Article

External Validation with Accuracy Confounders of VCO\textsubscript{2}-Derived Predicted Energy Expenditure Compared to Resting Energy Expenditure Measured by Indirect Calorimetry in Mechanically Ventilated Children

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Abstract: Optimal energy provision, guided by measured resting energy expenditure (REE) and determined by indirect calorimetry (IC), is fundamental in Intensive Care Units (ICU). Because IC availability is limited, methods to predict REE based on carbon dioxide production (VCO\textsubscript{2}) measurements (REE\textsubscript{VCO2}) alone have been proposed as a surrogate for REE measured by IC (REE\textsubscript{IC}). The study aimed at externally and internally validating the accuracy of the REE\textsubscript{VCO2} as an alternative to REE\textsubscript{IC} in mechanically ventilated children. A ventilator’s integrated gas exchange module (E-COVX) was used to prospectively measure REE\textsubscript{IC} and predict REE\textsubscript{VCO2} on 107 mechanically ventilated children during the first 24 h of admission. The accuracy of the REE\textsubscript{VCO2} compared to REE\textsubscript{IC} was assessed through the calculation of bias and precision, paired median differences, linear regression, and ROC analysis. Accuracy within ±10% of the REE\textsubscript{IC} was deemed acceptable for the REE\textsubscript{VCO2} equation. The calculated REE\textsubscript{VCO2} based on respiratory quotient (RQ) 0.89 resulted in a mean bias of −72.7 kcal/day (95% limits of agreement −321.7 to 176.3 kcal/day) and a high coefficient of variation (174.7%), while 51.4% of the calculations fell outside the ±10% accuracy rate. REE\textsubscript{VCO2} derived from RQ 0.80 or 0.85 did not improve accuracy. Only measured RQ (Beta 0.73, \(p < 0.001\)) and no-recorded neuromuscular blocking agents (Beta −0.13, \(p = 0.044\)) were independently associated with the REE\textsubscript{VCO2} – REE\textsubscript{IC} difference. Among the recorded anthropometric, metabolic, nutrition, or clinical variables, only measured RQ was a strong predictor of REE\textsubscript{VCO2} inaccuracy (\(p < 0.001\)). Cutoffs of RQ = 0.80 predicted 89% of underestimated REE\textsubscript{IC} (sensitivity 0.99; specificity 0.89) and RQ = 0.82 predicted 56% of overestimated REE\textsubscript{IC} (sensitivity of 0.99; specificity 0.56). REE\textsubscript{VCO2} cannot be recommended as an alternative to REE\textsubscript{IC} in mechanically ventilated children, regardless of the metabolic, anthropometric, or clinical status at the time of the evaluation.

Keywords: children; indirect calorimetry; resting energy expenditure; accuracy; critical care; prediction equations

1. Introduction

Indirect calorimetry (IC) is recommended by the American Society for Parenteral and Enteral Nutrition (ASPEN) and the European Society of Paediatric and Neonatal Intensive Care (ESPNIC) to measure resting energy expenditure (REE) and guide optimal energy provision in mechanically ventilated adult [1] and pediatric [2] patients. Indirect calorimetry (IC) is based on the volumetric measurement of oxygen consumption (VO\textsubscript{2}) and
carbon dioxide production (VCO\textsubscript{2}), deriving REE by Weir’s equation [3]. Recent technical developments allow integrated ventilators’ IC modules to measure breath-by-breath resting energy expenditure (REE\textsubscript{IC}) in mechanically ventilated patients [4,5].

Despite recent recommendations, REE\textsubscript{IC} is not measured routinely in most mechanically ventilated patients because of the lack of equipment, cost, and expertise to conduct IC and analyze results, while equations used to predict REE are inaccurate [6,7]. Suboptimal feeding, however, can lead to malnutrition, a longer duration of mechanical ventilation, and increased morbidity and mortality [8].

Novel equations to estimate REE based on VCO\textsubscript{2} (REE\textsubscript{VCO2}) derived from measurements of exhaled gas volume and CO\textsubscript{2} concentrations have been recently proposed as a surrogate for IC in pediatric and adult patients [9,10]. The REE\textsubscript{VCO2} predictive equation assumes a fixed respiratory quotient (RQ) value of (0.85) [11], (0.89) [10], or equal to an estimated RQ from oxidation of energy substrates [12]. However, the variability of RQ might interfere with the accuracy of the REE\textsubscript{VCO2} calculation [9,11].

The purpose of this study is to externally validate the accuracy of the REE\textsubscript{VCO2} and whether it could be considered as an alternative to REE\textsubscript{IC}, using a ventilator’s integrated IC module for both methods. A secondary objective is to identify and internally validate clinical or metabolic factors that might influence the performance of the REE\textsubscript{VCO2} equation in mechanically ventilated children.

2. Materials and Methods

2.1. Study Design

Mechanically ventilated critically ill children consecutively admitted to the academic Pediatric Intensive Care Unit (PICU) at the University Hospital, School of Medicine, University of Crete, Heraklion, from June 2015 through June 2018 were enrolled in the study. The Ethics Committee of the Institutional Review Board approved the study (approval ID14494/2011/9-1-2012). All of the data were de-identified, and the parents or guardians provided informed written consent. The present study was conducted in accordance with the principles of the Declaration of Helsinki (last revised guidelines from 2013), following the International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) standards [13].

Inclusion criteria: Hemodynamically stable, adequately sedated (Ramsey > 3), mechanically ventilated patients with a Fractional Inspired Oxygen (FiO\textsubscript{2}) < 60%, a respiratory rate below 35 breaths-per-minute, and an endotracheal tube (ET) leak below 10% [inspiratory tidal volume (TV\textsubscript{i}) – expiratory tidal volume (TV\textsubscript{e})/inspiratory TV × 100] were eligible for the study [14]. Exclusion criteria: (1) Patients expected to be extubated within 24 h of admission; (2) inborn errors of metabolism or primary endocrine disorders; (3) unexpected interruption of the measurement (destabilization, need for intervention in the ventilation settings, or other).

