Clinical Nutrition ESPEN 39 (2020) 137–143

Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

Original article

Resting energy expenditure by indirect calorimetry versus the ventilator-VCO_2 derived method in critically ill patients: The DREAM-VCO_2 prospective comparative study

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ARTICLE INFO

Article history:
Received 8 July 2020
Accepted 10 July 2020

Keywords:
Nutrition
Indirect calorimetry
Respiratory quotient
Resting energy expenditure
Mechanical ventilation

SUMMARY

Background & aims: Both overfeeding and underfeeding of intensive care unit (ICU) patients are associated with worse outcomes. Predictive equations of nutritional requirements, though easily implemented, are highly inaccurate. Ideally, the individual caloric target is based on the frequent assessment of energy expenditure (EE). Indirect calorimetry is considered the gold standard but is not always available. EE estimated by ventilator-derived carbon dioxide consumption ($EEVCO_2$) has been proposed as an alternative to indirect calorimetry, but there is limited evidence to support the use of this method.

Methods: We prospectively studied a cohort of adult critically ill patients requiring mechanical ventilation and artificial nutrition. We aimed to compare the performance of the $EEVCO_2$ with the EE measured by indirect calorimetry through the calculation of bias and precision (accuracy), agreement, reliability and 10% accuracy rates. The effect of including the food quotient (nutrition intake derived respiratory quotient) in contrast to a fixed respiratory quotient (0.86), into the $EEVCO_2$ formula was also evaluated.

Results: In 31 mechanically ventilated patients, a total of 414 paired measurements were obtained. The mean estimated $EEVCO_2$ was 2134 kcal/24 h, and the mean estimated EE by indirect calorimetry was 1623 kcal/24 h, depicting a significant bias of 511 kcal (95% CI 467–560, $p < 0.001$). The precision of $EEVCO_2$ was low (lower and upper limit of agreement −63.1 kcal and 1087. o kcal), the reliability was good (intraclass correlation coefficient 0.613; 95% CI 0.550–0.669, $p < 0.001$) and the 10% accuracy rate was 7.0%. The food quotient was not significantly different from the respiratory quotient (0.870 vs. 0.878), with a small bias of 0.007 (95% CI 0.000–0.015, $p = 0.54$), low precision (lower and upper limit of agreement −0.16 and 0.13), poor reliability (intraclass correlation coefficient 0.148; 95% CI 0.053–0.240, $p = 0.001$) and a 10% accuracy rate of 77.5%. Estimated mean $EEVCO_2$, including the food quotient, was 2120 kcal/24 h, with a significant bias of 496 kcal (95% CI 451–542; $p < 0.001$) and low precision (lower and upper limit of agreement −157.6 kcal and 1170.3 kcal). The reliability with EE estimated by indirect calorimetry was good (intraclass correlation coefficient 0.610, 95% CI 0.550–0.661, $p < 0.001$), and the 10% accuracy rate was 9.2%.

Conclusions: $EEVCO_2$, compared with indirect calorimetry, overestimates actual energy expenditure. Although the reliability is acceptable, bias is significant, and the precision and accuracy rates are unacceptably low when the VCO_2 method is used. Including the food quotient into the $EEVCO_2$ equation does not improve its performance. Predictive equations, although inaccurate, may even predict energy expenditure better compared with the VCO_2-method. Indirect calorimetry remains the gold standard method.

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https://doi.org/10.1016/j.clnesp.2020.07.005
2405-4577/

1. Introduction

Targeting optimal nutrition using energy goals is essential in critically ill patients, as both underfeeding and overfeeding have been associated with increased morbidity and mortality [1]. International guidelines recommend to prescribe calories based on energy expenditure (EE) measured by indirect calorimetry [2]. Due to the pathophysiological response to critical illness, iatrogenic interventions, and differences in body composition, EE is highly variable in and between critically ill patients [3]. Indirect calorimetry is considered the gold standard and can be used to assess EE reliably. However, indirect calorimetry is not available in many hospitals and not feasible in all patients. Even under the conditions of a prospective clinical study indirect calorimetry was effectively performed in only 40% of patients [4].

In the absence of indirect calorimetry, predictive equations have been used to assess EE. However, -most have been developed in specific, non-intensive care unit (ICU), patient populations and are not generalizable to ICU patients [5]. Moreover, multiple validation cohort studies among ICU patients report poor performance when compared with indirect calorimetry [6–8], with the best predictive equations reaching an accuracy of 35–45% [6,7].

