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Resting Energy Expenditure of Patients on Venovenous Extracorporeal Membrane Oxygenation for Adult Respiratory Distress Syndrome: A Pilot Study

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OBJECTIVES: The objectives of this study were to 1) in patients without pulmonary function, determine resting energy expenditure (REE) in venovenous extracorporeal membrane oxygenation (ECMO) acute respiratory distress syndrome (ARDS) patients by paralysis status and 2) determine the threshold tidal volume (TV) associated with meaningful gas exchange as determined by measurable end-tidal carbon dioxide elimination (et$\dot{V}CO_2$).

DESIGN: Retrospective observational study.

SETTING: A tertiary high ECMO volume academic institution.

PATIENTS/SUBJECTS: Ten adult ARDS patients on venovenous ECMO.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: The modified Weir equation, Fick principle, Henderson-Hasselbalch equation, ECMO flow, hemoglobin, and pre and post oxygenator blood gases were used to determine ECMO carbon dioxide production ($\dot{V}CO_2$), ECMO oxygen consumption, and REE. REE values were matched to patients' paralysis status based on medication flowsheets and compared using a paired *t* test. Linear regression was performed to determine the threshold TV normalized to ideal body weight (IBW) associated with measurable ventilator et$\dot{V}CO_2$, above which meaningful ventilation occurs. When lungs were not functioning, patients had significantly lower mean REE when paralyzed (23.4 ± 2.8 kcal/kg/d) than when not paralyzed (29.2 ± 5.8 kcal/kg/d) ($p = 0.02$). Furthermore, mean REE was not similar between patients and varied as much as 1.7 times between patients when paralyzed and as much as 1.4 times when not paralyzed. Linear regression showed that ventilator $\dot{V}CO_2$ was measurable and increased linearly when TV was greater than or equal to 0.7 mL/kg.

CONCLUSIONS: REE is patient-specific and varies significantly with and without patient paralysis. When TV exceeds 0.7 mL/kg IBW, ventilator $\dot{V}CO_2$ increases measurably and must be considered in determining total REE.

KEY WORDS: adult respiratory distress syndrome; physiology; resting energy expenditure; venovenous extracorporeal membrane oxygenation

Critically ill patients often have altered metabolic demands, which places them at risk for over or under feeding, leading to increased mortality and morbidity (1). Resting energy expenditure (REE) calculated through indirect calorimetry (IC) is considered the gold standard method to assess caloric needs of ICU ventilated patients (2). IC devices rely on values of inhaled and exhaled gas concentrations of oxygen and CO_2 as a way of physiologically measuring oxygen consumption and CO_2 production, a proxy of metabolic activity (3), which can then be used to calculate REE (4). However, it is

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logistically challenging to perform IC on a daily basis and clinicians are frequently left to rely on general weight-based or other predictive equations (5), which frequently show poor agreement with actual measured values (6).

Given the increased use of extracorporeal membrane oxygenation (ECMO) (7), especially secondary to acute respiratory distress syndrome (ARDS) due to the ongoing COVID-19 pandemic, adequate nutritional support is especially important for this high-risk population, yet there is a paucity of studies which examine nutritional status while on ECMO (8). ECMO patients represent a unique physiologic population since gas exchange may occur in both the native lung as well as the extracorporeal oxygenator, or only the latter, resulting in two separate components (ventilator and ECMO circuit) that contribute to REE (9).

One prior study used IC to obtain separate ventilator and ECMO contributions to measure total REE, which differed widely from predictive equation derived REE (10) calculations. Additionally, the loss of CO_2 from the membrane lung/oxygenator makes IC much more difficult to perform for the ECMO patient. Clearly, development and validation of accurate and convenient assessment of REE in ECMO patients is needed to optimize nutritional support. In this study, we describe a method to calculate REE in a pilot study of ECMO patients with ARDS directly from the ventilator and ECMO circuits without requiring IC. Second, using continuous waveform technology, we determine when pulmonary contribution to meaningful gas exchange occurs requiring consideration of ventilator contribution to REE.

