation not only varied, but was also difficult to predict from preoperative MAP and patient demographics. They calculated a continuous moving Pearson’s correlation coefficient between MAPP and near infrared spectroscopy to get a measure for CBF. They concluded, that using physiologic endpoints would prove to be a method for optimizing organ perfusion and improve outcome during CPB rather than using empirical endpoints. They found an independent correlation between duration of MAPP outside the limits for cerebral autoregulation and the risk for development of acute kidney injury (Ono 2013).

All mentioned research agree upon a pronounced lack of studies investigating conduct of CPB to ensure patient safety and improve patient outcome, including further investigations on the influence on MAPP in cardiopulmonary bypass to ensure an optimal perfusion and evidence based practice. A striking feature is that there is a scarcity of research literature, where CPB has been conducted at perfusion pressures at 40 mmHg. The only two trials we found were investigated by Haugen et al. on piglets. This indicates a profound need for investigating outcomes for patients at low perfusion pressures. As mentioned, the prevention of brain ischemia is necessary in all patients undergoing CPB and MAPP about 40 mmHg may be related to development of cerebral ischemia. Investigating
relevant literature leaves us with the impression that it is probably correlated with less morbidity and mortality to conduct CPB at perfusion pressures above 60 mmHg regarding the kidneys and the brain.

**Aim**

The aim of this study is to investigate, if there is a coherence between mean arterial perfusion pressure and impaired cerebral and kidney function in order to optimize perfusion and to ensure that our current protocol results in the best possible outcome for the patient.

**Hypothesis**

We hypothesize, that conducting CPB at perfusion pressures below 60 mmHg can lead to cerebral ischemia and impaired kidney function postoperatively.
Methodological considerations

Investigated literature has revealed a lack of knowledge according to MAPP at the lower level of 40 mmHg associated with CPB and patient outcome. Furthermore, literature concerning conduct of CPB agree, that not enough clinical trials have been made with high enough quality to recommend an evidence based practice. With this study we wish to optimize perfusion and stimulate to further investigations and trials leading to evidence based protocols and clinical guidelines.

Considering the need for scientific evidence in determining the range of perfusion pressure for performing optimal perfusion and improved patient outcome, we wanted to do a scientific study with statistical significance. This master thesis, though, does not leave us with adequate time. Considering this, we designed a pilot study that could lead to the performance of a larger, statistical significant prospective randomized blinded trial, in case we found indications that supported our hypothesis.

Making a retrospective study was not considered, because MAPP rarely exceeds 60 mmHg at our department. Furthermore, there is a limited amount of data available regarding perfusion, as we only recently implemented an automatic data management system, collecting continuous data. In a retrospective study, we would be limited by the existing data making it difficult to answering our hypothesis. For this reason, we chose to do a randomized prospective study, where we would be able to design the study regarding data recording methods. Through investigating relevant research literature, we found that using NIRS and S100Beta could be beneficial in answering our hypothesis.

We tried to be precise on the sample size and the exclusion criteria in order to select subjects that would be as comparable as possible. Regarding the time frame, we retrospectively evaluated database reporting to consider the expected volume of patients that met the criteria. It was estimated, that with a data collecting period of six weeks, it would be possible to include 20 patients.

By making an in vivo study, the researcher becomes ethically and therapeutically responsible for the participating subjects. There were no expectations about severe disadvantages or side effects. Methods used conducting CPB are well documented and impose no harm to the subjects. For these reasons, we chose to design our study as mentioned above.
Materials and methods

Study design
The study was designed as an interventionnal prospective randomized study including 20 patients in an in vivo setup. Patients were randomized to one of two groups including 10 subjects each, a low pressure group (LP), where perfusion was performed at pressures between 40-60 mmHg and a high pressure group (HP), where perfusion was performed at pressures between 60-80 mmHg. The randomization was performed using the envelope method, with a tag containing one of the numbers 1-20, where 1-10 were equal to the LP group and 11-20 were equal to HP group. Despite of a design of 20 subjects, only 11 were enrolled in the study, due to a narrow time frame and a lack of patients meeting the criteria for in- and exclusion. Five subjects were enrolled in the LP group and six in the HP group.

From February to April 2014, patients undergoing elective CABG on CPB at University Hospital Odense, Denmark, were enrolled. Exclusion criteria included: Epidural catheter, age under 60 years, previous stroke, stenotic carotides, acute patient/reoperation, diabetes mellitus, EF < 50%, elevated preoperative sc-creatinine above 200 µM and peroperative risk > 5 %.

Subjects
The act on Processing of Personal Data and Danish Data Protection Agency approved this project. The study complied with the Helsinki declaration and all patients gave informed consent (appendix 1, 2, 3).

Subjects were recruited by the researcher the day before surgery. The same researcher did all the recruitments, ensuring consistent information. Information was given in the morning the day before surgery, preferably before the preliminary consultation with the anaesthesiologist in order to ensure that subjects agreeing to participation did not receive an epidural catheter. Subjects in doubt of epidural catheter were referred to the anaesthesiologist for advisement of pros and cons. The recruiting included oral and written information, including information regarding rights participating in a research project. Names and phone numbers of the researchers conducting the investigation were available in the patient information, in need for further information and
clarifying questions. Subjects were given time to consider if they wished to participate or not. Preferably they were informed with a next of kin if possible (appendix 4, 5).

In doubt of patient enrolment, the operating surgeon or anaesthesiologist were consulted by the researchers.

**Intervention protocol**

The pressure in the LP group was consistent with normal standards according to department protocol (appendix 6) and the HP group received a higher pressure than standard. To manage the pressures during perfusion, pharmacological agents were used. Metaoxidrine was administered by the perfusionist in the HLM and norepinephrine was administered by the anaesthesiologist in case of perfusion pressures decreasing below limits. If pressure exceeded the upper limits in the groups, pressure was lowered using Sevoflurane. A protocol was constructed for both the anaesthesiologists and surgeons regarding interventions (appendix 7, 8).

The HLM was operated by one of the researchers, and the same researcher did all perfusions in order to ensure consistency in the runs. The other researcher obtained data during the procedure. This was done to ensure full focus on perfusion and ensure patient security, while not compromising data collection.

**Equipment and registration**

Standard CPB equipment consisted of a Stöckert S5 heart lung machine with roller pumps (Sorin) with medium occlusion settings. Dideco tubings with a Compactflo Evo adult membrane oxygenator and a Micro 40 adult arterial filter D734 (Sorin) was primed with 1800 ml Ringers Lactate solution (Fresenius Kabi) including 5000 IU Heparin, in an open system. Harefield cardioplegia solution was mixed with blood in an 1:4 ratio, and administered cold at 5°C using a Sorin cardioplegia heat exchanger CSC14. A triple transducer set, DTX Plus (Argon) was used for pre- and postoxygenator and cardioplegia pressure monitoring.
For the cannulation, a 24 Fr. arterial cannula and a thin-flex dual stage 36/46 Fr. venous cannula (Edwards) were used. For antegrade cardioplegia a 9 Fr. cannula (Maquet) including an aorta vent was used.

For monitoring patient parameters and data: CDI500 including shunt sensor for arterial and venous line (Terumo), ABL800 (Radiometer), Hemochorn Response (ITC), Data Management System, DMS32 software (Sorin) and Somanetics INVOS Oximeter cerebral/somatic (Covidien).

Cardiopulmonary bypass was performed according to department protocol (appendix 6).
Demographic data, medical history, operative data and blood chemistries were registered into a database, including; age, gender, height, weight, BMI, BSA, use of ACE inhibitor, baseline creatinine, baseline MAP, baseline NIRS, baseline haematocrit, CPB duration, calculated flow, cross clamp duration, use of side biding clamp, fluid balance, use of erythrocytes, use of Albumin, Metaoxidrine, Norepinephrine, intraoperative NIRS, intraoperative MAPP, number of grafts, lowest haematocrit, creatinine 24 and 72 hours, S100Beta, ICU duration, total LOS, CK-MB, TnI, cerebral injury and re-operation.

**Anaesthetics and CPB**

Standard anaesthesia techniques were applied for all patients. After preoxygenation, anaesthesia was induced with Sufenta (50 µg) followed by Propofol (150-300 mg). Relaxant was administered afterwards and the patients were intubated. Sevoflurane (2%) was used as maintenance of anaesthesia, administered through an in-line vaporizer on the ventilator and directly to the CPB circuit through the oxygenator on the HLM. Standard monitoring equipment was used.

After cannulation, CPB was initiated and maintained according to department protocol (appendix 6). Calculated flow was 2.4 L/m² BSA and maintained at the same level during CPB unless SvO₂ declined below 65 %. Only diversions were during application and removal of cross clamp and side biding clamp.

Activated clotting time (ACT) was maintained at or above 480 s. and machine suction was used, when ACT reached above 400 s. Temperature target was 36°C initially and during CPB. Rewarming was initiated, when the last proximal anastomosis or the LIMA graft was started. Temperature was set at 37.8°C to a target core temperature of 37.0°C.
Cardioplegia: Initially 200 ml, maintenance 75 ml, given every 20 minutes. In addition, individual wishes according to surgeons were met.

To ensure a comparable perfusion of the subjects during CPB, the limits of blood parameters according to department protocol (appendix 6) were narrowed; pCO2: 5.0-5.3 kPa, pO2: 17.0-22.0 kPa, pH: 7.35-7.43 and Hct>22.

Blood samples were drawn and ACT was measured every 30 minutes.

Standard fluid was Ringers Lactate, Human Albumin 5% or erythrocytes were administered if necessary. Fluid therapy was managed in corporation with the anaesthesiologist and the surgeon.

Cerebral perfusion was monitored using Near-infrared Spectroscopy (NIRS) pre- and intraoperatively and S-100beta was measured six hours postoperatively. Kidney function was evaluated by measuring se-creatinine preoperatively and postoperatively after 24 and 72 hours. MAPP was recorded every minute using the Data Management System.

**Cerebral monitoring**

Regarding the hypothesis that perfusion pressure below 60 mmHg can lead to cerebral ischemia, we chose to monitor the regional cerebral oxygenation by using near infrared spectroscopy (NIRS) and presence of cerebral ischemia using the protein S100B, registered in a postoperative blood sample.

**Near Infrared Spectroscopy**

NIRS is a non-invasive technique that allows continuous monitoring of the regional haemoglobin oxygen saturation (rSO2) index and it detects regional ischemia and warns of impending hypoxic damage.

Near infrared light photons are injected into the skin over the forehead. After being scattered about inside the scalp, skull and brain, some fraction of the injected photons survive to return and exit the skin. By measuring the quantity of returning photons as a function of wavelength, one can infer the spectral absorption of the underlying tissue and make some conclusions about its average oxygenation.

As a reliable bedside non-invasive assessment, NIRS is often used for detection of cerebral
ischemia on patients undergoing cardiac surgery (Murkin 2009; Tan 2008).

All subjects had The Somanetics INVOS Cerebral Oximeter system, which is designed specifically for measuring oxygen in the blood of the brain in the area underlying the sensor and uses two wavelengths, 730 and 810 nm, to measure changes in regional haemoglobin oxygen saturation (Covidien).

Sensors were placed on the subject's forehead and baseline was recorded before anaesthesia or oxygen supplement.

NIRS tracings were recorded every sixth second under the CPB procedure, analyzed and correlated with marked clinical events (initiation of anaesthesia, sternotomy, cannulation, initiation of CPB, cross clamp application, administration of cardioplegia and Metaxidrine, cross clamp removal and weaning from CPB). If a subject dropped below 40 % in NIRS tracings, the subject was excluded. If baseline was below 50 % the subject was likewise excluded.

*S100Beta*

S100Beta is a member of a large calcium binding associated gene family containing two EF-hand calcium binding motifs. It is found mainly in the nucleus or the cytoplasm, but in case of cell injury or cell death, S100Beta is released and elevated levels correlates with injury in the brain. It has been shown that S100Beta may be involved in the cellular response to ischemia. Ischemia in the brain rapidly leads to depletion of ATP. This has been shown to result in a rise in the concentration of adenosine and this leads to a release of S100Beta within an hour. It is important to notice that S100Beta is absent in erythrocytes. Haemolysis, which is unavoidable during cardiopulmonary bypass, will not result in rising levels of S100Beta. There is no consensus on the cut-off point for cerebral injury, but if the level of S100Beta is above 0.20µg/L, this is consistent with cerebral injury (Bloomfield, 2007). Because of this, S100Beta is used as a predictor of brain injury and adverse neurological outcome in patients after cardiac surgery undergoing CPB.

