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

Study protocol (updated 2022-02-21) and statistical analysis plan (updated 2025-04-08)

Primary investigator: Martin Sundström Rehal

Co-primary investigator: Olav Rooyackers

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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 multicenter 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 multicenter 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
- ICU source of admission (Emergency department, ward, operating theatre, other ICU).
    - If ward or operating theatre → days in hospital before ICU admission.
    - If other ICU → days in previous ICU before admission.
- 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 → 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)
- Sepsis during ICU stay (YES/NO, if yes → septic shock or sepsis)

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.

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.

Statistical analysis plan (updated 2025-04-08)

For descriptive statistics, continuous variables will be presented as means ± standard deviations (SD) or median [interquartile range (IQR)], as appropriate. Distributions will be visually inspected using histograms and assessed for normality using quantile-quantile plots.

Generalised linear mixed regression models will be used to study the association between primary (REE) as well as secondary outcomes (RQ, VO_2, VCO_2) and explanatory variables of interest. Explanatory variables will include a group of potentially relevant variables (days in ICU on measurement, age >/< 60 years, sex, airway pressure (PEEP), FiO_2, vasopressor therapy (yes/no), fever (body temperature ≥38.5°C at time of measurement), calories administered at time of measurement, Richmond Agitation-Sedation Scale (RASS), degree of inflammation (plasma CRP), renal replacement therapy (yes/no), body weight, diagnostic group (medical, surgical, presence/absence of sepsis[1])). Further variable selection will be conducted in a data-driven way, either backward or forward selection, as appropriate. For each outcome, the link function and model family will be chosen based on the visual inspection of their distribution and model fit diagnostics such as residual plots. Patient and study site will be included as random effects allowing for a random intercept for each. Random slopes over time will be included in the model if their respective estimated coefficients are statistically significant and if the model fit in terms of Akaike's information criterion (AIC) is improved compared to the random intercept model. Possible correlations between the random effects will be modelled using an unstructured covariance matrix unless the AIC suggests a different covariance structure for best describing the random variation in the data. Any additional explanatory variables will be treated as fixed effects. For each additional explanatory variable, we will investigate two research questions. First, we want to explore possible associations with each outcome variable. Second, we want to study how well the explanatory variables taken together explain the variation in each outcome variable. The best final adjusted models will be selected based on the AIC. Results will be reported as (exponentiated) regression coefficients and 95% confidence intervals. If a non-linear relationship between any outcome and any explanatory variable is suspected, using restricted cubic splines will be explored.

[1] Classified as Sepsis-3 och primary diagnosis of sepsis. Sepsis-3 coding is not available in the Australian cohort. A sensitivity analysis including or excluding the primary diagnosis of sepsis will be performed.

Frequencies and patterns of missing data will be investigated for each outcome and explanatory variable by studying summary tables and plots. If missing at random can be assumed and frequencies are below 3% at each time point, this missingness will be ignored, and observations dropped. Explanatory variables with more than 30% missing values at baseline will not be considered, except for the SOFA score, which is not available in the Australian subpopulation. SOFA score will be investigated in non-Australian patients only. As an exploratory analysis, the SOFA score will be imputed in the Australian cohort. Multiple imputation will also be investigated for explanatory variables between 3 and 30% missing values at baseline. If missing at random cannot be assumed, alternative modelling approaches will be considered. Conditional logistic regression will be used to calculate the inverse probability of censoring weights to control for selective drop-out in patients discharged alive from the ICU.

For hypothesis-generating purposes, longitudinal K-means clustering or clustering with dynamic time warping will be used to investigate potential subpopulation phenotypes based on transitions in energy expenditure over time, as appropriate.

All analyses will be performed in R version 4.4.0 or later. The predetermined level of statistical significance for the primary outcome is set to ≤ 0.05. For all other outcomes, no adjustments for multiple comparisons will be made due to the explorative nature of this part of the study. Hypotheses will be generated for target populations with similar characteristics as our sample population, leaving external validity investigations to future confirmatory studies.

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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