2.2. Clinical Data

At the time of each metabolic measurement, admission diagnosis, ventilatory settings, blood pressure, heart rate, sedation level by Ramsey scale, and main sedatives and vasoactive agents or inotropes were recorded. The last recorded temperature on a patient’s vital signs flowchart just before the REE measurement was documented. The severity of illness was assessed using the PRISM-III and the PELOD-2 scores [15], and the amount of care was assessed using the Therapeutic Intervention Scoring System (TISS) [16]. The energy intake was calculated from recorded intake of enteral or parenteral nutrition and glucose-containing maintenance fluids. Underfeeding and overfeeding were defined as energy intake of <90% and >110% of measured REE, respectively.

2.3. Anthropometry

The following anthropometric parameters were identified: age, sex, actual weight, ideal weight, height, and body mass index (BMI). The weight was measured using cal-
ibrated electronic bed scales. The ideal weight was defined as the weight for the 50th percentile of the actual height of each patient. The BMI was calculated as kg/m$^2$. The standard deviation scores, known as z-scores, of weight, height, and BMI for sex and age were calculated using WHO and CDC calculators [17]. Malnutrition indices were derived from the BMI for age and sex z-scores obtained at admission. Underweight was defined as a BMI z-score $<-1.644$, normal weight as $-1.644 \leq$ BMI z-score $< 1.036$, overweight as $1.036 \leq$ BMI z-score $< 1.644$, and obesity as BMI z-score $\geq 1.644$.

2.4. Indirect Calorimetry

An integrated gas exchange module (E-COVX) into the ventilator (Carescape R860, GE Healthcare, Milwaukee, WI, USA) was used to measure REE through indirect calorimetry during the ICU’s first 24 h. This module is able to reliably record spirometry and metabolic indices as early as 5 min after suctioning at different modes of ventilation [4,5]. It has no mixing chamber, and the sampling takes place with every breath. It has a fast differential paramagnetic O$_2$ and infrared CO$_2$ analyzer and a pneumotachograph housed in a connector, which measures inspired and expired volumes. In the P-Lite (15–300 mL) or D-Lite (>300 mL) flow sensor, located proximate to the Y-piece to the patient’s ET tube, the flow measurement is based on the pressure drop across a special proprietary turbulent flow restrictor. It uses mathematical integration of flow and time-synchronized continuous gas sampling to provide data. The gas sample is continuously drawn from the connector to the gas analyzer unit of the module. Both O$_2$ and CO$_2$ measures are based on the side-stream principle. E-COVX relies on tidal volume measurement for VO$_2$ calculation. The pneumotachograph derives the tidal volume from the pressure difference across a fixed orifice, potentially influenced, therefore, by acute changes of resistance in the spirometry tubing and undetected leaks in the system. We consistently used a heat- and moisture-exchange filter alone, avoiding heated water bath humidification, followed by regular checks on the spirometry tubing and checks for tidal volume consistency between the module and the ventilator.

The measurements were taken between 9 am and 12 pm when there had been a minimum of 45 min with no major physical activity, such as physiotherapy or dressing change. After an initial 20 min stabilization period, REE was measured for 30 min, during which time there was no interference with the child. The module uses the modified Weir formula (Equation (1)) and displays a 5 min average for REE but can display the 1 min averages with the S/5 Collect 1.0 Software (Datex-Ohmeda, GE Healthcare, Waukesha, WI, USA).

$$\text{REE}_{\text{IC}} \text{ (kcal/day)} = [3.941 \times \text{VO}_2 + 1.106 \times \text{VCO}_2] \times 1440$$  \hspace{1cm} \text{(1)}$$

The steady state was defined as a period of at least 5 min with less than 10% fluctuation in VO$_2$ and VCO$_2$ and less than 5% fluctuation in RQ, which is the VCO$_2$/VO$_2$ ratio. Measurements with RQ outside the physiologic range (>1.3 or <0.67) were excluded.

2.5. VCO$_2$-Derived REE

For the VCO$_2$-derived formula, REE$_{VCO2}$ was calculated using VCO$_2$ values measured by indirect calorimetry by assuming an RQ = 0.89, as has been previously proposed for mechanically ventilated children [10] (Equation (2)). For comparison, we analyzed Equation (2) with an expanded value of 5.534 instead of 5.5 [18].

$$\text{REE}_{VCO2} \text{ (kcal/day)} = 5.5 \times \text{VCO}_2 \text{ (L/min)} \times 1440$$  \hspace{1cm} \text{(2)}$$

The RQ values of 0.85, 0.80, and 0.89, using original equations derived from the modified Weir formula, which have been used in published validation research [19], were also examined (Equation (3)). As a control, we calculated Equation (3) using the IC-derived individual RQ (RQ$_{IC}$) along with the individual VCO$_2$ values, resulting in a VO$_2$ alone REE$_{VCO2}$–REE$_{IC}$ difference (Equation (3)).
REE\text{\textsubscript{VCO2}} (kcal/day) = ((5.5 \times (\text{VCO}_2/0.89 \text{ or } 0.85 \text{ or } 0.80 \text{ or } \text{RQ}_{\text{IC}})) + (1.76 \times \text{VCO}_2) - 26) \quad (3)

Basal metabolism was calculated based on the Schofield equation [20]. Hypometabolism and hypermetabolism were defined as measured REE of <90% and >110% of basal metabolic rate as predicted by Schofield’s equation, respectively [20]. The patients were stratified for subsequent subset analysis according to their nutritional status as per BMI for age and sex z-scores.

