Trial Description

Title

Perioperative changes of microbiome and metabolism in cardiac surgery patients

Trial Acronym

MetaHeart

URL of the trial

[---]*

Brief Summary in Lay Language

The aim of this project is to prospectively evaluate perioperative changes in the microbiome of different sampling locations in cardiac surgical patients following surgery with use of cardio-pulmonary bypass. In addition, the metabolome, the transcriptome and inflammatory markers are assessed. The combined investigation of microbiome, metabolome and transcriptome is supposed to helt to identify different clinical-metabolic phenotypes with their respective perioperative prognosis.

Brief Summary in Scientific Language

Patients undergoing surgery with the use of cardio-pulmonary bypass often develop a severe systemic inflammatory response due to ischemia / reperfusion injury with the release of pro-inflammatory cytokines and metabolites, e.g. reactive oxygen species (ROS). This inflammatory response can lead to organ dysfunction and failure and is associated with a worse postoperative outcome. In addition to the supportive therapy of vital organ systems (cardiovascular system, lungs, kidneys, liver), early enteral and parenteral nutrition therapy is also used to positively influence the outcome. Postoperatively, however, refractory insulin resistance, pronounced catabolic metabolism, and impaired immune system function due to pre-existing macro- and micronutrient deficiencies aggravate organ dysfunction. Large inter- and intra-individual differences in the endogenous substrate mobilization or the utilization capacity of exogenously supplied nutrient substrates over the course of the critical illness additionally lead to difficulties in the nutritional therapy of these patients. In addition, a supply of macronutrients exceeding the utilization capacities of the metabolism may possibly lead to a suppression of autophagy processes. Autophagy is a cellular-level essential repair mechanism that is responsible for the disposal of cell detritus and pathogenic microorganisms. To date, specific markers in the clinical routine to detect these intra- and inter-individual metabolic changes and the resulting metabolic tolerance of the patient are lacking. In addition to the use of indirect calorimetry to determine energy expenditure, the assessment of the metabolic status is limited to the measurement of glucose and lactate levels, triglycerides and urea values in serum. The targeted analysis of so-called "metabolomics" is a promising method to better map metabolites as markers of individual metabolic changes depending on the postoperative course of the disease or the resulting effect of nutritional therapy. To study metabolites of metabolic pathways and processes could lead to a comprehensive analysis from gene expression to the "clinical-

metabolic phenotype" of patients. Initial studies on targeted metabolome analysis in healthy volunteers and intensive care patients have shown that critical illness leads to a massive disruption of normal metabolic pathways, with certain metabolites overexpressed and correlated with specific patient characteristics. Previous research has shown that clinically identical phenotypes react differently with suppression in lipid or protein metabolism. Gastrointestinal dysfunction, which may be either the cause or the consequence of the inflammatory response, is closely linked to the success of patients' enteral nutrition or utilization capacity. In particular, we focus on the intestinal microbiome, i.e. the complex host-specific composition of the microflora in the gastro-intestinal tract. In cardiac surgery patients with an acute systemic inflammatory response and often necessary antibiotic therapy, a significant impact on the microbiome is likely. However, to what extent the individually different number and diversity of the microbiome influences the severity of systemic inflammation and contributes to the course of the disease has not been studied so far in cardiac surgery patients. Likewise, there are no clinically prospective data on the possible influence of artificial nutritional therapy on the microbiome.

Organizational Data

- DRKS-ID: **DRKS00016493**
- Date of Registration in DRKS: **2019/03/15**
- Date of Registration in Partner Registry or other Primary Registry: **[---]***
- Investigator Sponsored/Initiated Trial (IST/IIT): **yes**
- Ethics Approval/Approval of the Ethics Committee: **Approved**
- (leading) Ethics Committee Nr.: **D 401/19 , Ethikkommission der Christian-Albrechts-Universität zu Kiel**

Secondary IDs

Health condition or Problem studied

- ICD10: **I25.1 - Atherosclerotic heart disease**
- ICD10: **R65.2 - Systemic Inflammatory Response Syndrome of non-infectious origin without organ failure**
- ICD10: **F05.8 - Other delirium**
- ICD10: **T81.1 - Shock during or resulting from a procedure, not elsewhere classified**
- ICD10: **R57.2 - Septic shock**
- ICD10: **J95.1 - Acute pulmonary insufficiency following thoracic surgery**
- ICD10: **K56.7 - Ileus, unspecified**
- ICD10: **R65.1 - Systemic Inflammatory Response Syndrome of infectious origin with organ failure**