The brain is not the only source of S100Beta. Extracranial sources of the protein include muscle and adipose tissue. This has to be taken into consideration regarding cardiac surgery patients, which leads to injuries to the muscle, fatty tissue and the bone marrow (Bloomfield 2007).
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It has been shown, that elevated levels are more predominantly in venous blood than in arterial blood, and for prognostic use, the samples should be obtained in a venous blood sample in order to get the most precise measure of S100Beta concentrations. When blood is sampled from the central venous catheter (CVC) it is believed that the sample is less polluted by fractions of S100Beta that arises from extracranial sources (Bloomfield 2007).

Venous blood samples from the CVC were taken postoperatively (6 hours after weaning from CPB) to measure S100Beta concentrations. The samples were collected by the investigator in gel sample tubes, marked according to a number thus protecting patient identity (2 meaning subject number 2, according to the envelope method) and left to clot for 30 minutes. Then they were centrifuged at 2000 G for 10 minutes and put in the refrigerator. The next day, serum phase was pipetted into a clean tube and stored at -80°C at KBF, University Hospital Odense. Samples were shipped to KBA, Rigshospitalet in Copenhagen for analysis using the Sandwich Elektrochemiluminescence- immunoassay (ECLIA) - photon counting essay (KBA, Rigshospitalet). Collaboration agreements were made with KBF, University Hospital Odense and KBA, Rigshospitalet Copenhagen.

Statistical methods
To estimate the power of this study, we investigated research literature regarding cardiopulmonary bypass impact on renal and cerebral function postoperatively. This revealed that according to renal function, creatinine is the strongest prognostic indicator. Further investigation on available literature showed that no comparable studies have been made to give an indication on estimated outcome. For this reason we had to perform a qualified assumption to make a statistical power calculation. From this we made an assumption of a 10 % increase in creatinine in the HP group and a 25 % increase in the LP group. According to S100Beta and rSO\(_2\) in CABG patients undergoing CPB, there is a lack of data, and furthermore at our department we do not measure S100Beta and only occasionally rSO\(_2\). For this reason, we only considered creatinine in estimating the power.

Creatinine reference intervals for females (45-90 µM) are different from males (90-105 µM) according to OUH protocol. As we are investigating both male and female subjects, we chose a reference interval of 45-105 µM. We expected to see a larger increase in se-creatnine in the LP-group than in the HP-group. We expected a rise of 10 % in the HP-group (49.5-115.5 µM) and in the LP-group a rise of 25 % (56.25-131.25 µM). Standard deviation (SD) is 17.8125µM and the
difference in mean creatinine between the groups is $11.25\mu M$. Regarding the SD, this is overestimated. We obtained the SD from the idea that all subjects increase with the same percentage. This is not quite true. In this we do not consider intra-personal changes. Looking at the intra-personal changes makes the SD smaller, perhaps down to half the value of the estimated SD. We consider 75% of the obtained SD to be a reasonable estimate, giving a SD-value of $13.34\mu M$.

Calculating sample size results in 22 subjects in each group, given a power ($\beta$) of 80% and a level of significance ($\alpha$) of 5%.

$$n = \frac{2K\alpha\beta}{\sigma^2} = 2 \times 7.8 \times \frac{13.34^2}{11.25^2} = 21.93 = \sim 22 \text{ subjects}$$

The power of this study will be weak, since we only have 10 subjects in each group. Because of this being a pilot study, it would not be expected to be statistically significant.

The results were statistical evaluated using EpiBasic and Excel. Results are presented as means with standard deviations. P-values are calculated using comparison of means with t-test, because of a small sample size. Fisher’s exact test was used to compare categorical variables, using two tailed p-values. When calculating percentage decline from baseline to intraoperative measurement, we looked at the intrapersonal changes using logarithmic scale.
## Results

11 patients were enrolled in the study.

### Table 1: Baseline demographic and clinical characteristics of the study population organised in the LP- and HP group

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>Age (years)</th>
<th>Gender (female/male)</th>
<th>Height (cm)</th>
<th>weight (kg)</th>
<th>BMI (kg/m²)</th>
<th>BSA (m²)</th>
<th>Use of ACE inhibitor (yes/no)</th>
<th>Baseline creatinine (µM)</th>
<th>Baseline MAP (mmHg)</th>
<th>Baseline NIRS Left side (%)</th>
<th>Baseline NIRS Right side (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LP group</strong></td>
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<tr>
<td>2</td>
<td>64</td>
<td>f</td>
<td>165</td>
<td>68.5</td>
<td>25.16</td>
<td>1.74</td>
<td>N</td>
<td>62</td>
<td>80</td>
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<td>24.77</td>
<td>1.44</td>
<td>N</td>
<td>88</td>
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Abbreviations: BMI (body mass index), BSA (body surface area), ICU (intensive care unit), LOS (length of stay), TnI (Troponin I) and CK-MB (Creatine Kinase-MB)

Note: NIRS was measured as regional saturation (rSO₂).

### Results; demographic, clinical, intra- and post-operative factors in general

Results based on the total number of patients (some listed in table 1) represented as mean (±SD)(range):

**Demographic**

Age was 70.6 years (±5.16)(64–77), 73 % were men, height was 166 cm (±7.41)(149–176), weight was 75.5 kg (±11.22)(55–87.9), BMI was 27.4 kg/m² (±3.28)(21.05–31.48) and BSA was 1.82 m² (±0.17)(1.44–2).
Clinical

9.1 % used ACE inhibitor, baseline creatinine was 91.3 µM (±19.52)(62-125), baseline MAP was 100.8 mmHg (±13.56)(80-118), baseline rSO₂ right side was 68.6 % (±8.42)(59-84) and left side was 68.6 % (±8.43)(59-85). Baseline haematocrit was 0.384 (±0.0387)(0.320-0.438).

Intraoperative

Duration of CPB was 96.5 min (±28.7)(45-140), calculated flow was 4.23 L/min (±0.405)(3.5-4.8), cross clamp duration was 57.5 min (±17.4)(24-80), 73 % use of side biding clamp, fluid balance was 2255 ml (±1279)(670-4790) and for transfusion; 18 % received erythrocytes and 18 % albumin. Lowest haematocrit was 0.279 (±0.0448)(0.218-0.342). Use of Metaoxidrine was 0.823 mg (±0.475)(0.35-1.8) and use of norepinephrine was 0.964 mg (±1.46)(0-5).

rSO₂ right side was 65.6 % (±7.80)(52.7(±2.0)-79.2(±1.67)), rSO₂ left side was 66 % (±6.88)(53.4(±2.18)-74.2(±1.15)), MAPP was 55.8 mmHg (±9.30)(41.2(±4.05)-66.9(±8.41)). According to rSO₂ and MAPP the results are stated as mean (±SD)(lowest mean(±SD) to highest mean (±SD)). Number of grafts were 3.27 (±0.90)(2-5).

Postoperative

Creatinine 24 hours postoperative was 84.3 µM (±17.1)(57-112) and after 72 hours 81.6 µM (±16.8)(51-102), S100Beta was 1.3 µg/L (±2.07)(0.076-5.52). Duration of ICU stay was 1.91 days (±2.21)(1-8), total length of stay was 6.55 days (±2.50)(4-11), CK-MB was 54 µg/L (±39.8)(12-155), TnI was 12656 ng/L (±11008)(2008-39163).

9 % had cerebral injury (developed cerebral complications postoperatively requiring treatment at a neurological department, subject 8) and 18 % were re-operated (one subject with cardiac tamponade and another with closed graft, subject 2 and 20).
Table 2: Comparison between the LP- and HP group, based on demographic, clinical, intra- and postoperative factors.

<table>
<thead>
<tr>
<th>Factor</th>
<th>LP group (n=5)</th>
<th>HP group (n=6)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ±SD</td>
<td>Mean ±SD</td>
<td></td>
</tr>
<tr>
<td><strong>Demographic factors</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Age (years)</td>
<td>70.4 ± 5.22</td>
<td>70.8 ± 5.60</td>
<td>0.91</td>
</tr>
<tr>
<td>Gender (female/male)</td>
<td>40 %/60 %</td>
<td>16.7 %/83.3 %</td>
<td>0.55</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163 ± 7.91</td>
<td>168.5 ± 6.59</td>
<td>0.24</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68.7 ± 13.2</td>
<td>81.2 ± 5.13</td>
<td>0.06</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.8 ± 3.66</td>
<td>28.7 ± 2.46</td>
<td>0.15</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.73 ± 0.208</td>
<td>1.90 ± 0.0892</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Clinical factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of ACE inhibitor</td>
<td>0 %</td>
<td>16.7 %</td>
<td>1.00</td>
</tr>
<tr>
<td>Baseline creatinine (µM)</td>
<td>83 ± 15.2</td>
<td>98.2 ± 21.3</td>
<td>0.21</td>
</tr>
<tr>
<td>Baseline MAP (mmHg)</td>
<td>97 ± 16.2</td>
<td>104 ± 11.5</td>
<td>0.42</td>
</tr>
<tr>
<td>Baseline NIRS Left side (%)</td>
<td>63.4 ± 5.03</td>
<td>73.0 ± 8.46</td>
<td>0.06</td>
</tr>
<tr>
<td>Baseline NIRS Right side (%)</td>
<td>63.6 ± 3.85</td>
<td>72.8 ± 9.13</td>
<td>0.07</td>
</tr>
<tr>
<td>Baseline haematocrit</td>
<td>0.374 ± 0.0419</td>
<td>0.392 ± 0.0377</td>
<td>0.48</td>
</tr>
<tr>
<td><strong>Intraoperative factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPB duration (min)</td>
<td>85.8 ± 35.3</td>
<td>105.5 ± 21.04</td>
<td>0.28</td>
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<tr>
<td>Calculated flow (L/min)</td>
<td>4.06 ± 0.439</td>
<td>4.37 ± 0.35</td>
<td>0.29</td>
</tr>
<tr>
<td>Cross clamp duration (min)</td>
<td>50 ± 22.4</td>
<td>63.7 ± 10.03</td>
<td>0.21</td>
</tr>
<tr>
<td>Use of side biding clamp</td>
<td>100 %</td>
<td>50 %</td>
<td>0.18</td>
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<tr>
<td>Fluid balance (ml)</td>
<td>2891 ± 1342</td>
<td>1724 ± 1043</td>
<td>0.14</td>
</tr>
<tr>
<td>Use of erythrocytes</td>
<td>40 %</td>
<td>0 %</td>
<td>0.18</td>
</tr>
<tr>
<td>Use of Albumin</td>
<td>20 %</td>
<td>16.7 %</td>
<td>1.00</td>
</tr>
<tr>
<td>Metoaxidrine (mg)</td>
<td>0.54 ± 0.238</td>
<td>1.06 ± 0.508</td>
<td>0.07</td>
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<tr>
<td>Norepinephrine (mg)</td>
<td>0.04 ± 0.0894</td>
<td>1.73 ± 1.63</td>
<td>0.047</td>
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<tr>
<td>NIRS left side (%)</td>
<td>61.9 ± 7.01</td>
<td>69.4 ± 3.45</td>
<td>0.045</td>
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<tr>
<td>NIRS right side (%)</td>
<td>61.3 ± 6.88</td>
<td>69.2 ± 7.07</td>
<td>0.09</td>
</tr>
<tr>
<td>MAPP (mmHg)</td>
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<td>63.5 ± 1.94</td>
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<tr>
<td>Number of grafts</td>
<td>2.8 ± 0.837</td>
<td>3.67 ± 0.816</td>
<td>0.12</td>
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<tr>
<td>Lowest haematocrit</td>
<td>0.247 ± 0.0344</td>
<td>0.306 ± 0.0335</td>
<td>0.02</td>
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<tr>
<td><strong>Postoperative factors</strong></td>
<td></td>
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<tr>
<td>Creatinine 24 hours (µM)</td>
<td>72.2 ± 10.3</td>
<td>94.3 ± 15.2</td>
<td>0.022</td>
</tr>
<tr>
<td>Creatinine 72 hours (µM)</td>
<td>76 ± 16.2</td>
<td>86.3 ± 17.1</td>
<td>0.34</td>
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<td>S100Beta (µg/L)</td>
<td>1.32 ± 2.35</td>
<td>1.29 ± 2.04</td>
<td>0.98</td>
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<tr>
<td>ICU duration (days)</td>
<td>2.4 ± 3.13</td>
<td>1.5 ± 1.22</td>
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<tr>
<td>Total LOS (days)</td>
<td>6.4 ± 2.30</td>
<td>6.67 ± 2.88</td>
<td>0.87</td>
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<tr>
<td>CK-MB (µg/L)</td>
<td>66.8 ± 54.9</td>
<td>43.3 ± 21.3</td>
<td>0.36</td>
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<td>TnI (ng/L)</td>
<td>17603 ± 14627</td>
<td>8533 ± 5131</td>
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<tr>
<td>Cerebral injury</td>
<td>20 %</td>
<td>0 %</td>
<td>0.45</td>
</tr>
<tr>
<td>Re-operation</td>
<td>20 %</td>
<td>16.7 %</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Abbreviations: BMI (body mass index), BSA (body surface area), ICU (intensive care unit), LOS (length of stay), TnI (Troponin I) and CK-MB (Creatine Kinase-MB)

Note: NIRS was measured as regional saturation (rSO2).
Note: Total LOS includes stay at ICU and thoracic department T, OUH.
Results; demographic, clinical, intra- and post-operative factors in comparison between the LP- and HP group (table 2)

Baseline demographics and clinical factors of patients in the LP- and HP group respectively were evaluated in order to determine, if the two groups were identical in relation to comparability, represented as mean (±SD)(range).