2.6. Statistical Analysis

The normality of the distribution was examined using the Shapiro–Wilk test. The descriptive data are reported as means and standard deviation (SD) or median and interquartile range (IQR) in case of skewed distributions or as frequencies and percentages when appropriate. The agreement of REE\text{\textsubscript{VCO2}} with REE\text{\textsubscript{IC}} was assessed through the calculation of bias and precision. Bias was defined as the mean difference between the measurements obtained from REE\text{\textsubscript{VCO2}} and REE\text{\textsubscript{IC}}. Precision was defined by the 95% limits of the agreement, including both systematic (bias) and random error. The paired median differences were also calculated, and relative variability (dispersion) and repeatability were assessed by calculating the coefficient of variation (CV), which is the ratio of the standard deviation to the mean of the population. Clinically significant percentage error (REE\text{\textsubscript{VCO2}}–REE\text{\textsubscript{IC}})/REE\text{\textsubscript{IC}} (%) was considered a difference of ≥±10%. The reliability was assessed by the intraclass correlation coefficient (ICC), calculated using the two-way mixed (Cronbach’s alpha). ICC was interpreted as follows: below 0.50: poor; between 0.50 and 0.75: moderate; between 0.75 and 0.90: good; above 0.90: excellent [21]. A linear regression model (backward method) was adopted to examine whether any of the recorded anthropometric, clinical, and metabolic variables are independently associated with the REE\text{\textsubscript{VCO2}}–REE\text{\textsubscript{IC}} difference. We first used univariate models to test if any of the studied variables were related to the REE\text{\textsubscript{VCO2}}–REE\text{\textsubscript{IC}} difference, with just one explanatory variable at a time; afterward, all variables that had shown a relaxed \( p \)-value of less than or equal to 0.1 were included in the multivariate models. To evaluate factors affecting REE\text{\textsubscript{VCO2}} accuracy, the areas under the receiver operating characteristic curves (AUROCs) for variables significantly predicting REE\text{\textsubscript{VCO2}}–REE\text{\textsubscript{IC}} differences outside the 10% clinically acceptable estimations were calculated. A two-sided significance level of 0.05 was used for statistical inference. Statistical analysis software (version 28, SPSS, Chicago, IL, USA) was used for all analyses, and GraphPad Prism 9.0 (GraphPad Software, Inc., San Diego, CA, USA) was used for the Bland–Altman analyses and illustrations.

3. Results

3.1. Study Population

During the study period, 486 patients were admitted to the PICU, of which 121 were eligible for inclusion (Figure 1). However, 14 patients were not enrolled due to logistic reasons \((n = 10)\), technical reasons \((n = 3)\), or no informed consent \((n = 1)\). The demographic, anthropometric, and clinical characteristics of the enrolled 107 patients are shown in Table 1. Twenty-three patients were underweight (21.5%), 10 were overweight (9.3%), and 27 obese (25.2%). All of the patients received sedation and/or analgesia. The energy received on PICU day 1 was provided by continuous enteral nutrition and non-nutritional energy sources \((n = 102, 95.32\%)\) or parenteral nutrition \((n = 5, 4.67\%)\) by clinicians who were blinded to the methodology of this study.
Figure 1. Flow chart.
Table 1. Demographic and clinical characteristics of the study population.

| Characteristic | Variable | N = 107 |
|----------------|----------|---------|
| **Demographic** |          |         |
| Age (years)    | 9.2 ± 5.3|         |
| Sex (boy/girl) | 75/32 (70.1%/29.9%)|         |
| Body weight (kg) | 35.9 ± 26|         |
| Height (cm)   | 129 ± 29 |         |
| BMI (kg/m²)   | 18.7 ± 6 |         |
| z-score weight for age | 0.33 (−1.5; 1.6) |         |
| z-score height for age | −0.02 (−0.48; 0.66) |         |
| z-score BMI for age | 0.22 (−1.26; 1.68) |         |
| Underweight    | 23 (21.5%)|         |
| Normal BMI     | 47 (43.9%)|         |
| Overweight     | 10 (9.3%) |         |
| Obese          | 27 (25.2%)|         |
| **Reasons for PICU admission** |          |         |
| Respiratory failure | 25 (23.4%) |         |
| Sepsis         | 20 (18.7%)|         |
| Surgical       | 9 (8.4%)  |         |
| Organ failure  | 2 (1.9%)  |         |
| Trauma         | 28 (26.2%)|         |
| Neurologic     | 23 (21.5%)|         |
| **Clinical data** |          |         |
| PRISM score    | 11 (8; 15) |         |
| TISS score     | 43 (36; 47) |         |
| PELOD score    | 7 (3; 19)  |         |
| FiO₂ (%)       | 35 (30; 50) |         |
| pH             | 7.38 (7.34; 7.42) |         |
| pO₂ (mmHg)     | 112 (94; 121) |         |
| pCO₂ (mmHg)    | 35 (33.9; 39.3) |         |
| HCO₃ (mEq/L)   | 22.2 (19.0; 23.9) |         |
| Heart Rate (bpm) | 98 (78; 117) |         |
| Respiratory rate (bpm) | 20 (16; 28) |         |
| Systolic Blood Pressure (mmHg) | 94 (75; 110) |         |
| Body Temperature (°Celsius) | 37.4 (36.7; 38.1) |         |
| Lactate (mg/dL) | 14.1 (6.9; 31) |         |
| Glucose (mg/dL) | 105 (94; 121) |         |
| Albumin (mg/dL) | 3.2 (2.6; 3.6) |         |
| C-Reactive Protein (mg/dL) | 9.7 (2.2; 18) |         |
| Vasoactive agents (yes) (%) | 58 (54.24%) |         |
| Sedatives and/or opioids > 2 (%) | 91 (85%) |         |
| Neuromuscular blocking agents (yes) (%) | 23 (21.5%) |         |
| Length of Stay (days) | 14 (7; 24) |         |
| Mechanical Ventilation (days) | 12 (7; 18) |         |
| Hospital Mortality | 4 (3.7%) |         |
Table 1. Cont.

| Characteristic | Variable | N = 107 |
|----------------|----------|---------|
| **Nutrition**  | Energy intake (kcal/day) | 720 (480; 1000) |
|                | Energy intake/IBW (kcal/kg/day) | 24 (13.2; 42.8) |
|                | Adequate feeding | 38 (35.5%) |
|                | Underfeeding | 50 (46.7%) |
|                | Overfeeding | 19 (17.8%) |

Continuous variables are reported as mean ± SD or median (interquartile range) as appropriate. Discrete variables are reported as the number and proportion (within brackets) of subjects with the characteristic of interest. Abbreviations: BMI = Body Mass Index; PRISM = Pediatric Risk of Mortality; TISS = Therapeutic Intervention Scoring System; PELOD = Pediatric Logistic Organ Dysfunction; IBW = Ideal Body Weight.

