Muscle-derived Amino Acids in Sepsis

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We hypothesize that muscle protein breakdown (i.e. amino acid release) is related to increased glutamine utilization by immune cells, gluconeogenesis and synthesis of acute phase proteins.

Ethische beoordeling	Positief advies
Status	Werving gestart
Type aandoening	-
Onderzoekstype	Observationeel onderzoek, zonder invasieve metingen

Samenvatting

ID

NL-OMON23895

Bron
NTR

Verkorte titel
MAAS

Aandoening

Sepsis

Ondersteuning

Primaire sponsor: Maastricht UMC+
Overige ondersteuning: Fresenius-Kabi, Bad Homburg

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

1. Across the leg phenylalanine and glutamine kinetics (indicator of muscle protein synthesis/breakdown and release of muscle derived glutamine respectively)
2. Glutamine substrate utilization for energy and immune cell funciton (i.e. incorporation of 13C in urea, glucose and citrate cycle intermediates such as citrate, fumarate, malate in

peripheral leukocytes as a marker of glutamine utilization by the immune system)
3. Correlation between outcome 1 and 2 (i.e. is increased substrate utilization associated with increase muscle breakdown and therefore a driver of muscle wasting in sepsis.

Toelichting onderzoek

Achtergrond van het onderzoek

Rationale: Skeletal muscle wasting is a common and major problem in the intensive care unit. The resulting ICU-acquired weakness is associated with increased mortality/morbidity, prolonged weaning from ventilator support and persistent functional impairment lasting far beyond the time of ICU discharge. It is conceived by many that muscle protein breakdown during critical illness is a phylogenetic phenomenon resulting in enhanced release of amino acids into the circulation to serve as substrate for central protein synthesis (acute phase response) or rapidly dividing cells including immune cells. However, the actual metabolic fate of amino acids released during muscle breakdown has been poorly characterized in critically ill patients. By tracing amino acids derived from protein breakdown, we aim to better characterize changes in AA kinetics in ICU patients and gain insight in the (patho)physiology and drivers of protein catabolism in sepsis.

Objective: To study the metabolic fate of amino acids derived from muscle protein breakdown in septic patients.
Study design: non-therapeutic interventional cohort study.

Study population: 21 patients with sepsis admitted to the ICU, 18 - 75 years old. Patients are eligible if they have an arterial catheter and a central venous catheter in the femoral vein.
Intervention: Patients participating in this study will receive a primed continuous intravenous infusion with non-radioactive stable isotope tracers after a 6 hour fast. 2H5 phenylalanine, 2H2 tyrosine and 13C glutamine will be infused for 6.5 hours. Both arterial and femoral venous blood samples will be collected through indwelling catheters and analyzed for tracer enrichments. Repeated bedside ultrasound of the leg will be performed to quantify muscle loss over time on the day 1, 5, 7 and 12.

Main study parameters/endpoints: Main study parameters will be protein breakdown and glutamine release from the leg (assessed by a two-pool model using AV leg gradients), albumin synthesis assessed by 2H5 phenylalanine incorporation. In addition we will study the incorporation of 13C in urea, glucose and citrate cycle intermediates such as citrate, fumarate, malate in peripheral leukocytes as a marker of glutamine utilization by the immune system. Moreover we will measure 13CO2 enrichment in exhaled air as a measure of total glutamine oxidation. Finally we will quantify muscle loss due to sepsis using repeated ultrasound measurements of the leg muscles.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Stable isotopes are non-radioactive molecules, which have been extensively used in both healthy and critically ill patients. Phenylalanine, tyrosine and glutamine are

amino acids that are part of normal nutritional formulas used in the ICU and will not pose any risk to the participants. In addition, the intravenous infusion will be performed using a tracer dosage, ensuring visualization but no metabolic alteration of the substrate metabolites. Both infusion and sampling will take place through indwelling catheters, meaning no additional punctures or line placements are required. The total amount of blood sampled will be approximately 72 ml (~1.0% of total circulating volume). This amount of blood sampling has been proven safe in previous studies in ICU patients and is unlikely to pose any risk or burden to the participant. Ultrasound measurements of the leg pose no harm or risk to the participant.

Doel van het onderzoek

We hypothesize that muscle protein breakdown (i.e. amino acid release) is related to increased glutamine utilization by immune cells, gluconeogenesis and synthesis of acute phase proteins.

Onderzoeksopzet

Plasma will be sampled before tracer infusion, when a steady state is reached (after 1,5 hours) every hour until 5 hours after steady state conditions.
Muscle ultrasound will be performed on day 1, 5, 7 and 12 of participation

Onderzoeksproduct en/of interventie

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Contactpersonen

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

1) Age >18 <75
2) Sepsis on admission (as defined by the Sepsis-3 criteria*)
3) Sepsis still persistent but stabilized as defined by continued need of vasopressive drugs
- norepinephrine dose, > 0.05-0.25 mcg/kg/min
4) Intubated and Mechanically ventilated
- PaO2/FiO2 ratio of >100 mm Hg (>13 kPa)
5) Femoral venous and peripheral venous line
6) Arterial line (any location) in situ
7) Expected ICU stay > 48 hours

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1) Patients who are moribund (not expected to be in ICU for more than 48 hours due to imminent death)
2) A lack of commitment to full aggressive care during the first week due to severity of illness, comorbidities and potential harm from maximal treatment (anticipated withholding or withdrawing treatments in the first week)
3) Any trauma with severe injury or fracture of any extremity.
4) Rhabdomyolysis
5) Proven (pre-existing) skeletal muscle weakness (e.g. due to neuromuscular disorders or immobility)
6) Renal dysfunction defined as a serum creatinine >171 umol/L or a urine output of less than 500 ml/last 24 hours
7) Patients requiring chronic veno-venous hemofiltration
8) Patients on any form of extracorporeal life support (ECMO/ELS)
9) Cirrhosis - Child’s class C liver disease
10) Metastatic cancer or Stage IV Lymphoma with life expectancy <6 months
11) Patients with primary admission diagnosis of burns (>30% body surface area)
12) Weight less than 50 kg or greater than 100 kg
13) Pregnant patients or lactating with the intent to breastfeed
14) Previous enrollment in this study
15) Previous participation in a 13C or 2H tracer study within the last year

16) Enrollment in any other interventional study

Onderzoeksopzet

Opzet

Type:	Observationeel onderzoek, zonder invasieve metingen
Onderzoeksmodel:	Anders
Toewijzing:	N.v.t. / één studie arm
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	22-04-2019
Aantal proefpersonen:	21
Type:	Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nog niet bepaald

Ethische beoordeling

Positief advies

Datum:	09-05-2019
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL7723
Ander register	CCMO : CCMO 18.0269 (NL63199.000.17)

Resultaten