Demographic
Age in LP was 70.4 years (±5.22)(64–77) and in HP 70.8 years (±5.60)(64–77) with a p-value of 0.91. 60 % were men in LP and 83.3 % in HP with a p-value of 0.55. Height in LP was 163 cm (±7.91)(149–168) and in HP 168.5 cm (±6.59)(157–176) with a p-value of 0.24. Weight in LP was 68.7 kg (±13.2)(55–87.9) and in HP 81.2 kg (±5.13)(73–86.4) with a p-value of 0.06. BMI in LP was 25.8 kg/m² (±3.66)(21.05–31.14) and in HP 28.7 kg/m² (±2.46)(24.71–31.48) with a p-value of 0.15. BSA in LP was 1.73 m² (±0.208)(1.44-2) and in HP 1.9 m² (±0.0892)(1.75-2) with a p-value of 0.06.

Clinical
No subjects in LP used ACE inhibitor compared to 16.7 % in HP with a p-value of 1.00. Baseline creatinine in LP was 83 µM (±15.2)(62-104) and in HP 98.2 µM (±21.3)(74-125) with a p-value of 0.21. Baseline MAP in LP was 97 mmHg (±16.2)(80-118) and in HP 104 mmHg (±11.5)(89-117) with a p-value of 0.42. Baseline rSO₂ right side in LP was 63.6 % (±3.85)(59-68) and in HP 72.8 % (±9.13)(63-84) with a p-value of 0.07. Baseline rSO₂ left side in LP was 63.4 % (±5.03)(59-71) and in HP 73.0 % (±8.46)(65-85) with a p-value of 0.06. Baseline haematocrit in LP was 0.374 (±0.0419)(0.320-0.434) and in HP 0.392 (±0.0377)(0.342-0.438) with a p-value of 0.48.

A p-value of ≤0.05 was considered to be of statistical importance. In relation demographic- and clinical factors, the groups are comparable with the remark that in regards to weight (p=0.06), BSA (p=0.06) and right and left side rSO₂ baseline (p=0.07 and p=0.06), the probability is borderline of becoming statistical significant.
Intraoperative

Duration of CPB in LP was 85.8 min (±35.3)(45-140) and in HP 105.5 min (±21.04)(81-130) with a p-value of 0.28. Calculated flow in LP was 4.06 L/min (±0.439)(3.5-4.7) and in HP 4.37 L/min (±0.35)(4.0-4.8) with a p-value of 0.29. Cross clamp duration in LP was 50 min (±22.4)(24-80) and in HP 63.7 min (±10.03)(53-75) with a p-value of 0.21. 100 % used side biding clamp in LP and 50 % in HP with a p-value of 0.18.

Fluid balance in LP was 2891 ml (±1342)(1475-4790) and in HP 1724 ml (±1043)(670-3290) with a p-value of 0.14. For transfusion; 40 % received erythocytes in LP, none in HP with a p-value of 0.18 and 20 % albumin in LP and 16.7 % in HP with a p-value of 1.00. Use of Metoxodrine in LP was 0.54 mg (±0.233)(0.35-0.95) and in HP 1.06 mg (±0.508)(0.5-1.8) with a p-value of 0.07. Use of norepinephrine in LP was 0.04 mg (±0.0894)(0-0.2) and in HP 1.73 mg (±1.63)(0.61-5.0) with a p-value of 0.047.

rSO₂ right side in LP was 61.3 % (±6.88)(52.7(±2.00)-67.9(±1.72)) and in HP 69.2 % (±7.07)(60.7(±4.05)-79.2(±1.67)) with a p-value of 0.09. rSO₂ left side in LP was 61.9 % (±7.01)(53.4(±2.18)-69.5±(1.98)) and in HP 69.4 % (±3.45)(61.4(±3.65)-74.2(±1.15)) with a p-value of 0.045. MAPP in LP was 46.5 mmHg (±3.88)(41.2(±4.05)-51.4(±6.07)) and in HP 63.5 mmHg (±1.94)(61.6(±1.88)-66.9(±8.41)) with a p-value of 0.000006. According to rSO₂ and MAPP the results are stated as mean (±SD)(lowest mean(±SD) to highest mean (±SD)). Number of grafts in LP were 2.8 (±0.837)(2-4) and in HP 3.67 (±0.816)(3-5) with a p-value of 0.12. Lowest haematocrit in LP was 0.247 (±0,0344)(0.218-0.304) and in HP 0.306 (±0.0335)(0.258-0.342) with a p-value of 0.02.

Postoperative

Creatinine 24 hours postoperative in LP was 72.2 µM (±10.3)(57-83) and in HP 94.3 µM (±15.2)(77-112) with a p-value of 0.022. Creatinine after 72 hours in LP was 76 µM (±16.2)(51-92) and in HP 86.3 µM (±17.1)(64-102) with a p-value of 0.34. S100Beta in LP was 1.32 µg/L (±2.35)(0.076-5.52) and in HP 1.29 µg/L (±2.04)(0.25-5.43) with a p-value of 0.98.
Duration of ICU stay in LP was 2.4 days (±3.13)(1-8) and in HP 1.5 days (±1.22)(1-4) with a p-value of 0.53. Total length of stay in LP was 6.4 days (±2.30)(4-10) and in HP 6.67 days (± 2.88)(4-11) with a p-value of 0.87. CK-MB in LP was 66.8 µg/L (±54.9)(23-155) and in HP 43.3 µg/L (±21.3)(12-70) with a p-value of 0.36. TnI in LP was 17603 ng/L (±14627)(5454-39163) and in HP 8533 ng/L (±5131)(2008-15661) with a p-value of 0.19. 20 % in LP had cerebral injury and none in HP with a p-value of 0.45. 20 % in LP were re-operated and 16.7 % in HP with a p-value of 1.00.

Looking at the intra- and postoperative factors, the groups are significantly different regarding use of norepinephrine (p=0.047), MAPP (p=0.000006), rSO₂ left side (p=0.045), lowest haematocrit (p=0.02) and creatinine 24 hours postoperative (p=0.022). Further on, there is a trend towards a difference between the groups regarding use of Metaoxidrine (p=0.07), rSO₂ right side (p=0.09) and fluid balance (p=0.14). Despite not being statistical significant, we chose to consider these as well, given the fact that the power of the study is weak, because of the small sample size.

The five factors that are considered to be statistical significant different and the three factors that shows a trend will be discussed. Further on, we will also investigate and discuss the relationship between MAPP and S100Beta even though not being statistical significant (p=0.98). The reason for considering S100Beta is that it is relevant considering our hypothesis in evaluation of cerebral ischemia.
Discussion

We obtained some significant factors (p<0.05) relevant for answering our hypothesis. Furthermore, we chose to include and discuss tendencies regarding fluid balance, Metaoxidrine, rSO2 right side and S100Beta as described in the last section.

Subject 2 and 20 experienced postoperative complications requiring reoperation. We assume that the subjects have met conditions with ischemia during these complications, which may have polluted the postoperative results. For this reason we choose to discuss the postoperative results of S100Beta in the entire study population and with exclusion of subject 2 and 20, with a clear statement on inclusion or exclusion in the discussion of the findings. Regarding creatinine the findings from subject 2 and 20 are used as available case, and the results will be included in the discussion. The reason for not excluding the two subjects in general, is that we consider the pre- and intraoperative data as valid and useful.

Conducting a randomized study on a very small sample size holds a significant risk for groups to become incomparable, because of differences regarding demographic and clinical data. This is seen in this study, where the groups are different regarding weight (p=0.06), BSA (p=0.06) and baseline rSO2 right and left side (p=0.07 and p=0.06).

The most important factor in this study is the mean arterial perfusion pressure, and in the following we will be comparing MAPP to factors previous mentioned as relevant and interesting.

Primary, we have managed to make a study with a significant difference in MAPP between the groups, where MAPP in LP, as a mean, was 46.5 (±3.88) and in HP 63.5 (±1.94) with a p-value of <0.000006. This is important for the design of the study, but also because we were concerned, that there would be no gap between the pressure ranges in the LP- and HP group. This could have led to the problem of subjects in the LP group being in the high end of the range (40-60 mmHg) and in the low end of the range (60-80 mmHg) in the HP group, resulting in the groups becoming to incomparable. A similar concern regarding meeting the criteria for range derived from the fact that
our department is not used to conducting CPB at high pressures. To prevent a possible resistance, colleagues were informed verbally and in writing, but still some communication intraoperatively were required to maintain the pressure in the HP group. Looking at the range in the HP group the values were in the low end, but the mean values for the two pressure groups were within the desired limits.

**MAPP and rSO$_2$**

We hypothesized, that a MAPP value below 60 mmHg could lead to cerebral ischemia and in order to detect incidents of cerebral ischemia, we chose to use NIRS measured as rSO$_2$.

None of the participating subjects were excluded for baseline values of rSO$_2$ below 50 % or intraoperative values of rSO$_2$ below 40 %, according to the exclusion criteria of the study.

Interestingly, there was a borderline significant difference between the groups, regarding baseline values of rSO$_2$ in both left and right side of the cerebral hemisphere, with baseline means in the LP group at 63.4 % ($\pm$5.03) left side and 63.6 % ($\pm$3.85) right side and in the HP group 73.0 % ($\pm$8.76) left side and 72.8 % ($\pm$9.13) right side, and with a p-value left side of 0.06 and right side 0.07.

According to a literature study by Tan (2008), a generally accepted normal value of rSO$_2$ has not been established, but a mean at 67 % ($\pm$10) has been observed in healthy individuals and cardiac patients. This is in agreement with a study by Murkin (2007), where 200 coronary artery bypass patients were randomized to either intraoperative rSO$_2$ with active display and treatment intervention protocol (intervention, n=100), or underwent blinded rSO$_2$ monitoring (control, n=100). Patients in the control group had a baseline of 68.9 % ($\pm$7.2) and the intervention group 70.3 % ($\pm$7.1) with a p-value of 0.188. Furthermore, when differences occur, the cause can relate to carotid or intracranial arterial stenosis, intracranial space-occupying lesions, extra-cranial lesions, old infarcts and interference from the infrared emitting device. Still, monitoring rSO$_2$ is considered an important safeguard for cerebral function (Tan 2008; Murkin 2009). We tried to rule out the mentioned causes, according to exclusion criteria of this study. The findings of different values of rSO$_2$ in the LP- and HP group are unexplainable, meaning that the differences are completely random.
Following, we evaluated the obtained intraoperative results from rSO₂ in the LP- and HP group, to investigate the influence of MAPP on rSO₂ during CPB. We rediscovered the same difference between the groups, as seen in baseline. The highest mean value, found in the HP group, was 69.2% (±7.07) on the right side and 69.4% (±3.45) on the left side. In the LP group the results for rSO₂ right side was 61.3% (±6.88) and left side was 61.9% (±7.01). Looking at the mean values, there was a small decline from baseline to the intraoperative measurement in both groups, on both left and right side.