3.2. Performance of the REE$_{VCO2}$ Equation

Paired REE$_{VCO2}$ (910 (666; 1389) kcal/day)−REE$_{IC}$ (999 (703; 1416) kcal/day) median differences were significant (−71.01 (−92.9; −49.9), p < 0.001). Although the REE$_{VCO2}$ reliability, as assessed by the ICC, was excellent (Cronbach’s alpha, 0.979, p < 0.001), 51.4% of the calculations fell outside the 10% accuracy rate, especially among underweight (61%) or obese patients (55.6%). The inaccuracy profile varied from underestimation (45.8%) to overestimation (5.6%) (Table 2).

| Variables | N = 107 |
|-----------|---------|
| $VO_2$ (mL/min) | 144.8 (105; 207.5) |
| $VCO_2$ (mL/min) | 115 (84.2; 175.4) |
| Respiratory Quotient | 0.81 (0.75; 0.91) |
| REE$_{IC}$ (kcal/day) | 999 (703; 1416) |
| REE$_{VCO2}$ (kcal/day) | 910.8 (666; 1389) |
| REE$_{IC}$/IBW (kcal/kg/day) | 32.8 (24; 48.6) |
| REE$_{VCO2}$/IBW (kcal/kg/day) | 29.3 (29.3; 44) |
| Mean Bias ± SD (kcal/day) * | −72.73 ± 127 |
| Limits of Agreement (kcal/day) * | −321.7 to 176.3 |
| 95% CI Lower-Upper (kcal/day) * | −92.8 to −49.9 |
| Coefficient of Variation (%) * | 174.7 |
| Median of Differences (95% CI) (kcal/day) # | −71.01 (−92.9; −49.9) |
| p value # | <0.001 |
| Cronbach’s alpha (kcal/day) † | 0.979 (0.970; 0.986) |
| p value † | <0.001 |
| REE$_{VCO2}$ ± 10% of REE$_{IC}$ ** | 52 (48.6%) |
| REE$_{VCO2}$ > 10% of REE$_{IC}$ ** | 6 (5.6%) |
| REE$_{VCO2}$ < 10% of REE$_{IC}$ ** | 49 (45.8%) |
| Normometabolic * | 20 (18.7%) |
Table 2. Cont.

| Variables            | N = 107 |
|----------------------|---------|
| Hypometabolic *      | 63 (58.9%) |
| Hypermetabolic *     | 24 (22.4%) |

Continuous variables are reported as mean ± SD or median (interquartile range) as appropriate. Discrete variables are reported as the number and proportion (within brackets) of subjects with the characteristic of interest. Abbreviations: VO$_2$ = Volumetric Oxygen Consumption; VCO$_2$ = Volumetric Carbon Dioxide Production; REE = Resting Energy Expenditure; IC = Indirect Calorimetry; REE$_{VCO2}$ = REE based on VCO$_2$ measurements alone; REE$_{IC}$ = REE measured by IC; IBW = Ideal Body Weight; SD = Standard Deviation; CI = Confidence Interval.* Bland–Altman; † Hypometabolic, hypermetabolic, and normometabolic are defined as REE$_{VCO2}$ of <90%, >110%, and between 90% and 110% of basal metabolic rate as predicted by Schofield’s equation, respectively [20]. ** Clinically significant percentage error (REE$_{VCO2}$−REE$_{IC}$)/REE$_{IC}$ (%). Statistical significance was considered for $p < 0.05$.

The calculated REE$_{VCO2}$ resulted in a mean bias of −72.7 with a wide dispersion of values as expressed by the 95% limits of agreement (precision) (−321.7 to 176.3 kcal/day) and a high coefficient of variation (174.7%). The mean percentage bias (−6.57 ± 10.4%), 95% limits of agreement (−26.9 to 13.8%), and 95% confidence intervals (−8.6 to −4.6%) are presented in the Bland–Altman plot of Figure 2.

![Bland–Altman plot](image)

**Figure 2.** Bland–Altman plot whereby resting energy expenditure (REE) based on volumetric carbon dioxide production (VCO$_2$) alone is compared to REE measured by IC (REE$_{IC}$) at ICU Day-1. The solid line indicates the percentage of agreement bias (%), and the light shade with the fine dotted lines indicates the limits of agreement (bias ± (1.96 × SD) = precision). Dark shade represents the 95% confidence intervals of the mean (bias).

