A longitudinal investigation of Energy exPenditure and substrate utilization In Critically ill patients (EPIC): a prospective observational multi-center study.

Study Protocol (2021-12-07)

Primary investigator: Martin Sundström Rehal

Co-primary investigator: Olav Rooyackers

Clinicaltrials.gov Identifier: NCT05124860

Background

Critical illness has profound effects on human metabolism. The most prominent feature in the early phase is an upregulation of catabolic pathways, which promotes the production of endogenous energy substrates and net protein breakdown [1].

Historically, it was assumed that intensive care unit (ICU) patients have an increased requirement of energy substrates [2, 3]. This belief was supported by small observational studies using indirect calorimetry [4, 5]. More recent studies have called this into question, finding that critically ill patients on average have a metabolic rate similar to that of healthy subjects [6]. Energy expenditure in the individual patient is highly variable and cannot be accurately estimated from population characteristics [7]. Metabolic rate may change over time, and is likely influenced by the underlying cause and trajectory of critical illness.

Energy expenditure is readily measured in the clinical setting by indirect calorimetry. This method has been available in intensive care for several decades. Despite this, there is very little published data describing trends of energy expenditure and substrate utilization in patients with a prolonged ICU stay. While this group only constitutes a small fraction of ICU patients, it

accounts for a large part of ICU resource allocation, morbidity and suffering [8]. Several studies have been conducted in recent years to better characterize patients with persistent critical illness, focusing on markers of catabolism and inflammation [9, 10]. It is not known if these changes are associated with alterations in energy metabolism and substrate utilization.

Bridging these knowledge gaps will improve our understanding of the nutritional needs and metabolism of patients beyond the early phase in ICU. A better characterization of the relevant physiology is an essential step towards improving patient outcomes. We therefore plan to conduct an observational multi-center study to address these questions.

Aim

The overall aim of this project is to describe longitudinal changes of energy expenditure and associated clinical characteristics in a large prospective cohort of patients with a prolonged ICU stay.

Hypothesis

There is a significant change in mean energy expenditure and respiratory quotient (RQ) between the early (day 1-3), intermediate (day 4-10) and late (>10 days) phase in ICU.

Methods

Study design

Prospective mutli-center longitudinal cohort study.

Population

Inclusion criteria

1. ≥18 years old.
2. Admitted to the ICU of a participating study site.
3. At least one measurement of energy expenditure performed during ICU stay.

Exclusion criteria

1. Patients readmitted to the ICU of a participating study site >72 hours after ICU discharge and already included in the study (≥1 measurement of energy expenditure performed during prior admission). If a patient is readmitted within ≤72 hours of ICU discharge this is considered as a continuation of the last ICU admission for the purposes of this study.
2. Burns >20% of body surface area.
3. Pregnancy.

Intervention/exposure

Study subjects will be followed until ICU discharge or death, whichever occurs first.

All participating centers are encouraged to modify local nutrition protocols to recommend that:

- Indirect calorimetry is performed under standardized conditions (Appendix 1).
- Indirect calorimetry is performed within 3 days of ICU admission.
- Indirect calorimetry is repeated every 3-4 days until ICU discharge, death or in the event of limitations in treatment to best supportive care.
- Oxygen consumption (VO_2), carbon dioxide production (VCO_2), RQ and resting energy expenditure (REE) are documented in the patient's medical records.

Interpretation of investigations and energy prescriptions are left to the discretion of the attending physician or dietician and are not regulated by the study protocol in any way.

Outcomes

Primary:

- Change in REE (kcal/kg adjusted body weight*/24 hours) over time in patients who stay in ICU for >10 days.

  Adjusted body weight is calculated as Ideal Body Weight (length in cm - 100) + ⅓(Admission Body Weight - Ideal Body Weight). If admission body weight is less than ideal body weight, this value is used instead of adjusted body weight.

Secondary:

- Change in RQ over time in patients who stay in ICU for >10 days.

- Change in REE and RQ over time in patients who stay in ICU for ≤10 days.

Exploratory:

Correlations between metabolic rate and CRP, albumin, urea/creatinine ratio, degree of organ failures (SOFA), ICU mortality, age and gender will be analyzed for hypothesis-generating purposes.

Data collection

Pseudonymized patient data is reported from participating study sites through a secure online platform (Redcap™) on 1) admission, 2) on the day of each indirect calorimetry, and 3) on ICU discharge or death.

Participating centers are responsible for creating and maintaining a secure code key linking the study number attributed to a patient with a patient ID, to be stored in a secure location at the study site.

On admission:

- Admission date
- Admission diagnosis (ICD-10)
- Surgery prior to admission (YES/NO), elective or emergent
- Outcome prediction score (SAPS 3, APACHE III/IV, MPM, etc.) and risk of death on admission (%)
- Demographic and anthropometric data:
    - Sex (male/female)
    - Age (years)
    - Actual body weight (kg)
    - Height (cm)
- Chronic comorbidities registered in electronic health records (YES/NO):
    - Hypertension
    - Ischemic heart disease
    - Heart failure
    - Diabetes mellitus
    - COPD
    - Chronic kidney disease

- End-stage renal disease
- Liver cirrhosis
- Active cancer (not in complete remission)
- Haematological malignancy
- Solid organ transplant

On the day of each indirect calorimetry:

