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Accuracy of a simplified equation for energy expenditure based on bedside volumetric carbon dioxide elimination measurement – a two-center study

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Background and Aims

Indirect calorimetry (IC) allows accurate assessment of resting energy expenditure (REE) from measured oxygen consumption (VO_2) and carbon dioxide elimination (VCO_2) (1). IC is recommended in critically ill patients for accurate measurement of REE and to guide energy prescriptions (2, 3). However, IC requires specialized equipment and trained personnel, factors that limit its availability. In multicenter studies, IC was reportedly used in only a minority of centers worldwide (4, 5). Estimates of REE and metabolic state utilizing prediction equations do not agree with measured values (6, 7). Inaccurate energy prescriptions can lead to unintended underfeeding or overfeeding in the critically ill patient (8-10). Suboptimal feeding can lead to adverse consequences such as malnutrition, longer length of stay, longer time to wean from ventilator and increased complications. In a recent multicenter study, we observed significantly higher mortality in mechanically ventilated children that received inadequate (less than 66% prescribed) energy intake during their stay in the PICU (5). A simplified and more readily available method to assess energy expenditure in the pediatric intensive care unit (PICU) to facilitate optimal energy prescription is desirable.

We aimed to examine the accuracy of REE values and metabolic classification of patients by a simplified metabolic equation that uses VCO_2 measurement alone. We hypothesized that a VCO_2 -based REE equation would provide a clinically reliable estimate of REE and would be more accurate compared to standard equations that are currently used to estimate REE in this cohort. Independent VCO_2 measurement capability is now available in most PICUs as

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stand-alone monitors or devices integrated into the mechanical ventilator. If the VCO_2 -REE equation is indeed reliable, then the benefits of metabolic assessment could be extended to a larger population in whom IC is currently not available, and for continuous metabolic measurement during mechanical ventilation.

Methods

Subjects

Children less than 18 years of age who were mechanically ventilated in the multidisciplinary tertiary PICU at 2 academic centers, and in whom IC was performed according to institutional guidelines, were included in the study. Subjects were either on enteral or parenteral nutrition. Continuous enteral feeds or parenteral nutrition was not held for the test. Steady state gas exchange measurements from consecutive IC tests at Boston Children's Hospital (Boston, USA) obtained with the Vmax® Encore (Viasys Healthcare, Loma Linda, CA) were used to derive the simplified metabolic equation that included VCO_2 values only. IC measurements from Sophia Children's Hospital (Rotterdam, Netherlands) obtained with the Deltatrac II® (Datex-Ohmeda, Finland) were used as to test the accuracy of REE obtained by the simplified equation in comparison to the estimated energy expenditure by the Schofield equation. IC tests with respiratory quotient (RQ) outside the physiologic range (>1.3 or <0.67) were excluded. Steady state was defined as a period of at least 5 minutes with less than 10% fluctuation in VO_2 and VCO_2 , and less than 5% fluctuation in respiratory quotient (RQ, which is the ratio of VCO_2 : VO_2) (11).

Equation Derivation

The modified Weir equation was used to generate the simplified equation. The mean RQ from the derivation dataset was determined. The VO_2 in the modified Weir equation was then replaced with VCO_2/RQ , to derive the simplified equation (VCO_2 -REE) that included only the VCO_2 value (12).

Energy Expenditure and Metabolic State Determination by the new equation

Using gas exchange measurements from the validation dataset we compared the accuracy of the simplified equation (VCO_2 -REE) with the estimated energy expenditure (EEE) by Schofield equation in predicting the actual measured REE (MREE) by IC. Further, in order to clearly illustrate the limitations of the RQ assumption and its impact on accuracy of the VCO_2 -REE equation we computed the expected error for a range of RQ values.

To examine the effect of dietary composition information on predicting the MREE, RQ_{macro} (based on the ratio of carbohydrate to fat in the diet) was determined for each subject in the validation set (13). REE was now calculated by substituting RQ_{macro} for RQ in the modified Weir equation and utilizing VCO_2 measurements (VCO_2 - RQ_{macro}). Finally, we examined the difference between RQ_{macro} and actual RQ in relation to energy balance.