METHODS

Patients

With prior review and approval from the Johns Hopkins Medicine Institutional Review Boards (IRB Protocol IRB00268338, "REE of patients on ECMO," approved February 15, 2021, with waiver of informed consent), we performed a retrospective analysis of adult ARDS patients ($n = 10$) on venovenous ECMO in our academic cardiovascular surgical ICU. Procedures were followed in accordance with the ethical standards of the Johns Hopkins Medicine Office of Human Subjects Research and with the Helsinki Declaration of 1975. Blood gases were taken from the venous side and arterial side of the oxygenator in the ECMO circuit three times a week (Monday, Wednesday, Friday) allowing for ECMO REE (eREE) determination (see below). Relevant laboratory results over the entire course of venovenous ECMO and additional relevant clinical information, such as ideal body weight (IBW) and paralysis status, were extracted from hospital electronic medical records. Four of these patients had been placed on ventilators (Servo-u Ventilator; Maquet-Getinge, Göteborg, Sweden), which enabled export of ventilatory parameters and waveforms to a virtual care and analytics platform every 2 seconds (Sickbay; Medical Informatics Corp., Houston, TX), that provides real-time ICU data to physicians and also allows storage of these data in a data repository for research purposes. Although this platform allows the export of many different types of ICU waveforms, for this study, four waveforms were extracted: CO_2 minute production, end-tidal CO_2 concentration (mm Hg), expiratory minute volume, and inspired tidal volume (TV). This allowed determination of when pulmonary associated meaningful gas exchange (carbon dioxide production [$\dot{V}CO_2$] > 0) occurred (see below).

Determination of REE and Statistical Analysis

eREE was determined using the modified Weir formula:

$$eREE = 1.44 \times ((3.94 \times eVO_2) + (1.11 \times eVCO_2))$$

Where eVO_2 = AVO_2 difference × 10 × (ECMO Flow in L/min)

= (CaO_2.arterial−CaO_2.venous) × 10 × (ECMO Flow in L/min)

= {[(1.34 × Hemoglobin in g/dL × arterial O_2 saturation in %/100) + (0.003 × PO_2.arterial)]−[(1.34 × Hemoglobin in g/dL × venous O_2 saturation in %/100) + (0.003 × PO_2.venous)]} × 10 × (ECMO Flow in L/min)

And $eVCO_2$ = (pre-oxygenator $[HCO_3^-]^\psi$−post-oxygenator $[HCO_3^-]^\psi$) × 22.4 × ECMO Flow in L/min + (0.003 × PCO_2.venous−PCO_2.arterial) × (ECMO Flow in L/min)

$^\psi$Determined by Henderson-Hasselbalch using measured pH and PCO_2 pre and post oxygenator.

Statistical analysis was performed using STATA (College Station, TX). Linear regression was performed to determine the threshold of TV normalized to IBW that was associated with a measurable increase in ventilator V_{CO_2}. A paired *t* test was then performed to compare the eREE normalized by IBW in patients' lungs that were not participating in gas exchange accordingly based on TV, by paralysis status based on administration of neuromuscular blockers in the medication flowsheets.

RESULTS

Of the 10 ARDS venovenous ECMO patients, 7 patients whose lungs were not participating in ventilation had available eREE values both when paralyzed and when not paralyzed, allowing the use of a paired *t* test for comparison. First, total REE, in this case determined by the ECMO circuit alone as the lungs were not participating in gas exchange, varied widely between patients ranging from 15.5 to 31.7 kcal/kg/d when paralyzed, and from 16.8 to 44.1 kcal/kg/d when not paralyzed. For example, there was a patient who had REE as low as 15.5 kcal/kg when paralyzed, and as high as 44.1 kcal/kg when not paralyzed (2.8 times). Paralyzed patients had significantly lower mean REE, 23.4 ± 2.8 kcal/kg/d ranging from 19.7 to 27.9 kcal/kg/d, compared to when not paralyzed (29.2 ± 5.8 kcal/kg/d) ranging from 21.8 to 36.2 kcal/kg/d ($p = 0.02$) (**Fig. 1**). This corresponds to mean REE values when not paralyzed having a ratio of 0.88 to 1.57 times that of mean REE values when paralyzed. Mean REE varied as much as 1.7 times between patients when paralyzed and as much as 1.4 times when not paralyzed.