Alternative methods in estimating EE have been suggested, including the use of carbon dioxide consumption (VCO_2) measurements made by volumetric capnography, derived from mechanical ventilators ($EEVCO_2$) based on an adjusted version of Weir's equation. Weir's equation defines EE (kcal/day) as (3.941 * VO_2 + 1.1106 * VCO_2) * 1440. However, mechanical ventilators can only measure VCO_2, and not the oxygen consumption (VO_2). Weir's equation is adjusted in order to calculate EE (3.941 * VCO_2/RQ + 1.106 * VCO_2) * 1440. This approach assumes the respiratory quotient (RQ) to be either equal to the food quotient or a fixed value derived from population-based means (0.86) [9–11]. Thus far, only one study of sufficient sample size has compared the $EEVCO_2$ with the EE from indirect calorimetry. This study found $EEVCO_2$ acceptably accurate and more precise than predictive equations of [10].

This study aimed to prospectively compare the performance of the $EEVCO_2$ in adult mechanically ventilated critically ill patients with indirect calorimetry. Also, we analyzed whether the use of the food quotient leads to further improvement of the performance of the $EEVCO_2$ compared with using a fixed RQ of 0.86.

2. Materials & methods

We performed a prospective observational study in critically ill patients receiving artificial nutrition at the mixed medical-surgical adult ICU of Gelderse Vallei Hospital, Ede, The Netherlands between October 29th, 2015, and December 2nd, 2015, and between May 27th, 2016, and August 27th· 2016. Patients were included when they met the following inclusion criteria: adult critically ill patients (age ≥ 18 years) requiring endotracheal intubation and mechanical ventilation and artificial nutrition (either enteral nutrition, parenteral nutrition, or a combination of both).

Exclusion criteria were: expected to be in the ICU for less than 48 h after inclusion, expected to die shortly after ICU admission, continuous renal replacement therapy or intermittent haemodialysis, indirect calorimetry and/or ventilatory assessment of VCO_2 was technically not possible or expected to be inaccurate (i.e. in case of FiO_2 >0.6, PEEP≥12 cmH_2O, body temperature <32 °C or >42 °C, major air leaks through cuffs or around the endotracheal tube, subcutaneous emphysema, tracheal-oesophageal fistula, chest tubes draining air or air leaks around the chest tube, ventilatory modes using bias flow or leak compensation). In addition, patients were not enrolled when informed consent was not provided by the patient or his/her representative or when indirect calorimetry was unfeasible due to logistic reasons.

2.1. Methods of assessing EE

2.1.1. Ventilator derived energy expenditure

For each patient, the mean VCO_2 measured by the mechanical ventilator (Hamilton-S1, Hamilton Medical AG, Bonaduz, Switzerland) during the 10-min measurement of the metabolic monitor was recorded. Because VO_2 is not measured by the mechanical ventilator, an adjusted version of Weir's equation was used to estimate ventilator derived energy expenditure:

$$\text{Energy expenditure} = 3.941 * VCO_2(\text{L/min})/RQ + 1.106 * VCO_2(\text{L/min}) * 1440$$

We assumed the RQ to be either a fixed value of 0.86 [9,10] or equal to the food quotient. The food quotient is the RQ estimated from the oxidation of the administered nutrients or total caloric intake. The calculation of the food quotient was based on the actual intake of all (non)nutritional macronutrients of the patients during the 2 h before the measurements. We assumed RQs of 1.0 for carbohydrates, 0.8 for proteins, 0.7 for fat, and 1.33 for citrate [10–12]. The weighted average RQ was used as the food quotient. An example is provided in supplement 1.

2.1.2. Energy expenditure from indirect calorimetry

Indirect calorimetry was performed with the Quark RMR Metabolic Monitor (Cosmed, Rome, Italy) [13–16]. Before each (series of) measurement(s) the gas- and flowmeter were calibrated, and the heat and moisture exchanging filter was changed according to the manufacturer's instructions. A 10-min measurement was deemed valid when the variability of VCO_2 and VO_2 within the measurement period was less than 10%. The metabolic monitor continuously recorded VCO_2, VO_2, RQ and EE from indirect calorimetry during the measurements.