Metabolic state for each subject in the validation set was determined using the ratio of MREE measured by IC to EEE by the Schofield equation, which incorporates body weight,

gender and age in the estimate (14, 15). Subjects were classified as hypometabolic when $MREE:REE < 0.9$, normometabolic when $MREE:REE = 0.9-1.1$, or hypermetabolic when $MREE:REE > 1.1$. We then examined the accuracy of metabolic classification of each subject in this dataset, using the $VCO_2-REE:REE$ ratio (i.e., substituting the derived REE from VCO_2 for the measured REE by IC).

Statistical Analysis

Statistical analyses were performed with Prism (v 5.04, GraphPad® Software Inc. La Jolla, CA). Values are expressed as mean \pm standard deviation (SD) or as median and interquartile range (IQR) according to distribution. The Mann-Whitney test was used to test for differences in patient demographics between the derivation and validation datasets. Bland-Altman analysis was used to assess the agreement between estimated (VCO_2-REE , VCO_2-RQ_{macro} and Schofield) and IC measured REE values. Two-by-two contingency tables were constructed for each of hypo-metabolism and hyper-metabolism diagnostic tests. Fisher's exact test, sensitivity, specificity, positive and negative likelihood ratios and odds ratios were calculated in order to assess the performance of the metabolic classification of subjects using VCO_2-REE .

Results

Derivation dataset

Steady state data from 79 cases were included in the analyses. Mean RQ (\pm SD) of the derivation cohort was 0.89 ± 0.09 . Using this mean RQ value, a simplified equation was derived;

a. Modified Weir equation (12)

$$REE(kcal/day) = [3.941(VO_2) + 1.106(VCO_2)] \times 1440$$

Assume RQ = 0.89 (from the derivation dataset) and rearrange for $VO_2 = VCO_2/0.89$

b.

$$\begin{aligned} REE &= [3.941(VCO_2/0.89) + 1.106(VCO_2)] \times 1440 \\ &= [4.428(VCO_2) + 1.106(VCO_2)] \times 1440 \\ &= 5.534(VCO_2) \times 1440 \end{aligned}$$

$$REE(kcal/day) = 5.5 \times VCO_2(L/min) \times 1440.$$

The VCO_2 and RQ_{macro} values were added to the modified Weir equation to derive REE:

$$VCO_2-REE \text{ with } RQ_{macro}(kcal/day) = [3.941(VCO_2/RQ_{macro}) + 1.106(VCO_2)] \times 1440$$

Validation dataset

Steady state data from 94 mechanically ventilated children were included in the validation dataset. Daily median (IQR) energy intake was 54.5 (31.9, 68.5) kcal/kg. Patient demographics and gas exchange values from the 2 datasets are depicted in Table 1. The validation and derivation sets included subjects with significantly different characteristics. Subjects in the validation set were younger, smaller and expended more energy per body weight. The RQ was similar between the groups. The test for agreement (Figure 1) between MREE obtained by the IC using the modified Weir equation (utilizing both VCO_2 and VO_2 values) and the VCO_2 -REE revealed a mean bias (limits of agreement) of -0.65% (-14.4 to 13.1%).

Figure 2 shows the expected error introduced by the VCO_2 -REE equation over a range of actual RQ values. There was no error in predicting MREE when the actual RQ was 0.89 (i.e., matched with the assumed RQ for the equation). For an RQ range of 0.7 to 1.2, the percentage expected error ranged from -20 to $+20\%$ respectively. The proportion of patients who fell within this RQ range was 99.9% in the validation cohort. Further, for an RQ range of 0.79 to 1.02, the expected error ranges from -10 to $+10\%$. This RQ range represents 80.9% of validation subjects.