The HP group declines 0.9 % more than the LP group on the left side and 0.4 % on the right side. If this is not only related to the lack of power, then this means that the population of this study are not dependant on MAPP in relation to maintaining adequate cerebral perfusion. The fact that the HP group holds the largest decline could indicate that they received a pressure above the threshold for autoregulation, knowing that the difference is minimal. As previously mentioned there is a continuously ongoing debate in regards to estimating limits for cerebral autoregulation. There is no consensus on where the limits are and previous research has concluded on different values in the range of 20-90 mmHg. For normothermic patients, the limit for cerebral autoregulation is believed to be within the range of 50-90 mmHg (Plestis 2001; Murphy 2009). It seems unlikely that subjects in the HP group have received pressures above the threshold for cerebral autoregulation, considering that the mean MAPP in HP group was 63.5 mmHg (±1.94).

When evaluating data from the individual subjects, we detected a drop in rSO₂ from baseline up to 39.7 %. All subjects experienced decline from baseline. These drops were related to initiation of CPB, which may be due to hemodilution and low perfusion pressure (Murkin 2007). Four subjects experienced a drop larger than 20 % from baseline, which is considered to be the threshold of regional cerebral ischemia and potentially harmful to patients (Tan 2008). If we look at the four subjects, neither has experienced cerebral injury caused by ischemia. There are no correlations between these drops in the two pressure groups. 50 % of the subjects that experienced a drop larger than 20 % were in the LP group and the other 50 % were in the HP group.

In general, the two subjects in the HP group had the longest period of rSO₂ below 80 % of baseline. Considering the subject, with the longest period of rSO₂ below 80 % of baseline (431 seconds; accumulated drops on both left and right side), we discovered that this is also the subject with the second highest drop in rSO₂ (36.5 %) and the highest level of S100Beta (excluding the two subjects
with postoperative complications). Periods of longer desaturation are, in literature, being linked to longer intensive care stay (Tan 2008; Murkin 2007). Regarding this subject, this is not true, since he experienced no cerebral injury postoperatively and was discharged on day 4 (including one day at ICU).

Looking at rSO$_2$ in relation to MAPP in HP group, 50% of the subjects have a tendency of decline in MAPP and increase in rSO$_2$ (figure 1) and the remaining 50% experience an increase in both rSO$_2$ and MAPP throughout the CPB (figure 2).

Figure 1: An example of tendencies from rSO$_2$ monitoring (subject 17).
In the LP group, there is a tendency for a slight increase in both MAPP and rSO2 during CPB. We see this tendency in the LP group in all but one subject (subject 8), where there was a decrease in both MAPP and rSO2 throughout CPB. Subject 8 developed cerebral complications postoperatively requiring treatment at a neurological department. The subject did not have the highest decline in rSO2 at initiation of CPB, but drops in rSO2 throughout the CPB seen as spikes (figure 3). These spikes can be explained by a recurrent high central venous pressure during the procedure. This is consistent with the findings by Harilall et al. (2014) showing that occurrence of cerebral desaturation was predominantly associated with appliance or removal of aortic cross clamp and during distal anastomosis of the coronary arteries. The same is observed by Murkin et al. (2007) with the supplement that also manoeuvres that require decreased or stopped pump flow results in cerebral desaturation. During distal anastomosis, there is an increase in central venous pressure. Special surgical procedures trying to fixate the heart for better access on the distal side, increase

Figure 2: An example of tendencies from rSO2 monitoring (subject 6).
central venous pressure. In relation to the above mentioned subject, the central venous pressure lies in a range of 20-46 mmHg for 5 minutes. This caused desaturation, despite active intervention with administered Metaoxidrine raising MAPP reaching 58 mmHg.

Figure 3: rSO₂ monitoring from subject 8.

According to a study with a treatment intervention protocol used to maintain rSO₂, the conclusion is that one of the most frequent and effective way to maintain rSO₂ is by raising MAPP (Murkin 2007). In our study, we are not able to see a clear connection between rSO₂ and MAPP. Overall we are not able to conclude that rSO₂ is influenced by MAPP.

**MAPP and S100Beta**

When investigating the results of S100Beta in the different pressure groups, including subject 2 and 20, we found no significant differences between the groups (p=0.98). We cannot conclude on the
value of S100Beta in relation to MAPP and development of cerebral ischemia in our study. As previously mentioned, subject 8 developed cerebral complications requiring treatment at a neurological department. This subject had a S100Beta of 0.191 µg/L, which would be considered safe and without development of cerebral injury. It should be mentioned though, that subject 2 and 20 that developed postoperative complications had largely elevated levels of S100Beta (5.52 µg/L and 5.43 µg/L). For these two subjects, it seems like there could be a relation between the elevated levels and cerebral ischemia, because they both suffered periods of hypotension in the first postoperative period. It should be mentioned, that neither of the two subjects had cerebral injuries. Other explanations for the elevated levels of S100Beta could be pollution from extracranial sources.

If the elevated levels of S100Beta were caused by ischemia or pollution, we are not able to differentiate between intraoperative and postoperative factors. If we exclude these two patients and compare the LP- and HP group again in regard to S100Beta, we get a p-value of 0.19. Considering this, the trend is towards elevated levels in HP, indicating that there is an increased risk of cerebral ischemia in the HP group (figure 4). This is in contrast to a study by Harilall et al. (2014), where 40 coronary artery bypass patients were randomized to either intraoperative rSO\(_2\) with active display and treatment intervention protocol or underwent blinded rSO\(_2\) monitoring. S100Beta was taken pre- and postoperatively in both groups. They concluded that there was a highly significant increase in S100Beta concentration in the control group with no interventions compared to the intervention group that used MAPP as one of the interventions for maintaining rSO\(_2\).

Figure 4: S100Beta as a function of mean MAPP with tendency line (excluding subject 2 and 20).
It can be problematic that we are unaware of the baseline values for the subjects. This makes it difficult to conclude on the obtained differences. We decided not to sample for baseline values of S100Beta, after evaluating available literature regarding the subject. Grocott et al. (1998) made a prospective study of 156 patients, evaluating the relationship between cerebral emboli and levels of S100Beta. They made baseline measurements for all patients. The obtained result was a mean value of baseline S100Beta of 0.00 µg/L (±0.00). This is confirmed in a study by Wiesmann et al. (1998), who investigated the relationship between baseline levels of S100Beta, age and gender, in 200 healthy adults. They found a mean value of 0.052 µg/L with no differences according to age or gender. We consider our population as normal distributed in relation to exclusion criteria ruling out arteriosclerosis and previous cerebral injury influencing elevated levels of S100Beta. From this we concluded, that it would be reasonable to consider S100Beta to be absent in subjects undergoing elective cardiovascular surgery in this study. Another issue is the fact that we were not able to get an analysis of S100Beta at our institution, which increased the costs for analysis considerably.

From this we have to assume that the influence of baseline S100Beta in this study is inconsiderable in most of the subjects. The only exception is subject number 6 with a postoperative measure of S100Beta of 0.076 µg/L, close to the mean of 0.052 found by Wiesmann et al.

Further on, there is a lack of consensus in regard to assessing optimal sample time. If the samples are collected to early in order to exclude released S100Beta from extracranial sources, then this will be a source of contamination, which makes sample timing difficult. Some researchers recommend that sampling should be at 24 hours postoperative, because the released extracranial S100Beta has a short half-time of 20-25 minutes and levels originating from these sources retrieve to normal within 20 hours (Bloomfield 2007). Grocott et al. (1998) looked at levels of S100Beta just after weaning from CPB and then 150 and 270 minutes after cross clamp release. They obtained the highest levels of S100Beta directly after weaning. The two next samples continued to decline. This could perhaps be explained by the short half-time of the protein from extracranial sources. If this is true, it should be plausible to conclude that there is not a major contamination from extracranial sources, when measuring S100Beta six hours after weaning from CPB, considering our sample time as valid.

Grocott et al. (1998) found a correlation between duration of cross clamp time and age in relation to increased risk for cerebral injury. Because of conflicting results in our study regarding S100Beta, we investigated if S100Beta was influenced by cross clamp time and age. Figure 5 shows the relation between S100Beta and cross clamp duration (excluding subject 2 and 20).
There is a strong tendency towards a positive correlation between increased cross clamp duration and increased levels of S100Beta in our study.

Looking at the relation between age and S100Beta, we found no correlation. This could be a result of the criteria for participating in the study, where we have excluded patients younger than 60 years, with a mean of 70.6 years (±5.16).

This could indicate that factors other than MAPP influence release of S100Beta. This has an impact on our data, in the sense that it becomes difficult to isolate the MAPP in order to evaluate the impact of this factor.

**MAPP and creatinine**

None of the subjects participating in the study developed renal insufficiency.

In general, in relation to baseline creatinine (p=0.21) and creatinine after 72 hours (p=0.34), we found no significant difference between the groups (including subject 2 and 20). But looking at
creatinine after 24 hours, we found a significant difference between the groups with a p-value of 0.022.

When investigating the mean values of creatinine from baseline to 24 hours in the two pressure groups, the LP group declines 4.6% more than the HP group, with a statistical significant difference. When looking at the mean values from baseline to 72 hours, the HP group decreases 1.4% more than the LP group. The decline at 72 hours is interesting even though not being statistical significant. It is interesting because in general the HP group declines in the entire measured postoperative period, whereas the LP group has a decline from baseline to 24 hours but increases, from 24 to 72 hours (figure 6). We realise that we are unaware of creatinine concentrations after 72 hours, not knowing the development. It might be beneficial regarding kidney function, defined by level of creatinine, to conduct CPB at higher MAPP, because of a continuous drop in the HP group, not seen in the LP group. This difference might be connected to the lower fluid balance seen in the HP group. Further on, we had an observation regarding larger urine production during CPB in the HP group. Unfortunately we did not measure urine output in the study hence it remains observations. We will elaborate further on fluids in the next section.

![Development of creatinine](image)

**Figure 6: Development of creatinine levels in the LP- and HP group.**
The findings of our study are surprising in the sense that we expected to see a rise in creatinine postoperatively. Comparable to our study, Sirvinskas et al. (2012) conducted a study including 122 patients (70 years or older) with normal renal function. They randomized the patients into three different pressure groups, LP (45-59.9 mmHg), MP (60-69.9 mmHg) and HP (70-95 mmHg). Creatinine was measured preoperatively and on the first and second day postoperatively. A continuous rise in creatinine was seen in all three groups, with the largest measure at the second postoperative day. They also measured urine output, and found a larger urine output intraoperatively in the MP- and HP group, but no differences postoperatively. In consistency with Sirvinskas, Shaw et al. (2008) found, that rise in creatinine postoperative has a profile related to the type of cardiac surgery performed. When investigating the pattern for CABG procedures, there is an insignificant rise in creatinine after 24 hours with a peak after 72 hours. (Shaw 2008). The findings of our study are in contrast to Sirvinskas and Shaw. Generally, we did not see a rise in creatinine.

Furthermore, we discovered a drop in creatinine on the third postoperative day in the HP group, where Shaw found the largest increase. Lombardi (2008) investigated risk factors for acute kidney injury, these factors included: Low intraoperative haematocrit, CPB time and hypotension during surgery (low MAPP). We found no significant difference regarding CPB duration (p=0.28) but a significant difference in lowest haematocrit intraoperatively (p=0.02) and MAPP (p=0.000006). There is a significant difference in MAPP between the groups, considering hypotension during surgery as a risk factor. Without knowing Lombardi’s definition of hypotension during CPB it is difficult to conclude on this factor. Hypotension during CPB though, is not the same as hypotension without CPB. We maintain a cardiac index of 2.4, and thereby ensure the flow. If we do choose to look at the LP group as hypotensive, it might explain the drop from 24 to 72 hours seen in the HP group, but not in the LP group. Looking at lowest haematocrit during CPB, we have a significantly lower haematocrit in the LP group compared to the HP group. Haematocrit will be further discussed in the next section. This may render the LP group more vulnerable than the HP group and could indicate that maintaining a higher pressure during CPB would be associated with enhanced kidney protection.