Interventions/Observational Groups

- Arm 1: **The study visits take place at fixed times (visit I - V) until discharge from hospital or death, if this event occurs before discharge. The visits take place at the following times: visit I on the day before surgery, visit II after induction of anesthesia, visit III after admission to the intensive care unit, visit IV at discharge from the intensive care unit, visit V at hospital discharge. On day 28 after enrollment, length of hospital stay and survival status should be recorded. Study visit VI will be a follow-up visit to determine survival status and whereabouts of study participants will be performed on day 90 after hospital discharge with sampling of a stool and urine sample for microbiome analysis. Overall, seven observation and / or sampling times thus result from the preoperative day up to day 90 after hospital discharge.**
After screening and obtaining informed consent from the participant study visit I will record the history of the patient along with the documentation of the patient's medical history using established nutrition questionnaires, the Frailty Score, the NRS score and SGA Scores and obtaining a stool sample. During study visit II immediately after induction of anesthesia and prior to administration of routine antibiotic prophylaxis, microbiome sampling is performed from the nasopharynx, the perianal region, and from an urine sample previously catheterized for surgery by default, as well as blood collection for metabolome and inflammation analysis. During study visits III, IV and V (after admission and before discharge from the intensive care unit as well as before hospital discharge) documentation of medical history, microbiome and blood sampling is performed. In addition, the questionnaires are again collected at the time of hospital discharge and on day 90 after the hospital discharge. Documentation from the patient record is based on demographic variables and patient characteristics as well as the course of treatment and vital signs on the day of the operation and postoperatively during treatment in the intensive care unit.

Characteristics

- Study Type: **Non-interventional**
- Study Type Non-Interventional: **Other**
- Allocation: **Other**
- Blinding: **[---]***
- Who is blinded: **[---]***
- Control: **Other**
- Purpose: **Diagnostic**
- Assignment: **Other**
- Phase: **N/A**
- Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels): **N/A**

Primary Outcome

The primary endpoint of the microbiome analysis is the quantitative change in the

diversity of the four dominant bacterial phyla Firmicutes, Bacteroidetes, Proteobacteria and Actinobacteria between baseline and the other investigation times. An exploratory analysis will identify microorganisms that may be drivers, protectors or biomarkers of metabolic disorders associated with poor postoperative outcome or altered metabolic processes.

Secondary Outcome

Secondary endpoints include the determination of typical metabolic metabolites from patients' blood samples using mass spectrometry-based technologies and the correlation of metabolite concentration changes with clinical outcome parameters.

Countries of recruitment

- DE **Germany**

Locations of Recruitment

- University Medical Center **Universitätsklinikum Schleswig-Holstein, UKSH, Campus Kiel, Kiel**

Recruitment

- Planned/Actual: **Planned**
- (Anticipated or Actual) Date of First Enrollment: **2019/04/01**
- Target Sample Size: **100**
- Monocenter/Multicenter trial: **Monocenter trial**
- National/International: **National**

Inclusion Criteria

- Gender: **Both, male and female**
- Minimum Age: **18 Years**
- Maximum Age: **no maximum age**

Additional Inclusion Criteria

Scheduled surgery using the use of cardio-pulmonary Bypass; male and female patients (age> 18 years); written informed consent of the patient.

Exclusion criteria

Patients receiving antibiotic therapy; anal Stenosis; Perianal Bleeding or infections; Emergency indication for surgery; Endocarditis; Immunosuppression or

therapy with glucocorticoids above the Cushing threshold (> 7.5 mg prednisolone equivalent); Existing chronic inflammatory bowel disease; Non-consenting Patient; Child Pugh Class C; Women during pregnancy and lactation; Participation in a clinical trial (intervention study) within the last 30 days; Current participation in another clinical trial (intervention study); Participation of the patient in this study earlier; Therapy restriction or setting (e.g., DNR order)

Addresses

- **Primary Sponsor**

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Sources of Monetary or Material Support

■ **Institutional budget, no external funding (budget of sponsor/PI)**

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Status

- Recruitment Status: **Recruiting planned**
- Study Closing (LPLV): **[---]***

Trial Publications, Results and other documents

** This entry means the parameter is not applicable or has not been set.*

**** This entry means that data is not displayed due to insufficient data privacy clearing.*