Median (IQR) value for RQ_{macro} , obtained from dietary information, in the validation dataset was 0.9 (0.85, 0.96). Using the individual RQ_{macro} values for each subject in the modified Weir equation to derive REE, the agreement between MREE and VCO_2 - RQ_{macro} revealed a mean bias (limits) of -2.0% (-42.9 to 38.9%). The difference between actual RQ and RQ_{macro} was inversely related to the ratio of energy intake to measured energy expenditure. (Figure 3)

The agreement between MREE and EEE (Schofield) revealed a mean bias (limits) of 0.09% (-40.5 to 40.7%). Figure 1 shows the Bland Altman plots for agreement between the different methods. The mean bias (limits) for agreement between MREE and a) VCO_2 -REE, b) VCO_2 - RQ_{macro} and c) EEE by Schofield equation were, -0.6 (-14.4 to 13.1), -2.0 (-42.9 to 38.8) and 0.1 (-40.5 to 40.6) respectively. Using VCO_2 -REE (in place of MREE), the overall diagnostic accuracy for metabolic classification in the validation set was 86.2% for hypometabolic and 81.9% for hypermetabolic subjects. Sensitivity, specificity and other results are depicted in Table 2.

Discussion

We have described a VCO_2 -based equation, which was able to predict the measured REE and metabolic state of critically ill children undergoing mechanical ventilation in the PICU. This simplified equation predicted measured REE in the validation dataset with much higher accuracy (narrow limits of agreement) compared to the Schofield equation. Thus, VCO_2 based REE prediction may be a superior alternative to standard equations that are currently used to estimate energy expenditure and are frequently inaccurate. Due to a fixed RQ assumed for the simplified equation, there is inherent error in the prediction when actual RQ is higher or lower than 0.89. However, in over 80% of the subjects in the validation cohort, the difference between actual and predicted REE was $\pm 10\%$. Furthermore, VCO_2 -REE

helped classify patients according to their metabolic state with high sensitivity and specificity. Bedside VCO_2 monitoring is increasingly available in the PICU as devices measuring VCO_2 are incorporated into mechanical ventilators or as stand-alone monitors (16). Therefore, the results of our study indicate a unique opportunity for continuous metabolic assessment in the PICU population.

A reliable VCO_2 based technique could make metabolic assessment available for a large number of mechanically ventilated patients who are currently deprived of this testing in centers without an IC. VCO_2 has been previously used to derive REE in critically ill children with the use of a Douglas bag to collect expired air for VCO_2 measurements (17). This method however is not practical and is typically only feasible in a research setting. The results of our study suggest the possibility of a bedside technique for metabolic assessment based on VCO_2 measurements. With the advent of stand-alone VCO_2 monitors employing infrared technology or modern ventilators incorporating VCO_2 modules, minute-to-minute VCO_2 values will be increasingly available in most PICUs. In steady state conditions, VCO_2 reflects CO_2 production at the cellular level and is dependent on the metabolic activity of the tissues and the composition of the nutrient mixture delivered and utilized for energy metabolism. Any change in minute ventilation significantly alters VCO_2 until a new steady state is reached. For measured VCO_2 to reflect the metabolic production of CO_2 , enough time should be allowed for the body pool of CO_2 to reach equilibrium. Future studies will need to define steady state criteria for VCO_2 values obtained by stand-alone monitors.

An assumed RQ value was essential when attempting to derive REE from VCO_2 alone. It allowed a simplification of the Weir equation where we substituted the VO_2 value by the assumed RQ and measured VCO_2 . Table 3 shows RQ values reported in critically ill infants and children with a variety of illnesses. The mean RQ for this group of studies is 0.87 and a majority of patients had values within a narrow range. Hence, the assumed RQ utilized in the equation reflects the value reported in literature. Furthermore, the mean RQ at the 2 institutions in our study were nearly identical, 0.89. Hence, we used a universal RQ value of 0.89 to derive our simplified equation. Clearly this is an oversimplification and ignores variation in RQ between individual patients. RQ reflects substrate handling, which may be altered during critical illness and actual values may be distinct from the assumed 0.89 in some patients. Figure 2 shows the degree of the error in predicting the MREE of individual patient, based on the deviation of the actual RQ from the assumed RQ. For a majority of the patients in the validation set with RQ ranging from 0.79 to 1.02, this error was approximately 10%.