- REE (kcal/24 h), RQ, VO_2 (ml/min), VCO_2 (ml/min) and date of investigation
- Invasive mechanical ventilation (YES/NO) or renal replacement therapy (YES/NO)
- If YES to invasive mechanical ventilation:
    - fraction of inspired oxygen
    - positive end-expiratory pressure (cm H_2O)
- Sequential organ failure assessment (SOFA) score
- Fever (≥38.5 ℃) within 2 hours of measurement (YES/NO/MISSING)
- Results of daily blood tests if available from routine testing:
    - P-CRP (mg/L)
    - P-albumin (g/L)
    - P-urea (mmol/L)
    - P-creatinine (µmol/L)
    - Haemoglobin (g/L)
- Infusions of vasoactive medications (YES/NO, if YES → name of medication(s))
- Infusions of sedatives or analgesics (YES/NO, if YES → name of medication(s), if propofol → infusion rate at time of measurement)
- Infusions of parenteral and/or enteral nutrition (YES/NO, if YES → brand name, formulation and rate at time of measurement)
- Richmond Agitation-Sedation Scale (RASS) score on day of measurement

On discharge:

- Discharge date
- Survival status (ALIVE/DEAD)

On completion of enrollment at an individual study site:

- Total number of patients admitted during the study period.

Sample size considerations

The goal of this study is to include ≥200 patients with an ICU length of stay of >10 days. Based on data from the Swedish Intensive Care Registry between 2015-2019, these patients accounted for 5% of all ICU admissions [9]. This proportion is comparable to results from a registry study conducted in Australia and New Zealand of over one million ICU admissions [8]. Based on these figures we intend to screen 6000 unique patients for study participation, accounting for the possibility that multiple measurements of indirect calorimetry are not consistently performed. Based on Swedish registry data approximately 1250 unique patients with at least one measurement of indirect calorimetry will be included in the analysis.

Statistics

Descriptive data will be presented as mean +/- standard deviation or median (interquartile range) as appropriate. The primary and secondary outcome measures will be analysed using a generalized linear mixed-effects model. Exploratory outcomes will be analysed using generalized linear regression models. If values are found to be not missing at random, conditional logistic regression censoring will be used to calculate inverse probability weights for accounting for difference in drop-out probabilities. The predetermined level of statistical significance is set to ≤ 0.05.

A detailed statistical analysis plan will be published before the database is locked and analysis begins.

Timeline

2021: Ethical approval, clinical trials registration, data monitoring board, development of electronic case report form. Preliminary inclusion of first subjects at primary study site in December 2021.
2022: Recruitment of additional study sites.
2023: Enrollment anticipated to conclude in late 2023. Publication of statistical analysis plan.
2024: Data analysis. Reporting of results to co-investigators. Drafting of manuscript.

Ethics

The study has received approval from the Swedish Ethical Review Authority (Dnr 2021-02750) and has been granted a waiver of informed consent. Approval from ethical review boards at study sites outside of Sweden must be granted before enrollment can begin. Due to the observational nature of the study and pseudonymized reporting of routinely collected data, we recommend an application for a waiver of informed consent, or if this is not granted, the possibility for delayed consent from patients or next of kin if applicable.

Appendix 1.

Measurement standards when performing indirect calorimetry.

Accepted instruments for study purposes

- E-sCOVX (General Electric, Helsinki, Finland)
- Quark RMR (Cosmed, Rome, Italy)
- Q-NRG (Cosmed, Rome, Italy)
- BEACON Caresystem (Mermaid Care, Nörresundby, Denmark)

Prior to measurement

- The instrument must be calibrated according to manufacturer's recommendations. Investigators are responsible for keeping records of calibration procedures at the trial site.
- The recommended warm-up time for the instrument must be observed before performing a measurement.
- The requisite conditions for accurate measurements should be observed for each instrument. Check user´s manual for guidance if FiO_2 >0.70, PEEP >10, respiratory rate ≥35 and peak inspiratory pressure ≥30 cmH_2O.
- Measurements should be performed under resting conditions and not be preceded by potentially strenuous procedures. The steering group recommends a minimum of one hour's rest after patient hygiene and three hours after physiotherapy or a painful medical procedure.
- FiO_2, pressure support or tidal volume settings should ideally not be changed one hour prior to performing a measurement.
- Measurements should not be performed in the presence of significant leaks in the ventilator circuit or anatomical gas leaks. This should be checked by analysis of ventilator flow waveforms prior to measurements.
- Continuous renal replacement therapy may affect the accurate measurement of VCO_2 but is not a contraindication to performing indirect calorimetry [12].

During the measurement

- Connections to the ventilator circuit should follow manufacturer's recommendations and avoid excess dead space, which may affect the accuracy of measurements.
- FiO_2, pressure support or tidal volume settings should not be changed during measurements. Suctioning or concurrent delivery of nebulized medications should be avoided. In the event that this occurs, the measurements should be discarded and a new measurement performed at a minimum of one hour later.
- If active humidification or an inspiratory filter is used, the sampling point for inspired oxygen fraction should be connected distal to this point to ensure a stable concentration of inspired oxygen.
- Measurements should be conducted for a minimum of 15-30 minutes and inspected for stability in VO_2 and VCO_2. In general, a variability of <10% is recommended [13].

After the measurement

- Measured resting energy expenditure (REE) and respiratory quotient (RQ) should be documented in the patient's medical records. Documentation of oxygen consumption (VO_2) and carbon dioxide production (VCO_2) are ideal but not mandatory.

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