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Actual energy expenditure in patients on extracorporeal membrane oxygenation: a modified indirect calorimetry vs. traditional approaches

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ABSTRACT

Patients on extracorporeal membrane oxygenation (ECMO) are the most severe in ICUs and require complex treatment. Nutritional support (NS) is a vital component of critical care. Indirect calorimetry (IC) is the gold standard for bedside assessment of actual energy expenditure (AEE) in the ICU. However, two "gas exchange points" require monitoring of oxygen consumption and carbon dioxide elimination from lungs and membrane oxygenator. This significantly limits the capabilities of modern IC devices. We developed an original method for estimation of AEE in ECMO patients enabling synchronous gas analysis.

Objective. To compare AEE values obtained using a modified indirect calorimetry, predictive equations and empirical approaches in patients on veno-arterial ECMO.

Material and methods. A single-center prospective open cohort study included 15 patients on veno-arterial ECMO. AEE was assessed using a modified IC method based on simultaneous measurement of oxygen consumption and carbon dioxide excretion from lungs (via metabolic monitor) and membrane oxygenator (via pneumatic flowmeter and portable capnograph). These data were used to calculate AEE using the J.B. Weir equation. AEE values were compared with empiric data on energy expenditure in accordance with the guidelines of the Federation of Anesthesiologists and Reanimatologists (25 kcal/kg/day) and basal metabolic rate (Harris-Benedict formula).

Results. There were 15 measurements. Mean AEE was 2180 [1830—2446] kcal/day (29.2 [24.6—31.2] kcal/kg/day). These values significantly exceeded the recommended empirical value (25 kcal/kg/day, p=0.046) and the calculated BMR according to the Harris-Benedict formula (23.3 [20.5—25] kcal/kg/day, p<0.001).

Conclusion. Indirect calorimetry is feasible in ECMO patients with appropriate equipment. Energy expenditure in these patients significantly exceeds the recommended 25 kcal/kg/day and the calculated basal metabolic rate. The effect of ECMO on energy metabolism in critically ill patients requires further research.

Keywords: *extracorporeal membrane oxygenation, metabolism, energy expenditure, indirect calorimetry, oxygen consumption, respiratory quotient.*

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Introduction

Nutrition support (NS) is an important element of intensive care for critically ill patients. In case of hypermetabolism and hypercatabolism, adequate NS maintains muscle mass and balance of essential macro- and micronutrients in the body [1, 2]. On the contrary, nutritional deficiency prolongs ICU- and hospital-stay, increases the risk of in-hospital infections, duration of ventilation and likelihood of unfavorable clinical outcomes.

Hyperalimentation can lead to hyperthermia, hyperglycemia, hypertriglyceridemia, fatty liver infiltration, azotemia, hypercapnia and hyperventilation [3, 4]. Prevention of energy imbalance is extremely important for critically ill patients, since it significantly reduces the risk of dangerous consequences of inadequate NS. Various prognostic equations do not allow accurate analysis of energy expenditure in critically ill patients [5]. Currently, indirect calorimetry is the "gold standard" for bedside measurement of actual energy expenditure (AEE) in intensive care patients. Indirect calorimetry is proposed in the guidelines of the All-Russian public organization "Federation of Anesthesiologists and Reanimatologists" [6], the European Society for Clinical Nutrition and Metabolism (ESPEN) and the American Society for Parenteral and Enteral Nutrition (ASPEN) [1, 2]. It is necessary to assess AEE dynamics for control of NS effectiveness and prevention of energy imbalance in critically ill patients [4].

Patients on extracorporeal membrane oxygenation (ECMO) are among the most severely ill patients in ICUs. They require complex intensive care associated with prolonged hospital-stay and long-term rehabilitation. Moreover, there is high incidence of adverse clinical outcomes [7]. Extracorporeal circuit with oxygenator and, accordingly, the second point of gas exchange

in addition to lungs significantly complicate accuracy and feasibility of indirect calorimetry [8]. To calculate AEE in these patients, one should analyze gas exchange from lungs and membrane oxygenator [9, 10].