### 3.3. REE$_{VCO2}$ Using Different RQ Values

The reliability of REE$_{VCO2}$ using different RQ values remained excellent (RQ = 0.89, Cronbach’s alpha 0.980 for RQ = 0.89, 0.981 for RQ = 0.85, and 0.982 for RQ = 0.80, all $p < 0.001$). The median (IQR) of REE$_{VCO2}$ using arbitrary RQ values is presented in Table 3. REE$_{VCO2}$ derived from an RQ of 0.80 had the lowest median difference and bias (−8.7 kcal/day), an accuracy of 57% (within 10% of REE$_{IC}$ values), and the highest dispersion of values (CV 1427%). Equations using an RQ of 0.89 had the highest bias and significant median differences ($p < 0.001$), while accuracy was lower than 50% for all equations using an RQ of 0.85 or 0.89. The control equation using the individual RQ$_{IC}$ values presented the best accuracy (89.7%), but a significant median difference ($p < 0.001$), CV of 266%, and a bias of −38.48 (limits of agreement −239.1; 162.2) kcal/day (Supplementary Materials, Figure S1).
Table 3. Comparison analysis between the VCO\textsubscript{2} derived values and the resting energy expenditure measured by indirect calorimetry.

| REE Estimation            | Equation                                                                 | Median (IQR) | Mean Bias | SD       | Limits of Agreement | Median of Differences | 95\% CI of Differences | Lower | Upper   | CV (%) | p Value   | REE\textsubscript{VCO2} ≤ 10\% of REE\textsubscript{IC} | REE\textsubscript{VCO2} > 10\% of REE\textsubscript{IC} | REE\textsubscript{VCO2} fixed RQ = 0.89 | REE\textsubscript{VCO2} fixed RQ = 0.85 | REE\textsubscript{VCO2} fixed RQ = 0.80 | REE\textsubscript{VCO2} measured RQ by IC |
|---------------------------|--------------------------------------------------------------------------|---------------|-----------|----------|--------------------|-----------------------|------------------------|-------|---------|-------|-----------|---------------------------------------------|---------------------------------------------|------------------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|
| REE\textsubscript{IC} [3] | [3.941 × VO\textsubscript{2} + 1.106 × VCO\textsubscript{2}] × 1440 | 999.0 (703; 1416) |           |          |            |           |            |       |         |       |           |                               |                             |                          |                               |                               |                               |                          |                             |
| REE\textsubscript{VCO2} [10] | 5.5 × VCO\textsubscript{2} (L/min) × 1440 [10] | 910.8 (667; 1399) | −72.73    | 127.0    | −321.7; 176.3 | −71.01 | −92.8; −49.9 | 174.7 | <0.001  | 49 (45.8) | 52 (48.6) | 6 (5.6)                         |                               |                          |                               |                               |                               |                          |                             |
| REE\textsubscript{VCO2} [10] | 5.5 × VCO\textsubscript{2} (L/min) × 1440 [10] | 916.4 (671; 1398) | −66.56    | 126.5    | −314.4; 181.3 | −64.02 | −87.2; −41.8 | 190  | <0.001  | 47 (43.9) | 53 (49.5) | 7 (6.5)                         |                               |                          |                               |                               |                               |                          |                             |
| REE\textsubscript{VCO2, fixed RQ = 0.89} [10] | (0.5 × (VCO\textsubscript{2}/0.89)) + (1.76 × VCO\textsubscript{2}) – 26 | 887.1 (642.5; 1367) | −96.24    | 126.8    | −344.8; 152.3 | −94.38 | −116.6; −73.17 | 131.8 | <0.001  | 58 (54.2) | 46 (43) | 3 (2.8)                        |                               |                          |                               |                               |                               |                          |                             |
| REE\textsubscript{VCO2, fixed RQ = 0.85} [10] | (0.5 × (VCO\textsubscript{2}/0.85)) + (1.76 × VCO\textsubscript{2}) – 26 | 920.5 (667; 1418) | −59.62    | 124.3    | −303.3; 184.1 | −64.73 | −84.62; −41.49 | 208.5 | <0.001  | 46 (43) | 51 (47.7) | 10 (9.3)                       |                               |                          |                               |                               |                               |                          |                             |
| REE\textsubscript{VCO2, fixed RQ = 0.80} [10] | (0.5 × (VCO\textsubscript{2}/0.80)) + (1.76 × VCO\textsubscript{2}) – 26 | 967 (701.1; 1489) | −8.70     | 124.0    | −251; 234.4  | −29.66 | −46.21; 6.47  | 1427 | 0.332  | 21 (19.6) | 61 (57) | 25 (23.4)                     |                               |                          |                               |                               |                               |                          |                             |
| REE\textsubscript{VCO2 measured RQ by IC} [10] | (5.5 × (VCO\textsubscript{2}/RQ\textsubscript{IC})) + (1.76 × VCO\textsubscript{2}) – 26 | 973.5 (686.6; 1442) | −38.48    | 102.4    | −239.1; 162.2 | −24.15 | −26.61; −13.48 | 266  | <0.001  | 9 (8.4) | 96 (89.7) | 2 (1.9)                        |                               |                          |                               |                               |                               |                          |                             |

Continuous variables are reported as mean ± SD or median (interquartile range) as appropriate. Discrete variables are reported as the number and proportion (within brackets) of subjects with the characteristic of interest. Abbreviations: VO\textsubscript{2} = volumetric oxygen consumption; VCO\textsubscript{2} = volumetric carbon dioxide production; REE = Resting Energy Expenditure; IC = Indirect Calorimetry; REE\textsubscript{VCO2} = REE based on VCO\textsubscript{2} measurements alone; REE\textsubscript{IC} = REE measured by IC; RQ\textsubscript{IC} = Respiratory Quotient measured by IC; IQR = interquartile range; SD = Standard Deviation; CI = Confidence Interval; CV = Coefficient of Variation.* Bland–Altman; † Wilcoxon matched pairs signed rank test; * Clinically significant percentage error (REE\textsubscript{VCO2}−REW\textsubscript{IC})/REW\textsubscript{IC} (%). Statistical significance was considered for p < 0.05.
3.4. Factors Affecting the REE\textsubscript{VCO2} Accuracy

There were no significant differences in the ±10% accuracy rates of REE\textsubscript{VCO2} among patients with different nutrition (under- or overfeeding, \( p = 0.57 \)) or metabolic patterns (hypo- or hypermetabolism, \( p = 0.18 \)). Bivariate analysis showed that REE\textsubscript{VCO2}–REE\textsubscript{IC} difference (\( r^2 = 0.35, p = 0.013 \)) and RQ (\( r^2 = 0.32, p = 0.022 \)) correlated with lactate but not with BMI z-scores, age, metabolic status, TISS, PRISM, PELOD, heart or respiratory rate, blood pressure, temperature, blood gases, glucose, albumin, C-reacting protein, or energy intake.