Further investigations have to be performed in order to see if this is reproducible and explore the implications.
Looking at fluid balance we find a trend towards increased MAPP during CPB leading to less need for supplement of fluid (p=0.14). The fluid balance is exclusive urine output, and if the subjects in the HP group have a higher urine output during CPB (as previous mentioned), then we have to assume that the net balance is even smaller than for the subjects in LP. This would probably render fluid balance even more towards becoming statistical significant. As mentioned previously, Sirvinskas (2012) found an increased urine output during CPB in patients receiving a pressure above 60 mmHg on the day of surgery. These findings are in compliance with our observations. Of course, the need for fluid can also be related to the condition of the patient, including age, weight and comorbidity.

Regarding fluid, hemodilution and low haematocrit are risk factors in relation to kidney injury for patients undergoing CPB (Sirvinskas 2012). In general, all patients undergoing CPB are hemodiluted resulting in a decrease in haematocrit. At low haematocrit levels the kidneys become ischemic because of a lack of oxygen supply (Murphy 2009). Kidneys are autoregulated under normal physiological conditions. During CPB kidneys are more sensitive to pressure and flow. According to Sirvinskas et al. (2012), the kidneys are not autoregulated during CPB and this is supported by Plestis and Gold (2001). Further on they argue that it is not correct to assume that the threshold for autoregulation of the brain is the same as for the kidneys. The assumption is that the kidneys require a higher pressure to be able to autoregulate renal blood flow. This could indicate that the kidneys are more vulnerable to low haematocrit at low pressures.

Looking at the subjects in our study, we found no significant difference in baseline haematocrit with a p-value of 0.48, but a significant lower intraoperative haematocrit in the LP group (p=0.02). This, together with the higher degree of hemodilution and the decreased pressure, may increase the risk for kidney injury in the LP group. This might also explain the differences observed in the groups regarding creatinine development from 24 to 72 hours.

Low haematocrit and hemodilution also influence the brain. Low haematocrit can result in ischemia in the same way as in the kidneys. Considering a lower haematocrit in the LP group with no significant difference from the HP group regarding rSO₂, this may be explained by maintenance of cerebral autoregulation. For this to be true, the lower limit for cerebral autoregulation must be above 40 mmHg.
According to vasoactive drugs, the HP group received significantly higher mean doses of Metaoxidrine (p-value 0.07) and norepinephrine (p-value 0.047), as expected. Sevoflurane was also used, but only as maintenance of general anaesthesia (not used as a vasodilator to decrease pressure).

If we look at the LP group, four subjects received from 0.35-0.5 mg Metaoxidrine and no norepinephrine. Subject no. 8 in the LP-group received 0.95 mg Metaoxidrine and 0.2 mg norepinephrine and developed cerebral complications postoperatively requiring treatment at a neurological department. Vasoactive drugs as Metaoxidrine and norepinephrine increase systemic vascular resistance resulting in an increased MAPP and a reduced CBF (Brassard 2013). If the neurological complications are related to the use of vasoactive drugs, then we would expect to see a higher rate of neurological complications in the HP group. In contrast, there are no reportings of neurological complications in the HP group despite increased use of vasoactive drugs. Brassard et al. (2013) made a study looking at the relation between the use of norepinephrine and decline in cerebral oxygenation. They concluded that non-diabetic patients have no risk for reduced cerebral oxygenation during administration of norepinephrine undergoing CPB. From this we assume that it is safe to use vasoactive drugs to maintain a high MAPP during CPB in relation to development of neurological complications.

**ΔMAPP and rSO₂**

As mentioned earlier on, it could be interesting to consider MAPP in relation to habitual factors of the subjects. Ono et al. (2013) suggested the use of physiological endpoints rather than empirical MAPP management during CPB, and Kanji et al. (2010) looked at the relationship between mean arterial pressure (MAP) and mean arterial perfusion pressure (MAPP). In view of this, we evaluated our results the same way. We calculated a ΔMAPP as a measure of the difference between MAPP during CPB and the preoperative mean arterial pressure measured the day before surgery. We looked at the relation between ΔMAPP and rSO₂, showing a trend towards increased ΔMAPP resulting in decreased rSO₂ (figure 7). This point towards that ΔMAPP could be useful in determining an optimal perfusion pressure, maintaining rSO₂ in an acceptable range.
Further on, we evaluated the relation between ΔMAPP and S100Beta with the exclusion of subject 2 and 20. There is a weak tendency towards increased levels of S100Beta with an increased ΔMAPP. This is not true for two additional subjects (subject 6 and 8), who have high ΔMAPP and low S100Beta. If we omit these two subjects, we could argue, that subjects with a large difference from their normal mean arterial pressure and the pressure they receive undergoing CPB, is at larger risk of increased cerebral ischemia, knowing this conclusion is based on only 7 subjects (figure 8).
ΔMAPP and creatinine

Looking at creatinine and ΔMAPP, there is a tendency towards decrease in creatinine 24 hours in relation to an increase in ΔMAPP. For creatinine 72 hours there is a tendency towards increased levels of creatinine in relation to increased ΔMAPP (figure 9).

![Relation between ΔMAPP and creatinine](image)

**Figure 9: Creatinine 24 and 72 hours as a function of ΔMAPP with tendency lines.**

Based on this, it seems like that creatinine 24 hours benefits from high ΔMAPP, but creatinine 72 hours benefits from low ΔMAPP. With mean ΔMAPP in the LP group at 50.5 mmHg and in the HP group at 40.5 mmHg, it may be beneficial with a lower MAPP at 24 hours and a higher MAPP at 72 hours. This reconfirms that between creatinine 24 and 72 hours, there was a drop in the HP group, but a rise in the LP group.

It could be interesting to determine a cut-off point for ΔMAPP, to estimate an optimal MAPP interval for conducting CPB. Kanji et al. (2010) conclude that a ΔMAPP ≥ 26 mmHg is associated with a 2.8 times increased risk for development of acute kidney injury (AKI). This is estimated on a cohort of high risk patients for AKI, which makes it not directly comparable to our population. Further investigation has to be performed in order to confirm these findings and to determine the cut-off point for acceptable ΔMAPP.
To summarize, we identified some declines in rSO$_2$, but were not able to link it to desaturation and cerebral ischemia, nor were we able to see a clear connection between rSO$_2$ and MAPP.

According to S100Beta, we found no significant differences between the groups and relation to development of cerebral ischemia in our study. There was a trend towards elevated levels of S100Beta in the HP group and increased levels of S100Beta correlated with increased cross clamp duration. It might be difficult to isolate MAPP in order to evaluate the impact on S100Beta.

Looking at creatinine, we saw a decrease from baseline in both groups, with a continuous drop in the HP group. A higher pressure during CPB could be associated with enhanced kidney protection.

In the LP group, we found a significant lower intraoperative haematocrit and a higher degree of hemodilution. This may increase the risk for kidney injury in the LP group.

We found a trend towards increased ΔMAPP resulting in decreased rSO$_2$ and increased levels of S100Beta. This points towards ΔMAPP being useful in determining an optimal perfusion pressure for maintaining rSO$_2$ in an acceptable range and that subjects with a large difference from their normal mean arterial pressure and the pressure they receive undergoing CPB, is at larger risk of cerebral ischemia. Regarding ΔMAPP and creatinine, further investigations have to be performed.

**Limitations**

Our study has notable limitations. As mentioned earlier on, our study is small and prone to bias. We had an intension to include 20 patients, but we only achieved 11 (including 2 with postoperatively complications), resulting in a study based on tendencies, more than significant differences.

Available time was limited, we had a narrow time schedule and a determined deadline, not to be moved. Furthermore, the researchers of this study are perfusionist trainees. Regarding this, it would have been difficult starting this study earlier on, requiring experience related to practice. Further on, a perfusionist trainee is also needed in the department for practicing, learning procedures and is part of the perfusionist team according to daily schedule. Another limitation is that it takes time to implement a study in a department. The researcher has a deep understanding of the study and has conceived the hypothesis based on wonder or concern. This is not necessarily shared by the rest of the team. Even though we tried to inform co-workers in advance, both in writing and at meetings, implementing a study is still a process that requires time.
We conducted a search in the heart database in order to estimate the number of patients that met the inclusion criteria, before commencement of the study. From this it seemed realistic to include 20 subjects in the available time frame. But we had to realize that patient conditions are changing, requiring more complex surgery and with more comorbidity than just one year ago. Further on, it proved to be difficult to run two cases on the same day, because of logistics according to acute patients and the fact that planning in a surgical department changes constantly to optimize resources. For these reasons it was not possible to include the planned 20 subjects within the available time.

In evaluating cerebral status postoperatively in order to determine if the subjects had cerebral injuries, we were limited to the information in the medical record. From this it was difficult to discover diversities in the cerebral status, it was either injuries requiring treatment or the patients were described as relevant.

An important limitation of this study is, that our findings are difficult to compare to obtained research. Despite a thorough search in PubMed, Cinahl and The Cochrane Library, it has proven to be difficult to find literature to either substantiate or disprove our findings and the way the findings influence each other. Furthermore some of the literature is old, for a large part retrospective and has been focusing on high risk patients. This makes it difficult to compare to our study, where we prospectively are looking at low risk patients. An example of this is Kanji et al., looking at MAPP, but in a cohort of high risk patients. Other research literature has an indirect focus on perfusion pressure, where the findings regarding MAPP are revealed as a co-finding. Harilall et al. had an indirect conclusion on MAPP being one of the important factors for maintaining rSO₂ during CPB.

Being unexperienced researchers hold a risk for over- or underestimating the results, leading to elimination of important findings, when used literature is not directly comparable to the study.

The lack of comparable research literature also had the impact, that calculating power has proven to be difficult. We had to make assumptions on outcome without directly knowing what to expect. Investigated research, focused on high risk patients and found highly elevated levels of creatinine. Taking into account that we looked at low risk patients, makes it difficult to transfer to our study. Not knowing what the approximation of the expected result might be makes the power of the study uncertain.
Conclusion

We hypothesized that conducting CPB at perfusion pressures below 60 mmHg could lead to cerebral ischemia and impaired kidney function postoperatively.

Looking at methods for monitoring cerebral ischemia, we used NIRS and S100Beta. Regarding NIRS, we did find some declines in rSO$_2$, but we were not able to link it to cerebral ischemia, nor were we able to see a clear connection between rSO$_2$ and MAPP. Looking at the one patient developing cerebral injury, he had a tendency of a decrease in rSO$_2$ and MAPP throughout CPB, and periods of excessive central venous pressure. This might indicate a relation between MAPP and rSO$_2$. According to S100Beta, there was a tendency for increased levels in the HP group. This could indicate that there is an increased risk of cerebral injuries at perfusion pressures above 60 mmHg. The only subject with cerebral injury had a S100Beta value of 0.191µg/L, which is considered safe. This subject was in the LP group receiving a pressure below 60 mmHg and for this reason it is difficult to conclude on the findings from S100Beta and the value as a prognostic method in our cohort. When not being sure of the optimal sample time and cut-off point for development of cerebral ischemia in relation to patients undergoing cardiac surgery, the obtained results may not be valid for estimation of cerebral injury. Further on S100Beta is not only influenced by pressure. We also saw a trend towards elevated levels of S100Beta with prolonged cross clamp time, indicating that other factors than MAPP influence levels of S100Beta. In order to optimise the use of S100Beta in patients undergoing cardiac surgery, further investigations has to be performed regarding estimation of optimal sample time and cut-off point.

For monitoring renal function, we looked at creatinine. We found a significant difference in the creatinine at 24 hours. We saw a decrease from baseline in both groups, with a continuous drop in the HP group after 72 hours. This might indicate that a higher pressure during CPB could be associated with enhanced kidney protection. Interestingly we discovered a decrease in creatinine from baseline, where other studies have reported an increase, this calls for further investigations.

We found a significant lower intraoperative haematocrit and a higher degree of hemodilution in the LP group. This may increase the risk for renal ischemia in the LP group.
We also found a trend towards increased ΔMAPP resulting in decreased rSO\textsubscript{2} and increased levels of S100Beta. This points towards that subjects with a large difference from their normal mean arterial pressure and the pressure they receive undergoing CPB, is at larger risk of cerebral ischemia. Regarding ΔMAPP and creatinine, further investigations have to be performed.

Future studies with a larger population must be performed in order to make statements regarding optimal perfusion pressure during CPB in order to ensure a good patient outcome with reduced morbidity and mortality. From our study it seems like cerebral autoregulation is maintained at pressures above 40 mmHg. Maybe the results are pointing towards that low risk patients undergoing CPB is independent in relation to weather they receive high or low pressure. Future studies should be performed with focus on comparing low versus high risk patients.