Data extraction of ventilatory parameters from the venovenous ECMO courses of four adult ARDS patients yielded 868,799 ventilator V_{CO_2} data points, encompassing approximately 20 patient days. Linear regression demonstrated ventilator V_{CO_2} increased linearly when TV greater than or equal to 0.7 mL/kg (**Fig. 2**).

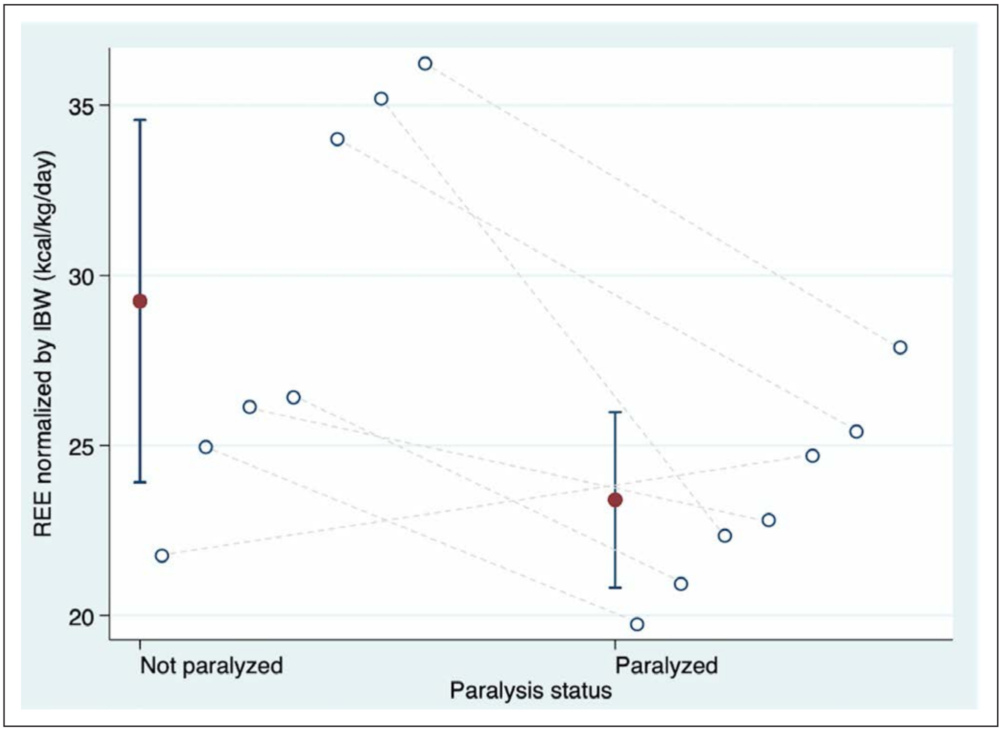

Figure 1. Strip plot of resting energy expenditure (REE) normalized by ideal body weight (IBW) (kcal/kg/d), grouped by paralysis status, when lungs are not functioning.

DISCUSSION

Although IC remains widely considered the gold standard method to assess nutritional status and caloric needs of critically ill ICU patients (2), it can be unnecessarily cumbersome and logistically challenging to perform on a daily basis. In this case series, we describe a method of calculating a patient's REE, available to every ECMO user around the world, applicable to any patient whose lungs are not contributing to gas exchange, that is, when TV is less than 0.7 mL/kg. By knowing ECMO flow, hemoglobin, and pre and post oxygenator blood gases, based on the biochemical basis for REE established by the modified Weir equation, and utilizing the Fick principle and Henderson-Hasselbalch Equation, one can determine a patient's total REE.

