To study the development of mitochondrial dysfunction in septic Intensive Care Unit patients with respect to the hypermetabolic inflammatory status

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We expect that the development of mitochondrial dysfunction lags behind the development of the hypermetabolic inflammatory state. Additionally, we hypothesize that the aggravation of factors related to the hypermetabolic inflammatory status, such as...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Infections - pathogen unspecified
Study type	Observational non invasive

Summary

ID

NL-OMON20834

Source
NTR

Brief title
MIC-Study

Condition

- Infections - pathogen unspecified

Synonym
Septic shock

Health condition

Sepsis, mitochondrial disfunction, hypermetabolic inflammatory status

Research involving
Human

Sponsors and support

Primary sponsor: Wageningen University
Source(s) of monetary or material Support: Wageningen University and Gelderse Vallei Hospital

Intervention

Outcome measures

Primary outcome

Mitochondrial capacity in PBMCs measured via functional respirometry.

Secondary outcome

The secondary study parameters are (a) parameters of hypermetabolic inflammatory status (concentrations of hormones, nutrients and cytokines in the plasma), (b) mitochondrial dynamics and autophagy and (c) data from medical records.

Study description

Background summary

Rationale: Sepsis is a major cause of admission to the intensive care unit (ICU) and may result in hospital death rates up to 40-60% of septic shock cases. Mitochondrial dysfunction has been demonstrated in a variety of cells in septic ICU patients, including peripheral blood mononuclear cells (PBMCs). Multiple studies have provided evidence for the association between the degree of mitochondrial dysfunction in PBMCs and the severity of sepsis and clinical outcomes. Sepsis can be defined as a hypermetabolic inflammatory state, that is characterized by a decrease in (lean) body mass and high circulating levels of catabolic stress hormones, inflammatory cytokines and nutrients. Several papers, suggest a relationship between the amount of nutrients (e.g. glucose) in the blood and severity of mitochondrial dysfunction in PBMCs and subsequently clinical outcomes. We pose the hypothesis that the degree of the hypermetabolic inflammatory status associates with the degree of mitochondrial dysfunction in PBMCs. To gain a deeper understanding of this hypothesis, we will perform consecutive measurements over time in septic ICU patients. Additionally, we will measure mitochondrial dynamics (in PBMCs), which have been shown to be essential for proper mitochondrial functioning.

Objective: The main objective is to investigate how mitochondrial function progresses over time in septic ICU patients. The secondary objectives are (a) to investigate how mitochondrial dynamics progress over time and how this is associated with mitochondrial function and (b) to investigate if and how parameters of the hypermetabolic inflammatory status are related with the progression of mitochondrial function and (c) to investigate if and how the progression of mitochondrial function/is related to physical performance and clinical outcomes.

Study design: Prospective cohort study with matched controls.

Study population: ICU patients diagnosed with sepsis (n=30) and metabolically healthy age and gender matched short-stay hospitalized patients (n=30).

Main study parameters/endpoints: The main study parameter is mitochondrial function in PBMCs. The secondary study parameters are (a) parameters of hypermetabolic inflammatory status (concentrations of hormones, nutrients and cytokines in the plasma), (b) mitochondrial dynamics and autophagy and (c) data from medical records.

Study objective

We expect that the development of mitochondrial dysfunction lags behind the development of the hypermetabolic inflammatory state. Additionally, we hypothesize that the aggravation of factors related to the hypermetabolic inflammatory status, such as nutrients, catabolic hormones and pro-inflammatory cytokines, associates with the degradation of mitochondrial function and dynamics, resulting in worse clinical outcomes.

Study design

T0 = Day 0 (inclusion)

T1 = Day 1 after inclusion

T2 = Day 3 after inclusion

T3 = Day 5 after inclusion

T4 = At discharge from ICU

T5 = At discharge from hospital

Intervention

None

Contacts

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Eligibility criteria

Age
Adults (18-64 years)
Adults (18-64 years)
Elderly (65 years and older)
Elderly (65 years and older)

Inclusion criteria

- Sepsis originated from abdomen or respiratory system

- Admission to the ICU of Gelderse Vallei Hospital

- Signed Written Informed Consent. The ethics committee/institutional review board approved informed consent form signed by the participant or the participant’s legal representative in accordance with local regulations. Participants unable to give their written consent may only be enrolled in the study with the consent of a legally acceptable (or designated) representative. The participant must also be informed about the nature of the study to the extent compatible with his or her understanding, and should the participant become capable, he or she should personally sign and date the consent form as soon as possible.

Exclusion criteria

• Patients younger than 18 years

• Patients with a haemoglobin level lower than 5,5 mmol/lL*

• Patients referred from another ICU

• Patients with a history of solid organ or bone marrow transplant

• Patients with active autoimmune disease involving the lung, heart, liver, small or large intestine, or neuromuscular system (e.g., myasthenia gravis, multiple sclerosis) AND currently requiring systemic immunosuppressive therapy

• Patients whom experienced a significant medical or surgical event leading to hospitalization within the previous year

• Patients with a disease process (e.g., end-stage cancer) with a projected survival of less than 6 months (pre-ICU admission)

• Patients whom received treatment with chemotherapy, immunotherapy or radiotherapy within the past 12 months

• Patients with a family history of mitochondrial disease(s)

• Patients with COPD Gold-Stadium III or IV or other severe respiratory disorders (FEV1 <30% and FEV1/FVC < 0.7) (pre-ICU admission) [25]

• Patients with any stage of chronic or acute renal failure (pre-ICU admission, pre-existent SOFA 0 for this SOFA element)

• Patients with any stage of chronic or acute liver failure (pre-ICU admission, pre-existent SOFA 0 for this SOFA element)

• Patients supported with hemodialysis or continuous hemofiltration

• Patients diagnosed with diabetes Mellitus type I and II (pre ICU-admission)

• Patients not able to understand the Dutch language

• Patients currently participating in intervention research

• Patients treated with any investigational agent within 12 months prior to study treatment administration.

• Pregnant patients

• Patients who are ≤ 6 months postpartum pregnancy testing to the discretion of the attending physician

• Patients whom consume more than 25 grams of ethanol daily (>2.5 alcoholic beverages/day) [26]

• Patients with a history of drug abuse

• Patients whom received treatment with corticosteroids or other immunosuppressive medications for active autoimmune disease involving the lung, heart, liver, small or large intestine, or neuromuscular system within 3 months prior to ICU-stay NOTE: Topical, ocular, intra-articular and inhalational corticosteroids (with minimal systemic absorption) are permitted

Study design

Design

Study phase:	N/A
Study type:	Observational non invasive
Intervention model:	Single
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-02-2018
Enrollment:	60
Type:	Actual

IPD sharing statement

Plan to share IPD: No

Ethics review

Approved WMO Date:	22-01-2018
Application type:	First submission
Review commission:	METC Oost-Nederland
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	Postbus 9101
	6500 HB Nijmegen
	024 361 3154
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Study registrations

Followed up by the following (possibly more current) registration

ID: 48792
Bron: ToetsingOnline
Titel:

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL5918
NTR-old	NTR6969
CCMO	NL63412.081.17
OMON	NL-OMON48792

Study results