Since RQ value is dependent on macronutrient composition (see Table 4), knowledge of the fuel partitioning (ratio of CHO to Fat) in the diet might help obtain a value of RQ that is closer to the actual value. This is referred to as the RQ_{macro} or the food quotient (FQ). If we used the RQ_{macro} in the equation and not the preset RQ of 0.89 we found a mean bias for agreement between MREE and VCO_2 -REE of -2.0%, but with wide limits. Subjects with disagreement between the 2 methods demonstrated intake to MREE ratios very low (<0.6) or very high (>1.2), which limits the utility of RQ_{macro} as a surrogate for true RQ. Indeed, RQ_{macro} may not always be accurate in predicting actual RQ as it is impacted by a complex interplay between fuel oxidation and other clinical factors (18). In a previous study, we have

shown that RQ and RQ_{macro} were approximated in less than half the subjects (13). The difference between RQ_{macro} and RQ in the validation set was related to the energy balance (intake compared to MREE) with a higher difference seen in cases with a positive energy balance. Any method that utilizes isolated VCO_2 values to derive REE must also account for the energy equivalents of CO_2 , (energy released/L CO_2 produced; $E_{eq}CO_2$) (19). The $E_{eq}CO_2$ may vary by up to 20% in patients on artificial nutrition. Table 4 shows RQ and energy equivalents values of O_2 and CO_2 for different macronutrients (20). The impact of accurate energy balance and macronutrient composition on REE derived from VCO_2 values must be taken into account and examined in future prospective studies.

Future studies must validate the VCO_2 -REE equation by using a stand-alone VCO_2 monitor against IC-derived REE or a stable isotope technique for REE. Different IC devices were used at the 2 sites in our study. Vmax Encore® and the Deltatrac® have been extensively used for clinical metabolic testing in children. Both centers have a long history of clinical application and published research with these devices. Furthermore, uniform procedures were used for metabolic testing, steady state criteria, data handling and classification of metabolic states. The mean age of subjects in the 2 cohorts was significantly different. However, the application of the equation derived from one dataset and its successful application in another dataset with distinct characteristics is reassuring and speaks to the generalizability of our results.

Conclusion

Accurate assessment of REE and metabolic state is essential to optimize nutrient intake in critically ill patients. A new metabolic equation, using real-time, bedside, steady state VCO_2 measurements, allowed assessment of energy expenditure in mechanically ventilated children. REE derived by this simplified method is superior to standard equations and permits accurate metabolic classification of patients. This equation could be used in mechanically ventilated patients at centers where IC is not available, or as a screening test in centers with limited IC resources. The availability of 24-hour continuous VCO_2 -based assessment would be a significant advantage over the snapshot assessment by IC. Stand-alone VCO_2 monitors are routinely available in most PICUs and can be obtained and maintained at a fraction of the cost of an IC. This method may be appropriate for resource-limited environments, extending the benefits of metabolic testing while limiting expenses and burden on personnel. Further evaluation of this equation with other CO_2 monitoring devices should be conducted.

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detailed composition of fuels. Am J Clin Nutr. 1988 Apr; 47(4):608–28. Epub 1988/04/01. eng. [PubMed: 3281434]

Abbreviations

VCO₂	volumetric carbon dioxide elimination
VO₂	volumetric oxygen consumption
RQ	respiratory quotient
REE	resting energy expenditure

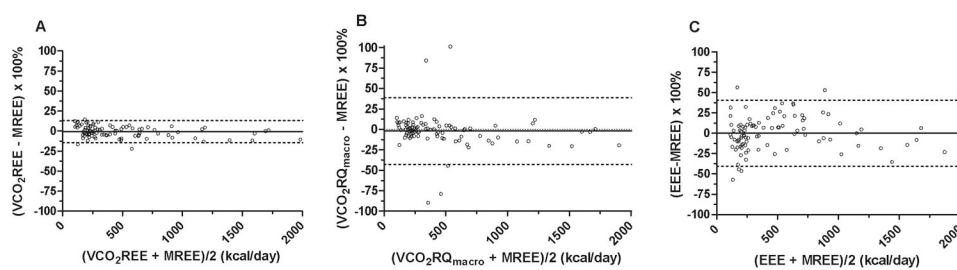


Figure 1.