In a linear regression model (stepwise, backward method), only measured RQ (Beta 0.73, \( p < 0.001 \)) and no-recorded neuromuscular blocking agents (Beta \(-0.13, p = 0.044 \)) were independently associated with the REE\textsubscript{VCO2}–REE\textsubscript{IC} difference. The non-linear least squares regression fit of REE\textsubscript{VCO2} predictions expressed as paired REE\textsubscript{VCO2}–REE\textsubscript{IC} differences over the range of recorded RQ values (polynomial (quadratic) equation) is shown in the scatterplot in Figure 3. The number of sedatives, opioids, or vasoactive drugs did not affect the difference between the two methods. Additionally, none of the patients’ demographics, BMI nutrition status (overweight, obesity), diagnostic category, the severity of illness, temperature, heart rate, blood gases, or CRP was independently associated with the REE\textsubscript{VCO2}–REE\textsubscript{IC} difference.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scatterplot.png}
\caption{Scatterplot of non-linear least squares regression fit of resting energy expenditure (REE) based on volumetric carbon dioxide production (VCO\textsubscript{2}) measurements (REE\textsubscript{VCO2}) predictions expressed as paired REE\textsubscript{VCO2}–REE\textsubscript{IC} calculated by indirect calorimetry (IC) (REE\textsubscript{IC}) differences over the range of recorded respiratory quotient (RQ) values (polynomial (quadratic) equation). Analysis of areas under the receiver operating characteristic curves (AUROCs) revealed that cutoffs of RQ = 0.80 predict 89% of REE\textsubscript{VCO2} underestimating REE\textsubscript{IC} (sensitivity 0.99; specificity 0.89) and RQ = 0.82 predict 56% of REE\textsubscript{VCO2} overestimating REE\textsubscript{IC} (sensitivity of 0.99; specificity 0.56) (areas outside the shaded rectangle).

In a ROC analysis, only the measured RQ was a strong predictor of REE\textsubscript{VCO2} \( RQ \leq 0.89 \) inaccuracy, underestimating REE\textsubscript{IC} for more than \( -10\% \) (AUROC 0.991 (95%CI 0.975–1.0), \( p < 0.001 \)) (Table 4).}
The “optimal” cutoff point of RQ for the best sensitivity-specificity combination was calculated by the Youden index (J) and confirmed by the Closest to (0, 1) Criteria (ER) [22]. Cutoffs of RQ = 0.80 reached a sensitivity of 0.99 and specificity of 0.89 for 89% of REE\textsubscript{VCO2 RQ 0.89} values underestimating REE\textsubscript{IC} measurements (Youden index 0.89, predicting 89% of underestimated measurements). The accuracy rates were not affected by other recorded metabolic, anthropometric, or clinical variables at the time of measurements (Figure 4).

Figure 4. An Area Under the Receiver Operating Characteristic Curve (AUROC) for predicting REE\textsubscript{VCO2 RQ 0.89} underestimating REE\textsubscript{IC} for more than −10%. Among various metabolic, demographic, and clinical variables, only the measured RQ was a strong predictor of REE\textsubscript{VCO2 RQ 0.89} inaccuracy (AUROC 0.991 (95%CI 0.975–1.0), p < 0.001). Abbreviations: REE\textsubscript{VCO2 RQ 0.89} = Resting Energy Expenditure (REE) based on volumetric carbon dioxide production (VCO\textsubscript{2}) measurements (REE\textsubscript{VCO2}) using assumed RQ of 0.89; REE\textsubscript{IC} = REE measured by indirect calorimetry (IC).
Regarding the smaller proportion of +10% inaccuracy, measured RQ (AUROC 0.804 (95%CI 0.643–0.966), p = 0.013) and a high PRISM III score (AUROC 0.819 (95%CI 0.646–0.992), p = 0.009) were strong predictors of \( \text{REE}_{\text{VCO2}} \) overestimating \( \text{REE}_{\text{IC}} \) for more than +10% (Table 5).

**Table 5. Area Under the Curve for variables predicting \( \text{REE}_{\text{VCO2}} \) inaccuracy by overestimating \( \text{REE}_{\text{IC}} \) for more than +10%.

| Test Result Variable(s) | Area    | Std. Error * | Asymptotic Sig. ** | Lower Bound | Upper Bound |
|-------------------------|---------|--------------|--------------------|-------------|-------------|
| \( \text{RQ} \)         | 0.804   | 0.082        | 0.013              | 0.643       | 0.966       |
| \( \text{PRISM III} \)  | 0.819   | 0.088        | 0.009              | 0.646       | 0.992       |
| Neuromuscular blocking agents (yes) | 0.569 | 0.128 | 0.573 | 0.319 | 0.819 |

Abbreviations: \( \text{RQ} = \) Respiratory Quotient (measured by IC); \( \text{PRISM} = \) Pediatric Risk of Mortality; * Under the nonparametric assumption; ** Null hypothesis: true area = 0.5.

Cutoffs of \( \text{RQ} = 0.82 \) (sensitivity 0.99, specificity of 0.56, Youden index 0.57) and of \( \text{PRISM II} = 16.5 \) (sensitivity 0.83, specificity 0.85, Youden index 0.68) predicted 56% and 68% of \( \text{REE}_{\text{VCO2}} \) values overestimating \( \text{REE}_{\text{IC}} \) measurements, respectively (Figure 5).

**Figure 5.** An Area Under the Receiver Operating Characteristic Curve (AUROC) for predicting \( \text{REE}_{\text{VCO2}} \) overestimating \( \text{REE}_{\text{IC}} \) for more than +10%. Only the measured RQ (AUROC 0.804 (95%CI 0.643–0.966), p = 0.013) and a high PRISM III score (AUROC 0.819 (95%CI 0.646–0.992), p = 0.009) were strong predictors of \( \text{REE}_{\text{VCO2}} \) inaccuracy.