2.2. Data collection

Several patient characteristics were recorded upon ICU admission including age, gender, weight, height, admission category (medical/surgical), admission diagnosis, Acute Physiology And Chronic Health Evaluation (APACHE)-II score, APACHE-IV score, modified Nutrition Risk in Critically Ill (NUTRIC) score, and sequential organ failure assessment (SOFA) score. Indirect calorimetry was performed in sessions of 10 min six times daily on six consecutive days or until withdrawal from endotracheal mechanical ventilation or death. Ventilator-derived VCO_2 was recorded simultaneously. Ventilator settings, respiratory parameters, and all macronutrient intake during the measurements, including both nutritional and non-nutritional calories, were routinely stored in our patient data management system (PDMS; iMDsoft MetaVision®, Tel Aviv, Israel). Also, patients were followed until hospital discharge. Length of mechanical ventilation, ICU, and hospital stay were recorded as well as ICU and hospital mortality.

2.3. Data analysis and statistical considerations

We performed a primary analysis evaluating the performance of the $EEVCO_2$ compared with the EE measured by indirect calorimetry through the determination of accuracy, agreement, reliability and 10% accuracy rates. In addition, a secondary analysis was performed evaluating the performance of the food quotient compared with the RQ measured by indirect calorimetry, and the performance of the EEVCO_2 including the food quotient compared with the EE measured by indirect calorimetry.

Accuracy was assessed through the calculation of bias and precision. Bias was defined as the mean difference between the measurements obtained from the mechanical ventilator and indirect calorimetry (the gold standard). A bias of <10% of the gold standard was deemed acceptable. Precision was defined as the random error of the measurements, visualized by the limits of agreement in Bland–Altman plots. Agreement is visualized by the complete Bland–Altman plots. Because of repeated measures and clustering of data, a multilevel random-effects model was used to estimate the mean values and the mean difference. Bland–Altman plots, including standard deviations and limits of agreement, were also corrected for repeated measurements.

In addition, reliability was assessed through the calculation of the absolute intraclass correlation coefficient. Reliability was considered poor with an intraclass correlation coefficient <0.40, fair between 0.40 and 0.59, good between 0.60 and 0.74 and excellent between 0.75 and 1.00.

Furthermore, accuracy rates were calculated, defined by the proportion of estimates for which the EEVCO_2 and food quotient predicted paired measurements by indirect calorimetry within 10%.

Additionally, a post-hoc analysis was performed assessing the predictive performance of four commonly used predictive equations. Accuracy, agreement, reliability and accuracy rates were calculated as described above.

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.

A p-value <0.05 was considered statistically significant. IBM SPSS Statistics for Windows, version 25.0 (IBM Corporation, released 2017, Armonk, New York, USA) was used to perform analyses. MedCalc version 19 (MedCalc bv, Ostend, Belgium) was used to create Bland–Altman plots.