Widespread ECMO in critical care medicine [11—13] necessities searching for new methods for assessing AEE that can overcome the above-described problems.

The purpose of the study was to compare AEE values obtained using a modified indirect calorimetry, predictive equations and empirical approaches in patients on veno-arterial ECMO.

Material and methods

A single-center prospective open cohort study included 15 patients who underwent veno-arterial ECMO in 2023—2024. The ethics committee of the Almazov National Medical Research Center approved the study (protocol No. 0710-22 dated October 3, 2022).

Inclusion criteria: veno-arterial ECMO for more than 48 hours; age 18—70 years.

Non-inclusion criteria: acute infectious diseases of the upper or lower respiratory tract; bleeding from the upper or lower respiratory tract; sepsis.

Exclusion criteria: pulmonary embolism; pneumothorax; hemothorax; acute gastrointestinal bleeding; stroke.

At the first stage, we assessed AEE using indirect calorimetry between the 3rd and the 20th day after implantation of veno-arterial ECMO system. The modified indirect calorimetry method for ECMO (patent dated 11.11.2024, registration number 2014133670) is based on simultaneous measurement of oxygen consumption (VO_2) and carbon dioxide release (VCO_2) from lungs and oxygenator. Lung-related measurements were performed using the autonomous Q-NRG+® metabolograph (COSMED S.R.L., Italy). To ensure more stable monitoring parameters, the device measures volumetric content of oxygen and carbon dioxide every 30 seconds from the mixing chamber, where gas samples are taken from ventilator circuit every respiratory cycle. The gas flow on ECMO and volumetric oxygen content were assessed using a pneumatic meter (pneumotester) AP1 (AO Krasnogvardeets, Russia). Capnometry was performed using a portable capnograph (Respironics Novametrix, Inc., USA).

Pneumotester measures volumetric gas flow when gas passes through a special channel. This method is based on gas pressure changes as it passes through a fine-meshed mesh woven from thin steel wire. Accordingly, there is no leakage as in gas sampling in devices with "side stream" method. Oxygen concentration is measured in this channel using a galvanic oxygen sensor. Respiratory bacterial filter with hydrophobic properties is connected to inlet of channel to prevent contaminants and moisture from getting on the flow and oxygen sensors. Portable infrared capnograph is connected to outlet of channel for analysis of volumetric content of carbon dioxide in gas mixture. There were no active procedures and body position changes an hour before examination. Ventilation parameters were not changed. In patients without mechanical ventilation, measurements were performed 2 hours after eating. Scheme of equipment is presented in **Fig. 1**.

Oxygen volumetric flow rate and concentration in gas-air mixture supplied to oxygenator are adjusted using a gas mixer depending on clinical situation. For accurate assessment of gas mixture from the mixer, we measured volumetric flow rate and concentration of oxygen using a pneumotester beforehand. Carbon dioxide content was taken as 0%. For this purpose, pneumotester was inserted into gas supply circuit **(Fig. 2)**. Then, gas composition was measured simultaneously in inhalation and exhalation using metabolograph. From oxygenator membrane, we measured gas composition using pneumotester and portable capnograph. The last ones were successively connected to oxygenator outlet through a 3/8 PVC tube. We made measurements until the values with<5% variability were obtained for 10 minutes. Thus, mean VO_2 (ml/min) and VCO2 (ml/min) from lungs, as well as volumetric flow rate (Q, l/min), oxygen