4. Discussion

In this study, we aimed to externally validate the accuracy of the \( \text{REE}_{\text{VCO2}} \) and internally identify factors that might influence the performance of the \( \text{REE}_{\text{VCO2}} \) in mechanically ventilated children. First, we showed that more than half of the \( \text{REE}_{\text{VCO2}} \) calculations fell outside the 10% accuracy rate compared to the measured \( \text{REE}_{\text{IC}} \). The calculated \( \text{REE}_{\text{VCO2}} \) resulted in a wide dispersion of values as expressed by the extended 95% limits of agreement and a high coefficient of variation. Second, we showed that only RQ and avoidance of neuromuscular blocking agents were independently associated with the \( \text{REE}_{\text{VCO2}} – \text{REE}_{\text{IC}} \) difference. Second, we showed that RQ <0.80 or >0.82 significantly underestimates or overestimates \( \text{REE}_{\text{IC}} \) measurements and that accuracy rates are not affected by other recorded metabolic, anthropometric, or clinical variables. Finally, we demonstrated that the accuracy
of REEVCO2 did not improve using RQ values of 0.80, 0.85, or 0.89. The wide dispersion of the values remaining when we substituted the fixed by the individual RQ recordings disclosed the key role of online measuring VO2 in calculating REE in mechanically ventilated patients. These results indicate that the REEVCO2 predictive equation cannot be recommended as an alternative to measured REEIC in mechanically ventilated children, regardless of the metabolic, anthropometric, or clinical status at the time of the evaluation.

In a cohort of adult ICU patients, the limits of agreement in the Bland–Altman plots (−356 to +314 for REEVCO2_0.85 and −367 to +272 for REEVCO2_FQ derived from Food Quotient) were close to the levels found in our study (−321.7 to +176.3 kcal/day) [12]. This wide range of 95% limits of agreement does not support the findings of an older validation dataset reporting narrow limits of agreement for the REEVCO2 equation [10].

Using a mass spectrometer and the REEVCO2 = 5.534 × VO2 (L/min) × 1440 equation in a cardiac, pediatric cohort, Mouzaki et al. showed that the REEVCO2–REEIC agreement was biased during a 72 h period following cardiopulmonary bypass (mean percentage error 11% ± 7%) [18]. Other studies have also demonstrated a low level of agreement of REEVCO2 vs. REEIC readings (limits of agreement >1000 kcal/day) [19], recommending indirect calorimetry as the method for RQ assessment in critically ill patients [18,19]. In our study, the low ±10% accuracy rates of the recommended [7] (48.6%) or other commonly used [19,23] REEVCO2 equations (43–57%) were worse than those reported in adult studies (61–78%) using different equipment, ventilators, and/or methodology [9,12]. A high accuracy rate of 89% obtained by Rousing using VCO2 derived from the metabolic monitor for both equations was characterized by large variations in minute ventilation, increasing the discrepancy between metabolic production and pulmonary uptake or CO2 excretion [11].

Using individual RQIC and VCO2IC values obtained through IC for both equations, we also recorded a high ±10% accuracy rate (89.7%). However, this is the first time to show the importance of the VO2IC variability in estimating REE of individuals in ICU. Because the time constant for VO2 equilibration is much shorter (2–3 min) than the VCO2 (10–20 min), variations in ventilation will affect the REEIC differently, incorporating the VCO2IC in the equation, compared to the REEVCO2, missing the breath-by-breath metabolic marker VO2IC quick measurements [24]. The wide scattering of VO2IC values in our control group verifies the vulnerability of the REEVCO2 in estimating the patient’s metabolism changes, precluding its use as an alternative to REEIC in mechanically ventilated patients.

Mehta et al. developed a simplified Weir equation, which performed well when validated using a separate group of critically ill children admitted to a second ICU [10]. They used an RQ of 0.89 defined by macronutrient administration, describing a mean percentage bias (limits for agreement) of −0.65% (−14.4 to 13.1%) kcal/day. The RQ of 0.89 was based on a cohort of younger patients with a median age of 2.34 for the derivation and 0.46 years for the validation datasets [10]. Using the same mean RQ of 0.89 in a cohort of neonates and infants of 5.1 months [18], Mouzaki et al. demonstrated a wide dispersion of values, resulting in approximately 50% of all observations falling outside the RQ limits of 0.8 and 1.0 and wide limits of agreement [18]. Using the same proposed equation based on RQ = 0.89, but in an older cohort of patients (mean age 9.2 years), we demonstrated a significantly higher mean percentage bias −6.57 ± 10.4% (−26.9 to 13.8%) kcal/day, with a measured median RQ of 0.81 (IQR 0.75 to 0.91), similar to an RQ of 0.81, previously reported in adult patients [11]. Importantly, we demonstrated that the accuracy of REEVCO2 did not improve using RQ values of 0.80, 0.85, or 0.89. Although the RQ in our study presented a trend for lower recordings in older patients, it also showed a wide spread of values across all age groups. This wide dispersion of values remained, even when we substituted the fixed by the individual RQ recordings, disclosing the key role of measuring VO2 in calculating REE in mechanically ventilated patients. However, the value of RQ, which is the main predictor of the REEVCO2 accuracy, will not be available in clinical practice, leading more than half of the patients to under or overfeeding.