We are not able to conclude that the conduct of CPB at perfusion pressures below 60 mmHg lead to cerebral ischemia and impaired kidney function.

**Perspectives**

Regarding our hypothesis, we chose to use S100Beta and NIRS to identify cerebral conditions related to MAPP. If only evaluating cerebral condition using S100Beta, we would not be able to identify intraoperative circumstances associated with observed postoperative S100Beta levels. In this sense, S100Beta is not useful as a stand-alone measurement method in an intraoperative setting. Furthermore it is expensive and time consuming to analyse. There are uncertainties regarding sample time and cut-off point for prediction of cerebral injury which is important to take into concern.

NIRS gives direct continuous measurements of the cerebral conditions, but no indication on postoperative cerebral injuries. It is useful as a stand-alone measurement method, but still expensive.
By using S100Beta and NIRS, we were not able to identify a correlation between MAPP and cerebral ischemia. We found a correlation between increased ΔMAPP with increased S100Beta and decreased rSO₂.

For future perspective, we suggest that studies focus on an attempt to find a cut-off value for ΔMAPP in order to identify the intrapersonal MAPP optimizing CPB conditions and hopefully reduce incidents of cerebral injury in patients undergoing cardiac surgery on cardiopulmonary bypass. We believe in S100Beta and NIRS being useful in estimating this ΔMAPP.
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Covidien: [www.covidien.com](http://www.covidien.com)

KBA, Rigshospitalet: [http://labvejl.rh.dk/Metodeliste.asp?Mode=Display&Id=3741](http://labvejl.rh.dk/Metodeliste.asp?Mode=Display&Id=3741)
Appendix

Appendix 1: Godkendelse fra De Videnskabelige Komitéer for Region Syddanmark

Appendix 2: Godkendelse fra Persondataloven

Appendix 3: Standardsamtykkeerklæring, udarbejdet af Det Videnskabsetiske Komitésystem

Appendix 4: Patientinformation

Appendix 5: Forsøgsprøves rettigheder i et sundhedsvæsenet forskningsprojekt, udarbejdet af Det Videnskabsetiske Komitésystem

Appendix 6: Vejledning til standard perfusion

Appendix 7: Anæstesiprotokol

Appendix 8: Information til kirurger
Appendix 1.1

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17. februar 2014
Projekt-ID: S-20130166
OMHvis

Forskningsprojekt: Har middelarterietryk i forbindelse med hjerte-lungemaskine behandling, betydning for cerebral og renal perfusion hos patienter, der får foretaget en bypass operation?

Endelig godkendelse.

Afgørelse

Godkendelsen gælder for de anmeldte forsøgssteder, de anmeldte forsøgsansvarlige i Danmark samt for den angivne forsøgsperiode. Komiteen antager, at den forsøgsansvarlige drager omsorg for at underrette de øvrige deltager i projektet om Komiteens afgørelse i sagen.

Godkendelse gælder til den 2. maj 2014 og følgende dokumenter er lagt til grund ved vurderingen:
- Underskrevet anmeldelse, dateret den 13. december 2013
- Protokol af 6. februar 2014, version 1.1
- Deltagerinformation med samtykkeerklæring af 6. februar 2014, version 1.1

Godkendelsen gælder for de anmeldte forsøgssteder og den anmeldte forsøgsansvarlige i Danmark.

Iværksættelse af projektet i strid med godkendelsen kan straffes med bøde eller fængsel, jf. komitélovens § 41.

Bemærkninger
Godkendelsen omfatter tilladelse til, at der kan videregives oplysninger fra patientjournalen til forsker i henhold til sundhedsloven § 46, stk. 1. Tilladelsen omfatter videregivelse af de oplysninger, der er oplistet i protokollen.

Region Syddanmark
Regionshuset, Dæhavensgade 12, 7100 Vejle
Tlf.: 7663 2220, 7663 2221, 7663 2222, 7663 132
www.regionsyddanmark.dk/komite
Appendix 1.2

Ændringer
Foretages der væsentlige ændringer i protokolmaterialet under gennemførelsen af projektet, skal disse anmeldes til komiteen i form af tillægsprotokoller. Ændringerne må først iværksættes efter godkendelse fra komiteen, jf. komitélovens § 27, stk. 1.

Anmeldelse af tillægsprotokoller skal ske elektronisk på www.drvk.dk med det allerede tildelte anmeldelsesnummer og adgangskode.

Væsentlige ændringer er bl.a. ændringer, der kan få betydning for forsøgspersonernes sikkerhed, fortolkning af den videnskabelige dokumentation, som projektet bygger på samt gennemførelsen eller ledelsen af projektet. Det kan fx være ændringer i in- og eksklusionskriterier, forsøgssdesign, antal forsøgspersoner, forsøgsprocedurer, behandlingsvarighed, effektparametre, ændringer om de forsøgsansvarlige eller forsøgssteder samt indholdsmæssige ændringer i det skriftlige informationsmateriale til forsøgspersonerne.

Hvor nye oplysninger betyder, at forskeren overvejer at ændre proceduren eller stoppe forsøget, skal komiteen orienteres om det.

Bivirkninger og hændelser
Løbende indberetning
Komiteen skal omgående underrettes, hvis der under projektet optræder formodet alvorlige, uventede bivirkninger eller alvorlige hændelser, jf. komitélovens § 30, stk. 1
Indberetningen skal ledsages af kommentarer om eventuelle konsekvenser for forsøget. Det er kun bivirkninger og hændelser forekommert i Danmark, der skal indberettes.
Underretning skal ske senest 7 dage efter, at sponsor eller den forsøgsansvarlige har fået kendskab til tilfældet.


Årlig indberetning
En gang årligt i hele forsøgsperioden skal komiteen have tilsendt en liste over alle formodet alvorlige (ventede og uventede) bivirkninger og alvorlige hændelser, som er indtruffet i forsøgsperioden sammen med en rapport om forsøgspersonernes sikkerhed, jf. komitélovens § 30, stk. 2.
Materialet skal være på dansk eller engelsk.


Afslutning
Den forsøgsansvarlige skal senest 90 dage efter afslutningen af projektet underrette komiteen herom, jf. komitélovens § 31, stk. 1. Projektet regnes som afsluttet, når sidste forsøgsperson er afsluttet.
Appendix 1.3

Afbrydes projektet tidligere end planlagt, skal en begrundelse herfor sendes til komiteen senest 15 dage efter, at beslutningen er truffet, jf. komitélovens § 31, stk. 2. Hvis projektet ikke påbegyndes, skal dette samt årsagen hertil meddeles komiteen. Komiteen beeder om kopi af den afsluttende forskningsrapport eller publikation, jf. komitélovens § 28, stk. 2. Vi skal i den forbindelse gøre opmærksom på, at der er pligt til at offentliggøre både negative, positive og inkonklusive forsøgsresultater, jf. komitélovens § 20, stk. 1, nr. 8.

Projekt-ID bedes anført ved fremsendelse af materiale til projektet. Henvendelser vedrørende projektet kan rettes til Komiteens sekretariat.

Tilsyn:
Komiteen færer tilsyn med, at projektet udføres i overensstemmelse med godkendelsen, jf. komitélovens § § 28 og 29

Følgende komitémedlemmer deltog i mødebehandlingen den 29. januar 2014:
- Jens Michael Hertz
- Henrik Steen Hansen
- Louise Winding
- Elsebeth Stenager
- Annette Wind Olesen
- Bente Gertz
- Mette Bossen Linnet
- Carsten Abild
- John Løhff


På Komiteens vegne, venlig hilsen

Birger Møller
Formand

/ 

Claus Kvist Hansen
Sekretariatsleder
Vedrørende anmeldelse af:
Lavt middelarterietryk er forbundet med cerebral iskæmi og nedsat nyrefunktion hos ældre patienter, der får foretaget en bypass ope-
ration

Ovennævnte projekt er den 30. december 2013 anmeldt til Datastyringsen via Region Syddanmarks parapy-
anmeldelse for sundhedsvidenskabelig forskning efter Persondatalovens § 43, stk. 1. Projekten medtages på
Region Syddanmark oversigt for parapyanmeldelsen 2008-08-0035 "Sundhedsvidenskabelig forskning i
Region Syddanmark.

Det fremgår af anmeldelsen, at du er projektansvarlig for projektets oplysninger. Behandlingen af oplysning-

Oplysningerne vil blive behandlet på følgende adresse: Odense Universitetshospital, Sdr. Boulevard 29,
5000 Odense C.

TILLADELS

Direktionssekretariatet på OUH Odense Universitetshospital meddelede hermed, på vegne af Region Syd-
danmark, tilladelse til projektets gennemførelse.

Region Syddanmark fastsætter i forbindelse med tilladelsen nedenstående vilkår:

Generelle vilkår

Tilladelsen gælder indtil: 30. maj 2014.

Ved tilladelsens udsted skal du særligt være opmærksom på følgende:
Hvis du ikke inden denne dato har fået tilkaldelse forlænget, går Region Syddanmark ud fra, at projektet er afsluttet, og at personoplysningerne er slettet, anonymiseret, tilintetgjort eller overtalt til arkiv, jf. nedenuæende vilkår vedrørende projektets afslutning.

Region Syddanmark gar samtidig omrørsom på, at al behandling (herunder også opbevaring) af personoplysninger efter tilladelsens udløb er en overtrædelse af persondataloven, jf. § 70.

1. **Line Larsen, Sygeplejerske, Hjerte-, lunge – og kærlighed Afdeling** er, som projektsælgelig på vegne af Region Syddanmark som dataansvarlig, ansvarlig for overholdelsen af de fastsatte vilkår.

2. Oplysningerne må kun anvendes til brug for projektets gennemførelse.


4. Enhver (herunder ansatte i Region Syddanmark), der foretager behandling af projektets oplysninger, skal være bekendt med de fastsatte vilkår.

5. De fastsatte vilkår skal tillige lagttes ved behandling, der foretages af databehandler.


7. Lokaler, der benyttes til opbevaring og behandling af projektets oplysninger, skal være indrettet med henblik på at forhindre uvedkommende adgang.


9. Oplysninger må ikke opbevares på en måde, der giver mulighed for at identificere de registrerede i et længere tidssrum end det, der er nødvendigt af hensyn til projektets gennemførelse.

10. En eventuel offentliggørelse af undersøgelsens resultater må ikke ske på en sådan måde, at det er muligt at identificere enkeltpersoner.

11. Eventuelle vilkår, der fastsættes efter anden lovgivning, forudsætter overholdt.
Appendix 2.3

Elektroniske oplysninger


13. Hvert halve år skal det kontrolleres, at projektlederne har de korrekte rettigheder.


15. Der skal foretages loggen af alle anmodninger af personoplysninger i forbindelse med projektet.
Loggen skal blive indholdt oplysninger om tidspunkt, bruger, type af anmodning og angivelse af den person, de anvendte oplysninger vedrører eller det anvendte sagekriterium.

16. Såfremt identifikationsoplysninger enter er krypterede, eller erstattet med et ID-nummer, skal loggen benytte logget oplysninger om bruger og tidspunktet for behandlingen (se, gemme, sæge, opdatere m.v.)

17. Loggen skal opbevares i 6 måneder, hvorefter den skal slettes. Ved særligt behov kan loggen opbevares i op til 5 år.


Manuelle oplysninger

22. Manuelt projektmateriale, udskriver, fæl- og kontrollister, m.v., der direkte eller indirekte kan henføres til bestemte personer, skal opbevares forsvarligt affæst og på en sådan måde, at uvedkommende ikke kan gøre sig bekendt med inholdet.

23. Manuelt projektmateriale skal slettes, når det ikke længere er relevant for projektet, dog senest ved projektets afslutning 30. maj 2014.

Oplysningspligt over for den registrerede

24. Hvis der skal indsamles oplysninger hos den registrerede (ved interview, spørgeskema, klinisk eller paraklinisk undersøgelse, behandling, observation m.v.) skal der uddeles/fremendes nærmere information om projektet. Den registrerede skal heri oplyses om den dataansvarliges navn, formålet med projektet, at det er frivilligt at deltage, og at et samtykke til deltage er enhver tid kan trekkes tilbage.

25. Den registrerede skal endvidere oplyses om, at projektet er anmeldt til Datatilsynet via Region Syd-Danmark efter Persondatalovens bestemmelser, samt at der for projektet er fastsat nærmere vilkår til beskyttelse af den registreredes privatliv.