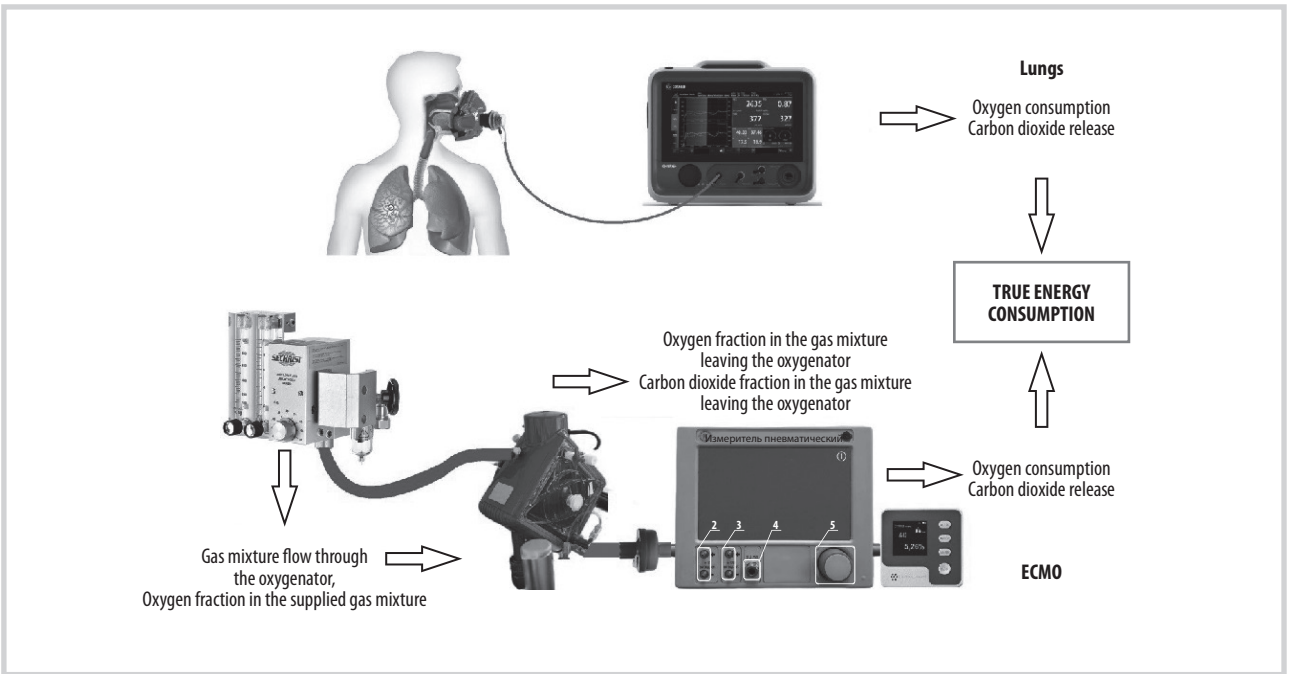

Fig. 1. **Scheme of gas analyzer connection for indirect calorimetry in ECMO patients.**



Fig. 2. **Pneumatic meter inserted into the circuit of gas mixture supply to the oxygenator.**

concentration in gas mixture at the oxygenator inlet (FiO_2, %), oxygen concentration at the oxygenator outlet (FeO_2, %) and carbon dioxide concentration at the oxygenator outlet ($FeCO_2$, %) from oxygenator were analyzed. Considering appropriate data, we made calculations using the following formulas:

$$VO_2(ECMO)=Q\cdot(FiO_2-FeO_2) \quad (1)$$

$$VCO_2(ECMO)=Q\cdot FeCO_2 \quad (2)$$

$$VO_2(total)=VO_2(ECMO)+VO_2(lungs) \quad (3)$$

$$VCO_2(total)=VCO_2(ECMO)+VCO_2(lungs) \quad (4)$$

$$AEE\ (kcal/day)=(3.94\cdot VO_2 total)+(1.11\cdot VCO_2 total)\cdot 1.44 \quad (5)$$

At the second stage, we compared AEE values based on indirect calorimetry and Harris-Benedict equation [14], as well as empirical data in accordance with Russian and European guidelines (25 kcal/kg/day) [2, 6]. Analysis was performed regarding absolute values and AEE in relation to body weight. In all patients, we performed indirect calorimetry in accordance with national guidelines. Target parameters of energy and protein supply were established as 25 kcal/kg/day and 1.2 g/kg/, respectively. We chose oral, enteral or parenteral NS depending on clinical situation.