This is the first study prospectively incorporating that measured by the integrated to ventilator gas exchange module (E-COVX®) VCO2 readings in the REEVCO2 predictive
equation, leaving that measured by indirect calorimetry RQ values as the only determinant of the REE\textsubscript{VCO2}−REE\textsubscript{IC} difference. In a retrospective adult study, the REE\textsubscript{VCO2} equation was analyzed using the VCO\textsubscript{2} measured by the Deltatrac\textsuperscript{®} Metabolic Monitor, leaving the assumed RQ = 0.85 as the only determinant of the REE\textsubscript{VCO2} accuracy [12]. Our results agree with those of a previous study, showing that the main determinant of bias of the REE\textsubscript{VCO2} calculations is the RQ, especially among those with an RQ < 0.80 [18]. Except for lactate, we did not find any correlation between RQ and the clinical, metabolic, or nutrition indices. In our study, energy intake was not associated with REE\textsubscript{VCO2} inaccuracy. In accordance with our methodology, Oshima et al. compared REE\textsubscript{VCO2} with REE\textsubscript{IC} with the VO\textsubscript{2}, VCO\textsubscript{2}, and REE measurements obtained exclusively from IC [12]. In contrast to the pediatric REE\textsubscript{VCO2} equations using an RQ of 0.89 [10], they used an RQ of 0.85 or an RQ related to nutritional intake [9]. They confirmed that RQ is neither a reliable indicator of the feeding status nor strongly associated with non-nutritional factors and concluded that REE\textsubscript{VCO2} could not be considered an alternative to REE\textsubscript{IC}. It has also been shown that feeding status is a factor that did not need to be considered in the assessment of RQ variability since no appreciable thermogenic effect of feeding occurs in continuously fed critically ill patients [25], and the RQ is not related to the feeding status or to ventilatory and acid-base disturbance [26]. Importantly, the VCO\textsubscript{2} and VO\textsubscript{2} slopes change between non-survivors and survivors [27], with the VO\textsubscript{2}/lactate ratio being significantly higher in survivors [28]. In accordance with our previous research, this study showed that RQ is highly variable and unpredictable in mechanically ventilated children [29], limiting its validity as an indicator of energy substrate oxidation [22], misleading energy provision targets [30], and enhancing the risk of underfeeding and overfeeding [31]. Using ROC analysis, we detected a bidirectional interference of RQ in predicting REE\textsubscript{VCO2} inaccuracy in mechanically ventilated children since 89% of patients with RQ < 0.80 underestimated REE\textsubscript{IC} by more than 10%, and 57% of those with RQ > 0.82 overestimated REE\textsubscript{IC} by more than 10%.

Although this study’s sample size is small, it is comparable to other single-center studies. Additionally, this is a prospective cross-sectional study, while the timing of the indirect calorimetry measurements reflects the acute only metabolic phase of illness. Although insignificant differences have been previously demonstrated during the critical first week of critical illness [12], other studies showed a pattern of early longitudinal repression of bioenergetics, the persistence of which is associated with poor outcomes [7,22,32]. Although the contribution of the acute-phase endogenously produced energy cannot be measured, the wide range of metabolic alterations, which cannot be accurately predicted, demand the daily use of indirect calorimetry to guide personalized nutrition in mechanically ventilated children to prevent cumulative energy balance excesses and deficits [33]. Along with the non-measured endogenously produced energy and the changing feeding pattern of the first ICU Day, the confirmed unreliability of the RQ as an indicator of the feeding status did not allow us to obtain a reliable RQ derived from Food Quotient.

Another limitation of the study is that the measurements of VCO\textsubscript{2} in the present study were from breath-by-breath indirect calorimetry through an integrated ventilator’s gas exchange module and not a product of a ventilator expiratory CO\textsubscript{2} concentration and volume, as in previous studies [9]. The within-device reliability of the VCO\textsubscript{2} measurements of the E-COVX\textsuperscript{®} has been shown to be 1.5 mL/min at FiO\textsubscript{2} 21–50% [34] with an accuracy rate from 7.2 to −5.2% [14], compared to a ±9% accuracy of the calculated expiratory VCO\textsubscript{2} [12]. Accordingly, it seems that the VCO\textsubscript{2} product calculated by a different ventilator might not improve the accuracy of the indirect calorimetry derived VCO\textsubscript{2} and thus influence the results of this study.

5. Conclusions

The wide limits of agreement and high percentage error suggest that the REE\textsubscript{VCO2} equation has limited clinical utility and that indirect calorimetry remains the gold standard to guide nutrition therapy in mechanically ventilated children. Since the accuracy of
REE\textsubscript{VCO2} may not be improved using various arbitrary or individual RQ values, online VO\textsubscript{2} measurements are critical in accurately calculating REE in mechanically ventilated patients. The predicted equation based on VCO\textsubscript{2} measurements alone cannot be recommended as an alternative to REE\textsubscript{IC}, regardless of the metabolic, anthropometric, or clinical status at the time of the evaluation. A new generation of user-friendly calorimeters, cost-effective, incorporated into ventilators’ hardware and software, are a one-way street to overcome the current limitations in reliably measuring real-time REE in an intensive care setting.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/nu14194211/s1, Figure S1: Bland–Altman plots whereby resting energy expenditure (REE) based on volumetric carbon dioxide production (VCO\textsubscript{2}) measurements (REE\textsubscript{VCO2}) using different RQ values are compared to REE measured by indirect calorimetry (IC) (REE\textsubscript{IC}) at ICU Day-1. Solid lines indicate the bias (kcal/day), and the light shades with the fine dotted lines indicate the limits of agreement (bias ± (1.96 × SD) = precision). Dark shades represent the 95% confidence intervals of the mean (bias). (A) REE\textsubscript{VCO2} RQ 0.89, assuming RQ of 0.89 compared to REE\textsubscript{IC}. (B) REE\textsubscript{VCO2} RQ 0.85, assuming RQ of 0.85 compared to REE\textsubscript{IC}. (C) REE\textsubscript{VCO2} RQ 0.80, assuming RQ of 0.80 compared to REE\textsubscript{IC}. (D) REE\textsubscript{VCO2} RQ IC using individual RQ values calculated by IC compared to REE\textsubscript{IC}.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The datasets generated and analyzed during the current study are not publicly available due the database is very extensive and includes data from other studies complementary to this but are available from the corresponding authors upon reasonable request.

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Conflicts of Interest: The authors declare no conflict of interest.

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