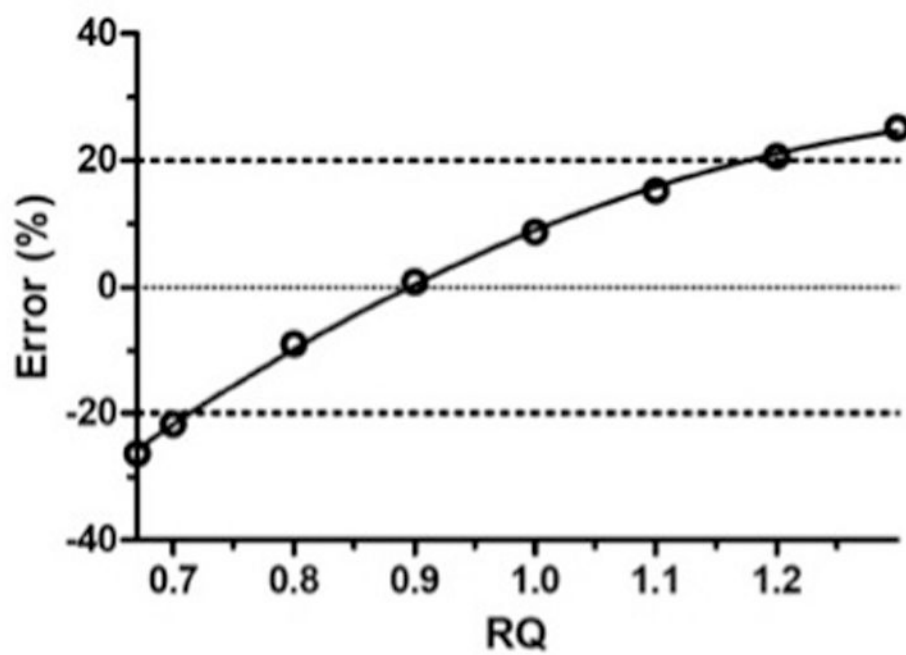


Figure 2.