Prior to this study, various ICU physicians in our unit had different personal thresholds for acknowledging significant pulmonary gas exchange, with TVs ranging from 0.5 to 2 mL/kg. As a result, their threshold for inclusion of IC for the measurement of total REE varied. In this study, using close to a million V_{CO_2} data points, we established that the TV threshold for meaningful gas exchange is 0.7 mL/kg (Fig. 2).

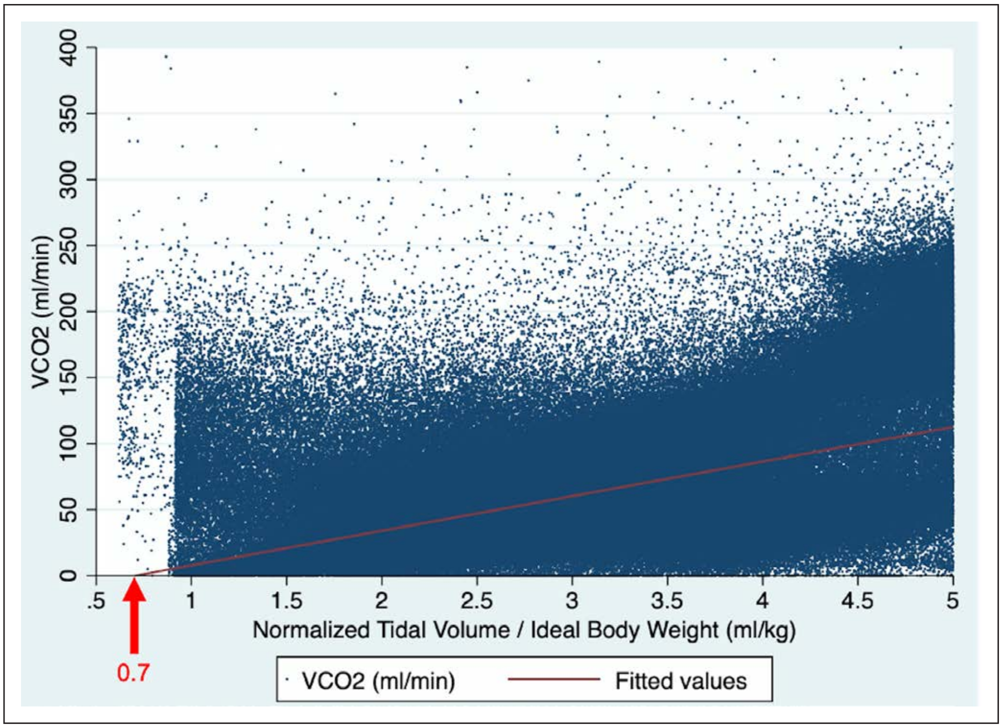

Figure 2. Scatter plot of ventilator carbon dioxide production ($\dot{V}CO_2$) (mL/min) versus tidal volume normalized by ideal body weight (mL/kg) with best fit line by linear regression.

In this present study, REE, normalized by IBW, varied widely patient to patient, and clearly was significantly affected by paralysis status (Fig. 1). While on ECMO, this study shows that direct measurement of REE is easily done and can ensure that patients on venovenous ECMO receive adequate nutrition for recovery while minimizing the morbidity and mortality associated with overfeeding or underfeeding. We hope our proposed method of calculating REE will enable all ICU physicians caring for ECMO patients to more accurately meet their patients' nutritional needs.

A limitation of this study is that the method of calculating individual REEs in this study has not been validated using IC, although this is not one of the objectives of this present study and can be part of a future study.

CONCLUSIONS

REE varies from patient to patient and is significantly lower when patients are paralyzed. When TV is greater than 0.7 mL/kg IBW, ventilator $\dot{V}CO_2$ increases measurably, and the contribution from the ventilator must be considered, in addition to the contribution from the ECMO circuit, in determining total REE.

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APPENDIX

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