Metabolic fate of amino acids derived from muscular protein breakdown in septic patients

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To study the metabolic fate of amino acids derived from muscle protein breakdown in septic patients.

Ethical review	Approved WMO
Status	Completed
Health condition type	Bacterial infectious disorders
Study type	Interventional

Summary

ID

NL-OMON50749

Source
ToetsingOnline

Brief title
Muscle-derived amino acids in sepsis / MAAS-study

Condition

- Bacterial infectious disorders
- Protein and amino acid metabolism disorders NEC
- Musculoskeletal and connective tissue disorders NEC

Synonym
Muscle wasting, Protein breakdown

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: Fresenius-Kabi

Intervention

Keyword: Amino acids, Muscle wasting, Protein metabolism, Sepsis

Outcome measures

Primary outcome

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 using repeated ultrasound measurements

Secondary outcome

nvt

Study description

Background summary

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 prolonged 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.

Study objective

To study the metabolic fate of amino acids derived from muscle protein breakdown in septic patients.

Study design

non-therapeutic interventional cohort study.

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 ultrasound measurements of the leg will be made to quantify muscle loss over time.

Study burden and risks

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. If patient is eligible, but no femoral line is in place a temporary catheter can be placed. Except for minimal discomfort due to a single puncture, the risk of accidental puncture of the artery is <1.5% and can be amended by applying local pressure for 10 minutes. The total amount of blood sampled will be approximately 56 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.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

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 ug/kg/min
4) Receiving enteral or parenteral nutrition
5) Intubated and Mechanically ventilated
- PaO2/FiO2 ratio of >100 and <300;
6) Femoral venous catheter in place OR eligible for femoral CVL placement
7) Arterial and peripheral venous line (any location) in situ
8) Expected ICU stay > 48 hours, * Sepsis as defined by the third international consensus definitions for sepsis and septic shock [17]:
- Suspected infection
- SOFA score >= 2

Exclusion criteria

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 *mol/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

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	18-06-2019
Enrollment:	21
Type:	Actual

Ethics review

Approved WMO Date:	13-09-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-03-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

No registrations found.

In other registers

Register	ID
CCMO	NL63199.000.17