Indsigtsret


Viderogivelse

27. Viderogivelse af personhenførbare oplysninger til tredjepart må kun ske til brug i andet statistisk eller videnskabeligt øjemed, der ikke er uforeneligt med det formål, hvortil dataene oprindeligt er indsamlet.


Ændringer i projektet

29. Væsentlige ændringer i projektet skal anmeldes/meldes til Direktionssekretariatet (som ændring af eksisterende anmeldelse).
Appendix 2.5

Ved projektets afslutning

30. Ændring af tidspunktet for projektets afslutning skal altid anmeldes/meddeles Direktionssekretariatet.

31. Senest ved projektets afslutning (medmindre særlige forhold gør sig gældende for projektet, som skal oplyses til Direktionssekretariatet) skal oplysningerne slettes, anonymiseres eller tilsigtes, således at det efterfølgende ikke er muligt at identificere enkeltpersoner, der indgår i undersøgelsen.

32. Alternativt kan oplysningerne overføres til videre opbevaring i Statens Arkiver (herunder Dansk Datatjek) efter arvelovens regler.

33. Overlæggelse af oplysninger fra elektroniske medier skal ske på en sådan måde, at oplysningerne ikke kan genetableres. Der bør i denne forbindelse tages kontakt til din lokale IT-afdeling (CoIT), jf. instrukser for brug af it Region Syddanmark (OUH har egen lokal instrukser, som skal følges)

Ovenstående vilkår er gældende indtil videre. Region Syddanmark forbeholder sig senere at tage vilkårene op til revision, hvis der skulle vise sig behov for det.

Region Syddanmark gør opmærksom på, at denne tiladelse alone er en tiladelse til at behandle personoplysninger i forbindelse med projektets gennemførelse. Tiladelsen indebærer således ikke en forpligtelse for myndigheder, virksomheder m.v. til at udeløvere eventuelle oplysninger til dig til brug for projektet.


Persondatafonden kan læses/hentes på Datatilsynets hjemmeside under punktet "Lovgivning".

Advarsel – ved brug af Excel, PowerPoint m.v.

Den dataansvarlige skal til enhver tid sikre sig, at dokumenter og andre præsentationer, som publiceres eller på anden måde gøres tilgængelige for andre på internettet, usædvanligvis eller på andet elektronisk medium, ikke indeholder personoplysninger.

Der skal vedes særlig øgpetgivningen i forbindelse med brug af grafiske præsentationer i Excel og PowerPoint, da de uforvarende kan indeholde indenfor persondata i form af regneark, tabeller m.v. Præsentation, der gøres tilgængelig på internettet, skal derfor omformateres til Portable Digital Format (PDF), da dette fjerner eventuelle indenfor Excel-tabeller.

OUH
Odense
Universitetshospital
Svendborg Sygehus
30. december 2013
Sagnr. 1043247
Side 53
Appendix 2.6
Appendix 3.1

DET VIDENSKABSETISKE KOMITÉSYSTEM

(S1)

Informert samtykke til deltagelse i et sundhedsvidenskabeligt forskningsprojekt.

Forskningsprojektets titel:
Hør-middelarterietryk i forbindelse med hjerte-lungemaskine behandling, betydning for cerebral og renal perfusion hos patienter, der får foretak en bypass operation?

Erklæring fra forsøgspersonaen:
Jeg har fået skriftlig og mundtlig information og jeg ved nok om formlæ, metode, fordøj og ulemper til at sige ja til at deltage.
Jeg ved, at det er friuligt at deltage, og at jeg almindelig kan trekke mit samtykke tilbage uden at miste mine nuærende eller fremtidige rettigheder til behandling.
Jeg giver samtykke til, at deltage i forskningsprojektet, og har fået en kopi af dette samtykkeark samt en kopi af den skriftlige information om projektet til eget brug.

Forsøgspersonaens navn: ____________________________________________

Data: ___________ Underskrift: ______________________________________

Ønsker du at blive informeret om forskningsprojektets resultat samt eventuelle konsekvenser for dig?:
Ja _____ (sæt x) Nej _____ (sæt x)

Erklæring fra den, der afgiver information:
Jeg erklærer, at forsøgspersonaen har modtaget mundtlig og skriftlig information om forsøg.
Efter min overbevisning er der givet tilstrækkelig information til, at der kan træffes beslutning om deltagelse i forsøg.
Navnet på den, der har afgivet information: Carina Dyhr Jørgensen

Data: ___________ Underskrift: ______________________________________

Projektidentifikation: ( fx komiteens Projekt-ID, EudraCT nr., versions nr./dato eller lign.)
Projekt-ID: S-20130166, februar 2014

__________________________
Appendix 4.1

Skriftlig deltagerinformation

Version 1.1, 6. Februar 2014

Har middelarterietryk i forbindelse med hjerte-lungemaskine behandling, betydning for cerebral og renal perfusion hos patienter, der får foretaget en bypass operation?

I forbindelse med din indlæggelse til en bypass operation, vil vi spørge dig om du vil deltage i en undersogelse.


Vi vil gerne undersøge, om et lidt højere blodtryk under en bypass operation kan gøre, at dine nyrer og din hjerne bliver illet bedre.

For at måle, at tiltningen i hjernen er tilstrækkelig, vil vi måle på din pande før og under operationen, ved hjælp af en infrarød måler. Vi vil også tage en blodproeve efter 5 timer, som kan sige noget om hjemmens tilnærmelse under operationen. Den udtages gennem et kædet, du i forvejen har i hånden, så du skal ikke have et ekstra stik.

Endvidere vil vi gerne kontrollere nyrernes funktion ved hjælp af en blodproeve. Undersøgelsen indebærer, at der skal tages 3 blodprover, 1 før og 2 efter operationen. Disse blodprover er prøver, man i forvejen får taget i forbindelse med en bypass operation.

Under forsøget vil vi ikke indhente flere personlige data, end vi normalt gør ved en bypass operation.


Det forventes ikke, at der vil være større risiko og gener ved deltage i denne undersøgelse, end der normalt er ved en bypass operation. Hvis der mod forventning opstår komplikationer i forbindelse med forsøget, vil forsøget blive afbrudt.

Denne undersøgelse er afsluttet, inden du udskrives fra afdelingen.
Appendix 4.2

Skriftlig deltagerinformation
Version 1.1, 6. Februar 2014

Deltagelse i undersøgelsen er frivillig. Et tilsagn om at deltage kan til enhver tid trækkes tilbage, og du kan til enhver tidspunkt træde ud af undersøgelsen, uden det vil påvirke den nuværende eller fremtidige behandling af dig. Såfremt du ikke ønsker at deltage, vil du blive behandlet i overensstemmelse med afdelingens sædvanlige standardbehandling.

Hjerte-lunge maskinen betjenes af en perfusionist. En perfusionist er en læge, sygeplejerske, ingeniør eller biomaltekniker, som har taget en 2-årig specialuddannelse i at betjene en hjerte-lunge maskine.

Spørgsmål til ovenstående kan rettes til perfusionistaspirant Carina Dyhr Jørgensen (40754185) eller perfusionistaspirant Line Larsen (26627019)

Vi anbefaler dig at læse vedlagte information fra Videnskabsetisk Komité "Forsøgspersoners rettigheder i et sundhedsvidenskabeligt forskningsprojekt".

Med venlig hilsen

Carina Dyhr Jørgensen og Line Larsen
Appendix 5.1

DET VIDENSKABSETISKE KOMITÉSYSTEM

Forsøgspersoners rettigheder i et sundhedsvidenskabeligt forskningsprojekt.

Som deltager i et sundhedsvidenskabeligt forskningsprojekt skal du vide at:

- Din deltage i forskningsprojektet er helt frivillig og kun kan ske efter, at du har fået både skriftlig og mundtlig information om forskningsprojektet og underskrevet samtykkeerklæringen.

- Du er tilmærket til at modtage skriftlig, mundtlig og skriftlig information om forsøgets fælles regler og forpligtelser, samt om eventuelle risici og fordele forbundet med forsøgspersoners aktive deltagelse.

- Du har ret til at tage del i det aktuelle undersøgelsesprojekt, som er fastlagt i det aktuelle forskningsprojekt.

- Du har ret til at opleve forskellige rettigheder, som er fastlagt i det aktuelle forskningsprojekt.

- Du har ret til at få information om, hvordan der opleves forskellige rettigheder, som er fastlagt i det aktuelle forskningsprojekt.

- Du har ret til at få information om, hvordan der opleves forskellige rettigheder, som er fastlagt i det aktuelle forskningsprojekt.

- Du har ret til at få information om, hvordan der opleves forskellige rettigheder, som er fastlagt i det aktuelle forskningsprojekt.

- Der er mulighed for at få adgang til et eller flere oplysninger vedrørende din deltage i forsøget, bortset fra de dele, som indeholder forretningshemmeligheder eller fortrolige oplysninger om andre.

- Der er mulighed for at klage og få erstatning efter reglerne i lov om klage- og erstatningsadgang inden for sundhedsvæsenet.

Dette tilæg er udarbejdet af den videnskabsætiske komitésystem og kan vedhæftes den skriftlige information om det sundhedsvidenskabelige forskningsprojekt. Spørgsmål til et projekt skal rettes til den regionale komité, som har godkendt projektet.

April 2012
Appendix 6.1

Pressure on Perfusion
Line Larsen and Carina Dyhr Jørgensen

OUH-THOR - Vejledning til standard perfusion, ver. 1

1) Formål
   1.1) Anvendelsesområde
   2) Fremgangsmåde
      2.1) Baggrund
      2.2) Definitioner
      2.3) Fremgangsmåde
   3) Dokumentation
      3.1) Dokumentation af aktivitet
      3.2) Udarbejdet af
   4) Referencer og litteratur
   5) Evidensbasering

1) Formål
   At beskrive en praktisk vejledning for standard perfusion, således at alle perfusionerne foregår på den mest optimale og sikre måde.

1.1) Anvendelsesområde
   Perfusionsområde, T-perfusion

2) Fremgangsmåde
   2.1) Baggrund
   2.2) Definitioner
   ECC: Ekstrakorporal circulation
   HLM: hjerte/lunge maskine
   ACT: Activated clotting time
   HCU: Hætter cooler unit

2.3) Fremgangsmåde
   Apparat
   Stækket S5 HLM- med følgende komponenter
   - 2 store rullepumpere: 1) Arteriepump " ½ " slange
     2) Maksinsug " ¼ " slange
   - 1 dobbelturpumper: 1) Aortavent " ¼ " slange
     2) Venstreventrkel/mitraalsug " ¼ " slange
   - 1 dobbelturpumper: Kardioplegipump: Master/Slave pump " ¼ " slange
   - Kontrol panel med sikkerhedsmonitorering af:
     a) Lowlevel sensor: med alarm og stop funktion
     b) Bubble sensor: med alarm og stop funktion
     c) Trykmonitorering: før/efter membranen med alarm og stop funktion.
     d) Trykmonitorering Kardioplegi med alarm og stop funktion.

mhtml:file:///C:\Documents and Settings\PFG17\Skrivebord\Appendix 1 - Vejledning... 09-12-2013
Appendix 6.2

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OUH-THOR - Vejdøning til standard perfusion, ver. 1
Side 2 af 6

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e) Elektronisk Veneklemme

f) Elektronisk gasmixer

**Andre komponenter som er tilkoblede på HLM**

- Gas fordamerper
- Gas udsug
- Skærm: visning af Ekg, tryk, puls, temp, CVP, PA
- CDI 500 monitor
- ACT-apparat
- HCU-apparat

**Medikamenter/vaske**

- Ringer-laktat
- Heparin 5000 ič/ml
- Metoxedrin 1 mg/ml
- Antibiotika- efter ordination

**Standard opsæt af hjertelungemaskine:**

- Hårdskal cardiotorinreservoar m. 30 micron filter.
- Hollowfiber oxygenetor.
- PVC slangesæt med silikone pumpslanger.
- Arteriefilter 40 micron.
- Prebypass filter 0,2 micron.
- CDI 500 shuntsensor.
- CDI 500 verucuvette.
- Gasfilter.
- 3 tryktransducers.
- Kardioplegi sæt: PVC slangesæt med silikone pumpslanger til blokkardioplegi med 0.2 micron krystalfilter.
Appendix 6.3

**Forberedelse til ECC.**

**CO2-flushing:** Slangesystem, oxygenator og arteriefilter flushes med Kuldioxid.

**Primervæske:** 2000 ml Ringer-Laktat tilsættes 5000 IE heparin.

**Kardioplegivæske:** Blanding til kold kardioplegi.

**Metaoxidrin:** 1 mg/ml: 1 ml metaoxidrin blandes i 9ml isotonisk NaCl

**Antibiotika:** Blandede efter ordination og efter afd. retningssilinier.

**CDI 500 Shuntsensor:** Kalibreres som beskrevet i produktvejledning og indsættes i A/V sammeline.

**CDI 500 venecuvette:** Kalibreres og påsættes cuvetten der er integreret i veneslangen.

---

**Tilslutning på stuen:**

- El
- It / Atmosfærisk luft
- Udsug (anaestesiogas).
- Heater – cooler sættes til 38 C°
- EKG - monitor.
- A / V line, Kardioplegi og sugeslanger

**Priming:**

Heater cooler starts på 38 C° på oxygenator og kardioplegi systemet, der kontroleres for lækage. Systemet primes som beskrevet i produktvejledning se i afsnittet for priming på (bilag1).