Statistical analysis was performed using Statistica 10.0 software. Quantitative variables were presented as mean (*M*), standard deviation (*SD*), median (Me), and interquartile range (Q_1—Q_3). Absolute values and percentages are used for qualitative variables. The obtained AEE values were compared with estimated and empirical data using the Wilcoxon t-test. For all statistical criteria, type I error was established at 0.05. The null hypothesis was rejected if the probability (p) did not exceed type I error.

Results

Characteristics of patients are presented in **Table 1**.

VO_2 (ECMO) was 89.5 [75—128.5] ml/min, VO_2 (lungs) — 212 [138—234] ml/min, VCO_2 (ECMO) — 70.2 [44.4—97.8] ml/min, VCO_2 (lungs) — 188 [141—243] ml/min. Mean AEE was 2129±340 kcal/day, respiratory quotient (RQ) varied from 0.7 to 1.1. Indirect calorimetry data are presented in **Table 2**.

Table 1. **Data of patients**

Variable	Patients (*n*=15)
Age, years	41 [33—56]
Men/women	12 (80%)/3
Height, cm	178 [170—180]
Body weight, kg	72 [66—81]
BMI, kg/m^2	24.1 [19.7—27.4]
Ventilation, *n*	5
Sedation/muscle relaxants, *n*	2/0
Indications for ECMO, *n*	
acute decompensation of CHF	10
postcardiotomy heart failure	4
extracorporeal CPR	1

Note. data are presented as Me [Q_1—Q_3]. BMI — body mass index; ECMO — extracorporeal membrane oxygenation; CHF — chronic heart failure; CPR — cardiopulmonary resuscitation.

Table 2. **Indirect calorimetry data**

Variable	Me [Q_1—Q_3]
VO_2, ml/min	302 [257—336]
VCO_2, ml/min	268 [231—291]
VO_2/kg, ml/kg/min	3.94 [3.48—4.5]
VCO_2/kg, ml/kg/min	3.55 [3.18—4.15]
AEE, kcal/day	2180 [1830—2446]
AEE/kg, kcal/lg/day	29.2 [24.6—31.2]
Respiratory quotient	0.88 [0.79—1.0]

RQ indicates a mixed type of carbohydrate and lipid consumption with mild predominance of carbohydrate oxidation. Although patients on ECMO are immobilized, mean VO_2 is higher than one metabolic equivalent by 0.5 ml/kg/min (p=0.053). AEE is 29.2 kcal/kg/day.

Basal metabolic rate (Harris-Benedict equation) was 1659 [1552—1800] kcal/day or 23.3 [20.5—25] kcal/kg/day. Comparison of AEE with empirical values and basal metabolic rate is presented in **Fig. 3**.

Thus, the estimated AEE was significantly higher than the recommended values (25 kcal/kg/day) and basal metabolic rate according to the Harris-Benedict formula.

Discussion

Until recently, indirect calorimetry was not used in patients on ECMO due to gas exchange on membrane oxygenator. This process cannot be taken into account in case of traditional indirect calorimetry [8].