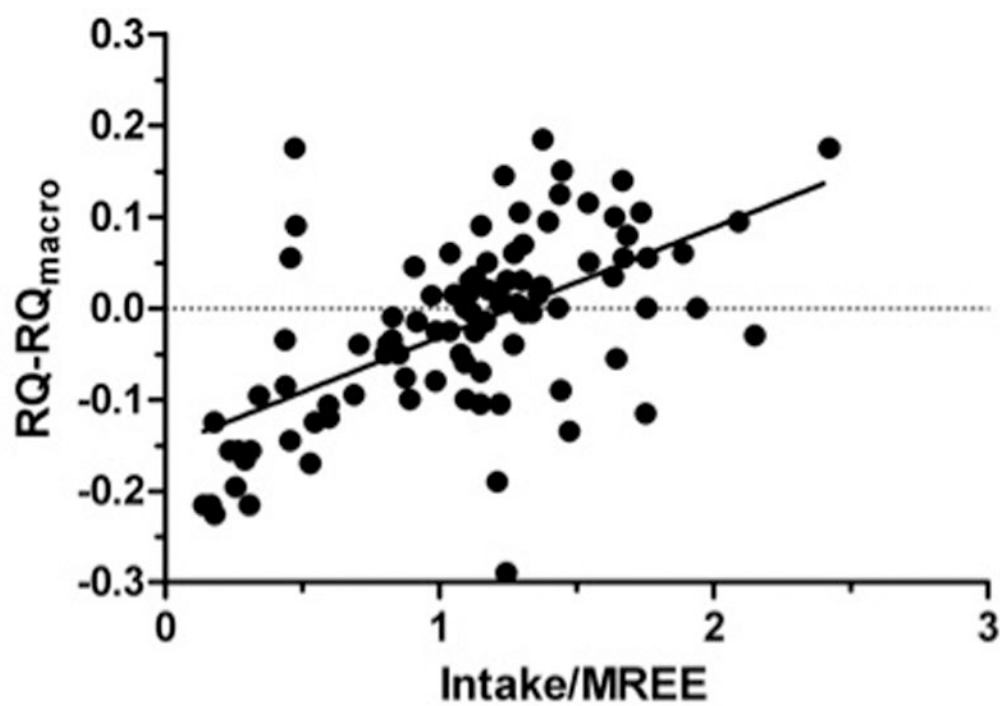


Figure 3.

Table 1

	Derivation		Validation		P
Age (y)	2.34	(7.83)	0.46	(2.13)	<0.05
Height (cm)	74	(48)	61	(36)	<0.05
Weight (kg)	10.9	(21.6)	5.8	(8.5)	<0.05
EEE (kcal/day)	656	(677)	313	(520)	<0.05
MREE (kcal/day)	518	(502)	316	(461)	<0.05
modREE (kcal/day)	505	(484)	305	(378)	<0.05
MREE (kcal/kg/day)	41	(24)	55	(13)	<0.05
modREE (kcal/kg/day)	43	(4)	51	(13)	<0.05
VCO ₂ (ml/kg/min)	5.4	(3.4)	6.4	(1.6)	<0.05
VO ₂ (ml/kg/min)	5.9	(3.6)	7.1	(1.6)	<0.05
RQ	0.89	(0.09)	0.89	(0.10)	ns

Values are expressed as median (interquartile range). Since the data were not normally distributed, the Mann-Whitney U test was utilized to determine difference between the derivation and validation datasets.

RQ = respiratory quotient, VO₂ = volumetric oxygen consumption, VCO₂ = volumetric carbon dioxide elimination, EEE = estimated energy expenditure, MREE = measured energy expenditure, modREE = modified REE from the VCO₂ based equation.

Table 2

Diagnostic accuracy of metabolic state determination by the VCO₂-based REE equation.

	Hypometabolism	Hypermetabolism
Diagnostic accuracy	0.862	0.819
Sensitivity	1.000	0.622
Specificity	0.833	1.000
Positive Predictive Value	0.55	1.00
Negative Predictive Value	1.00	0.74
Positive Likelihood Ratio	6.00	-
Negative Likelihood Ratio	0.00	0.38

* VCO₂ – volumetric carbon dioxide elimination; REE resting energy expenditure

Table 3
Respiratory quotient (RQ) values reported in critically ill infants and children (Total n = 638)

Author	Year	RQ	SD	Setting	n
Mehta (3)	2011	0.94	Range = 0.79 – 1.28	PICU	29
Hulst (22)	2005	NA	NA	PICU	98
Brassoulis (23)	2000	NA	NA	PICU	37
Smallwood (24)	2012	0.9	0.11	PICU	34
Brassoulis (25)	2010	0.89	0.01	PICU	77
Verhoeven (26)	1998	0.89	SEM = 0.01	Ventilator	50
Joosten (27)	1999	0.87	0.07	PICU	36
White (28)	2000	0.85	0.07	Ventilator	100
Vanderkuip (21)	2004	0.88	Range = 0.71 – 1.1	Ventilator	14
Framson (29)	2007	0.83	0.12	PICU	41
Framson (29)	2007	0.83	0.07	PICU	36
Framson (29)	2007	0.88	0.16	PICU	17
Vazquez-Martinez (30)	2004	0.78	0.01	PICU	43
Mehta (10)	2012	0.85	0.06	CICU	26

* Mean RQ for all reported values = 0.87

TABLE 4
Respiratory quotient (RQ) and energy equivalents (O₂ and CO₂) for individual macronutrients

	RQ	Energy equivalents (kcal/L)	
		O ₂	CO ₂
Fat	0.71	4.68	4.60
Protein	0.83	4.66	5.57
Carbohydrate	1.00	5.04	5.05
Alcohol	0.67	4.86	7.23