Kardioplegi system primes efter afdelingsinstruks. Sikkerhedsudstyr tilsluttes og kontroleres efter brugermanual for S5 maskine.

Der cirkuleres over prebypass filter ≥ 10 min og heater cooler sættes til hhv. 36 og 5 C°.

Efter endt priming sættes tang på arterielangae efter AV bypess og veneslangen. Veneklemme lukkes.

Checklisten kontroleres.
Der recirkuleres over oxygenatoren, indtil perfusionen starter.

**Heparinisering:**

Der gives Heparin 3mg/kg. - ACT måles efter 3 min.


Ved ACT > 480 kan perfusionen startes

**Kanyakering:**

Kanyakering i aorta med 24 Fr aortokænyle.

Kanyakering i hæ. atrium med Twostage 36/48 Fr eller efter aftale med kirurg. Kenylering i aortarod med 9 Fr kardioplegikænyle med ventport

**Nedenstående værdier tilstræbes under perfusion.**

**Biodflow:**

Ved normothermi: min. 2,4 l / m² BSA / min.

**Venerezervior volumen:**

min. 400 ml.

**Central Temperatur:**

Normothermi / let hypothermi 35° C.

eller efter aftale med kirurg.

**MAP:**

40 - 60 mmHg

Ved ; MAP, gives metaxedrin 0,1mg / ml

efter behov, og efter aftale med Anæstesien.

**Trykfordel (A.)**

Oxygenator /arteriefilter 100-150 mmHg.

Arteriefilter / patient < 100 mmHg.

**ACT:**

> 480 sec.

**Syre / Base:**

pH : 7,36 - 7,42

pO2 : 13,3 -20 kPa.

pCO2 : 5,0 - 5,7 kPa.

Svo2: > 70 %

Hct: > 0,20

**Perfusion:**

Perfusionen startes: pumpfløyet øges langsomt til det beregnede flow, samtidig åbnes venekæmmen
Appendix 6.5

OUH-THOR - Vejledning til standard perfusion, ver. 1

Side 5 af 6

langsamt til fuldåben. ITTflow øges, og FIO2 indstilles således at de ønskede gaskal oprås.

Når perfusionen kører stabilt kan aorta afklemmes og der gives kardioplegi efter afdelinginstruks.
Antibiotika gives efter ordination.

Efter ca. 10 min. perfusion, tages arterie og venes gasprøve og ACT kontrolleres.

CDI kalibreres efter ABL sver.

(se bilag 2)

**Kontinuerligt observeres:**

- Arterietryk.
- Venearføl.
- Oxygenator- og arteriefiltertryk.
- Temperaturen.
- EKG.
- CDI
- ACT kontrolleres ca. hver 30. min.

**Kardioplegi** suppleres ca. hver 20 min. efter afdelinginstruks eller efter aftale med kirurgen.

Ca. 10 min. før aortatangen fjernes, øges vandtemperaturen til 37,5°C og der værmes aktivt.

Når pt. er >36°C centralt, og alle værdier er tilfredsstillende, kan aftrappingen af ECC begyndes efter aftale med kirurg.

**ECC aftrapping:**

Arterie shunter lukkes.


Pumpeflow og gasflow reduceres, og perfusionen aftrappes langsamt efter aftale med anæstesiænke og kirurg. Veneklemmen lukkes og arterieslangen afklemmes, og der recirkuleres over oxygenator.


**Oprydning:**

Der laves væskeregnskab og anæstesiæn informeres. Perfusionsjournalen afdyreres og kopieres. Al
Appendix 6.6

engangsmateriale kasseres i gul spand.

Maskiren køres ud og afvaskes.

Maskiren sættes op og klargøres med mindre andet er aftalt med vagthavende perfusionist.

3) Dokumentation
3.1) Dokumentation af aktivitet
Aktiviteten registreres i Perfusionsjournalen.

3.3) Udarbejdet af
Perfusionist Mohamed ali Nuur og Anne Dorte Gilsaa

4) Referencer og litteratur
Stöckert S5 brugervejledning
Dideo, Compactflo brugervejledning
Kardiopleginstruks

5) Evidensbasering
Nej

Bilag:
1, Bilag 1 standard perfusion
2, Bilag 2 Standard perfusion
Appendix 7.1

Anæstesiprotokol

Vedrørende masterprojekt 3°P
Carina Dyhr Jørgensen og Line Larsen

Har middelarterietryk i forbindelse med hjerte-lungemaskine behandling, betydning for cerebral og renal perfusion hos patienter, der får foretaget en bypass operation?

Der inkluderes 20 forsøgspersoner i projektet, der løber fra 27/2-4/4 2014. De randomiseres til enten en LP (Low Pressure) eller en HP (High Pressure) gruppe. I cosine oplyses det, hvilken gruppe patienten er randomiseret til, hvilket også oplyses under time-curten.

Det er vigtigt, at der ved det pre-anestesiologiske tilsyn til projektpatienter tilbydes epiduralkateter, (er ekklusionskriterium). Inden tilsynet vil vi foresage at synliggøre, hvilke patienter der indgår i forsøget.

Line lever hjerte-lunge maskine og Carina laver datasamling, og er til rådighed for spørgsmål.

Monitoren og anæstesi skal køre efter vanlig instruk.
Under ECC (Ekstra Corporal Cirkulation) skal nedanstående trykgrænser holdes:

<table>
<thead>
<tr>
<th>LP-gruppe:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Perfusionstryk (MAP) 40-60 mmHg</td>
</tr>
<tr>
<td>• Noradrenaline er muligt op til brug ved behov</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HP-gruppe:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Perfusionstryk (MAP) 60-80 mmHg</td>
</tr>
<tr>
<td>• Noradrenaline opstilles efter normal protokol og øges til trykket ligger i referenceintervallet</td>
</tr>
</tbody>
</table>

Sevofluran øges, når perfusionstrykket overstiger trykgrænserne i trykgrupperne og ved manglende anæstesidrøbe.

Noradrenaline og Metoxidrin administreres, når perfusionstrykket faldet under trykgrænse i trykgrupperne.

NIRS-patchs placeres af Carina før anæstesiindledning, hvor der laves baseline. NIRS er blindet under forsøget og kan ses af Carina.

Det beregnede perfusionsflow holdes konstant under ECC og afviges kun, når aortastang/sidetang påsættes og aftages, samt ved afvikling af ECC.

Vi håber på et godt samarbejde :)

Med venlig hilsen Line og Carina, T-Perfusion

Vejledere: Claus Andersen og Poul Erik Mortensen
Appendix 7.2

**Anæstesiprotokol**

Vedrørende masterprojekt 3*P

Carina Dyhr Jørgensen og Line Larsen

**Tillægsprotokol for eksclusion af forsøgspersoner under projektet 3*P**

**NIRS:**
Hvis baseline er under 50 %, ekskluderes patienten.
Hvis saturationen på NIRS falder til under 40 % under ECC, ekskluderes patienten.

**SvO₂:**
Hvis SvO₂ falder til under 65 %, oges perfusionsflowet til SvO₂ igen er over 65 %.
Hvis SvO₂ efter 10 minutter med øget flow ikke er steget til over 65 % igen, ekskluderes patienten.

**Noradrenaline:**
Hvis patienten har behov for mere Noradrenaline end 0,3 mikrogram/kg/min konfereres med anæstesiologen og hvis det vurderes uforsvarligt at forståe med denne dosis, ekskluderes patienten.

**Sevoflurant:**
Hvis patienten har behov for mere end 4 % Sevofluran, konfereres med anæstesiologen og hvis det vurderes uforsvarligt at forståe med denne dosis, ekskluderes patienten. Der skal ikke forsøges med andre trykreducerende medikamenter.

**Patientens tilstand:**
Hvis det under operationen vurderes at forsøget skader patienten, ekskluderes patienten.
Appendix 8.1

Information til kirurger

Vedrørende masterprojekt 3ºP
Carina Dyhr Jørgensen og Line Larsen

Har middelarteritryk i forbindelse med hjerte-lungemaskine behandling, betydning for cerebral og renal perfusion hos patienter, der får foretaget en bypass operation?

Der inkluderes 20 forsøgspersoner i projektet, der løber fra 27/2-4/4 2014. De randomiseres til enten en LP (Low Pressure) eller en HP (High Pressure) gruppe. I cosmic oplyses det, hvilken gruppe patienten er randomiseret til, hvilket også oplyses under time-outen.

Ved det pre-anæstesiologiske tilsyn, tilbydes projektpatienter ikke epiduralkateter, (er ekklusionskriterium). Inden tilsynet vil vi forsøge at synliggøre, hvilke patienter der indgår i forsøget.

Line kører hjerte-lunge maskine og Carina laver dataopsamling, og er til rådighed for spørgsmål.

Monitorering og anæstesi kører efter vanlig instruk.

Under ECC (Exstra Corporal Circulation) skal nedenstående trykgrænser holdes:

<table>
<thead>
<tr>
<th>LP-gruppe:</th>
<th>HP-gruppe:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfusionstryk (MAP) 40-60 mmHg</td>
<td>Perfusionstryk (MAP) 60-80 mmHg</td>
</tr>
<tr>
<td>Noradrenalin er trukket op klar til brug ved behov</td>
<td>Noradrenalin opstares efter normal protokol og øges til trykket ligger i referenceintervallet</td>
</tr>
</tbody>
</table>

Sevofluran oges, når perfusionstrykket overstiger trykgrænser i trykgrupperne og ved manglende anæstesi dybe.

Noradrenalin og Metacoxidin adminstereres, når perfusionstrykket falder under trykgrænsen i trykgrupperne.

NIRS-patches påsættes af Carina for anæstesiindledning, hvor der laves baseline. NIRS er blindet under forsøget og kan kun ses af Carina.

Det beregnede perfusionsflow holdes konstant under ECC og afviges kun, når aortatang/sidetang påsættes og aftages, samt ved afvikling af ECC.

Vi håber på et godt samarbejde :-) 

Med venlig hilsen Line og Carina, T-Perfusion

Vejledere: Claus Andersen og Poul Erik Mortensen
Appendix 8.2

Information til kirurger

Tillægsprotokol for eksklusion af forsøgspersoner under projektet 3*P

NIRS:
Hvis baseline er under 50 %, ekskluderes patienten.
Hvis saturationen på NIRS falder til under 40 % under ECC, ekskluderes patienten.

$SvO_2$:
Hvis $SvO_2$ falder til under 65 %, oges perfusionsflowet til $SvO_2$ igen er over 65 %.
Hvis $SvO_2$ efter 10 minutter med øget flow ikke er steget til over 65 % igen, ekskluderes patienten.

Noradrenalin:
Hvis patienten har behov for mere Noradrenalin end 0,3 mikrogram/kg/min konfereres med
kirurgen/anæstesiologen og hvis det vurderes uforværligt at fortsætte med denne dosis, ekskluderes
patienten.

Sevofluran:
Hvis patienten havde behov for mere end 4 % Sevofluran, konfereres med kirurgen/anæstesiologen og hvis
det vurderes uforværligt at fortsætte med denne dosis, ekskluderes patienten. Der skal ikke forsøges med
andre trykreducerende medicin.

Patientens tilstand:
Hvis det under operationen vurderes at forsøget skader patienten, ekskluderes patienten.