To date, the proposed methods for indirect calorimetry in patients on ECMO are based on sequential gas analysis from "natural" lung and membrane oxygenator with further calculation of AEE using a modified equation by J.B. Weir [11]. This formula considers the summed values of oxygen consumption (VO_2) and carbon dioxide excretion (VCO_2) [9, 10]. Thus, De Waele E. et al. [9] calculated V O_2 and VCO_2 from oxygenator using metabolograph. T. Wollersheim et al. [10] analyzed blood

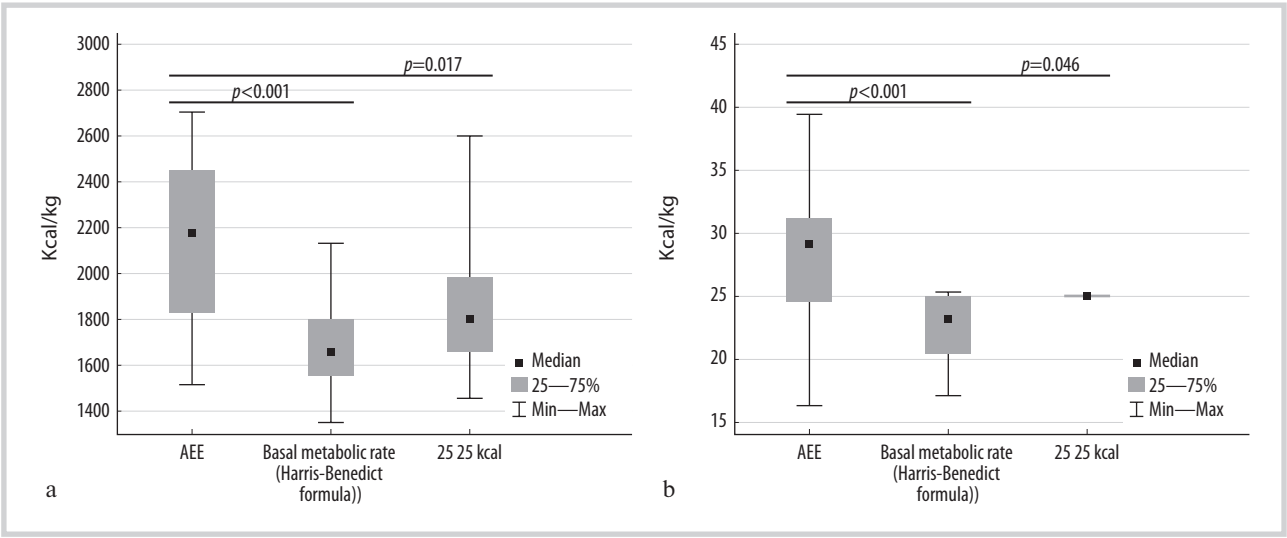

Fig. 3. **Absolute, empirical and estimated AEE values.**
a — AEE per a body weight; b — AEE per a kg of body weight. The data are presented as a box-and-whisker diagram.

gases "before and after" oxygenator using rather complex mathematical formulas. At the same time, some experts noted problems with indirect calorimetry in case of ECMO (for example, sequential (not simultaneous) sampling from lungs and oxygenator). Haldane transformation used in metabolographs at FiO_2>70% introduces errors in VO_2 measurement. Flow sensors in metabolographs are designed for inspiratory and expiratory flow lines and not suitable for measurements under constant stationary gas flow as in case of ECMO. Sidestream gas analysis implemented in most metabolographs can significantly affect the results at low fresh gas flow on ECMO. VO_2 and VCO_2 values based on blood gas analysis require blood sampling from high-pressure extracorporeal circuit (up to 350 mm Hg). This increases the risk of bleeding, embolic and infectious complications. Condensate in sampling lines also distorts the results and makes long-term continuous measurement impossible [12, 13].

In 2015, De E. Waele et al. [15] described the first experience of assessing the AEE in a patient with respiratory failure and venovenous ECMO. The authors first connected the metabolograph to the ventilator circuit. After recording the VO_2 and VCO_2 values from lungs, the metabolograph was switched via a special connector to membrane oxygenator. VO_2 and VCO_2 from ECMO side were calculated according to gas flow data, oxygen and carbon dioxide fractions. Finally, they calculated AEE using these data and Weir equation. Using this modification of indirect calorimetry, the authors analyzed 7 patients on venovenous (n=3) and venoarterial (n=4) ECMO. They obtained variable AEE (from 12 to 33 kcal/kg/day) [9]. Small sample size and clinical heterogeneity of patients did not allow characterizing their metabolic status. Wollersheim T. et al. [10] proposed another approach to indirect calorimetry (traditional indirect calorimetry from the lung side using metabolograph and calculation of VO_2/VCO_2 from the oxygenator side based on blood gas analysis from the extracorporeal circuit (difference in oxygen and carbon dioxide content before and after oxygenator) and volumetric perfusion rate). The authors included only patients with acute respiratory distress syndrome (ARDS) undergoing venovenous ECMO. In 20 patients, AEE averaged 2013 [1786/2332] kcal/day (body weight 78 [70—107] kg). There was no significant difference in AEE with the control group (ARDS without ECMO). O.A. Tatucu-Babet et al. [16] performed a similar study with assessment of energy metabolism in patients on veno-arterial ECMO. AEE was 22 [15—24] (n=14) and 25 [21—26] kcal/kg/day in 1 and 5 days after ECMO implantation, respectively (n=7). There was no significant difference with the control group.

Despite significant progress in indirect calorimetry for patients on ECMO, there are still many unresolved technical issues and obstacles associated with ECMO [12, 13]. Our scheme of indirect calorimetry significantly eliminates these limitations. The use of pneumotester and portable capnograph synchronously with metabolograph reduces errors in data following changing the ratio of volumetric blood flow rate in pulmonary circulation and through the ECMO device. This cannot be recorded with sequential measurements. Pneumotester implies measurement through direct flow technology without gas mixture leakage. This is especially important in low flow of gas mixture. The principle of pneumotester function does not imply dependence on phases of respiratory cycle. It is suitable for registration of stationary gas flow with available analysis of oxygen concentration in the range from 0 to 100%.

AEE (29.2 [24.6—31.2] kcal/kg/day) is slightly higher compared to literature data. This may be related to the fact that only 2 patients in the sample received sedation, and 5 patients were on mechanical ventilation. None received muscle relaxants. Accordingly, conscious and spontaneously breathing patients consumed more oxygen due to active breathing and higher mobility. In 2 patients receiving propofol for sedation, AEEs were 21.1 and 16.1 kcal/kg/day, respectively. The last patient had grade III obesity (body mass index 41 kg/m^2). This could be a cause of low energy consumption when extrapolated to 1 kg of body weight.

When analyzing energy expenditure using the Harris-Benedict formula, one should consider analysis of basal metabolic rate only. However, metabolic rate increases in stressful situations and, in particular, in case of injury. Motor activity, hyperthermia and injury should be considered [14]. Metabolic coefficients for activity and temperature are described in the literature. However, there are no significant data on the effect of extracorporeal circulation on energy expenditure.

The limitations of this study are small sample size with impossible comparison of patient subpopulations and influence of obesi-

ty or underweight, mechanical ventilation features, sedation, central or peripheral access for ECMO circuit on energy metabolism. In addition, measurements were performed once at different stages of critical illness (3 and 20 days). This does not allow assessing the dynamics of AEE in early and late stages of intensive care.

Conclusion

Indirect calorimetry is feasible in patients undergoing extracorporeal membrane oxygenation, if appropriate equipment is available. Actual energy expenditure in such patients exceeds the recommended 25 kcal/kg/day and basal metabolic rate based on the Harris-Benedict formula. Clear individual differences of energy metabolism in critically ill patients and independent effect of extracorporeal membrane oxygenation on hypermetabolism-hypercatabolism syndrome indicate the need to organize further research in this area.

Author contribution:
Concept and design of the study — Kanshaov N.Z., Leiderman I.N., Marichev A.O.
Collection and analysis of data — Kanshaov N.Z.
Statistical analysis — Kanshaov N.Z.
Writing — Kanshaov N.Z.
Editing — Leiderman I.N.

The authors declare no conflicts of interest.

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