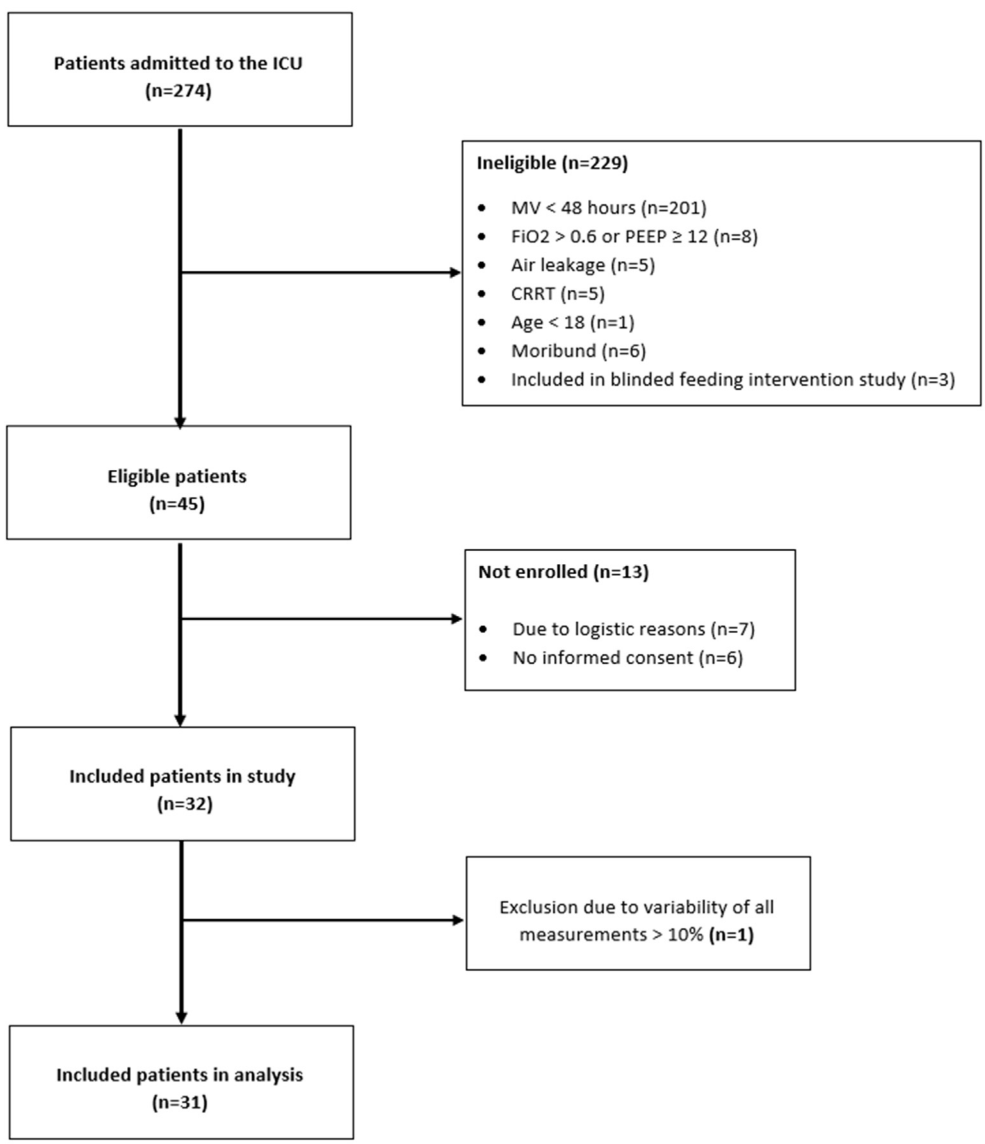

Fig. 1. Flowchart. Abbreviations: ICU: intensive care unit, MV: mechanical ventilation, FiO_2: the fraction of inspired oxygen, PEEP: positive end-expiratory pressure, CRRT: continuous renal replacement therapy.

3. Results

During the study period, 274 patients were admitted to the ICU, of which 45 were eligible for inclusion. However, 13 patients were not enrolled due to logistic reasons (n = 7) or no informed consent (n = 6). One patient was excluded from data analysis due to the variability of >10% of all measurements (Fig. 1). Baseline characteristics, nutritional, and ventilatory parameters are shown in Tables 1 and 2.

3.1. Primary analysis

The estimated mean $EEVCO_2$ was 2134 kcal/24 h compared with an estimated mean EE from indirect calorimetry of 1623 kcal/24 h (the uncorrected mean and median values are depicted in Table 3). This resulted in a significant bias of 511 kcal (95% CI 467–560 kcal; $p < 0.001$). Bias and precision, as visualized by the limits of agreement, are shown in the Bland–Altman plot in Fig. 2. Reliability was good, with an absolute intraclass correlation coefficient of 0.613 (95% CI 0.550–0.669, $p < 0.001$). The 10% accuracy rate was 7.0%, with $EEVCO_2$ overestimating and underestimating the EE in respectively 92.8% and 0.2% of cases.

3.2. Secondary analysis

3.2.1. Performance of the food quotient

The estimated mean food quotient was 0.870 compared with an estimated RQ by indirect calorimetry of 0.878. This resulted in an acceptable bias of 0.007 (95% CI 0.000–0.015, $p = 0.54$). Bias and precision, as visualized by the limits of agreement, are shown in the Bland–Altman plot in Fig. 3A. Because of proportional bias regression-based limits of agreement were also calculated as shown in Fig. 3B [17].

Reliability was poor with an absolute intraclass correlation coefficient of 0.148 (95% CI 0.053–0.240, $p = 0.001$). The 10% accuracy rate was 77.5%, with the food quotient overestimating and underestimating RQ in 13.8% and 8.7% of cases, respectively.

3.2.2. Estimating EE with ventilator derived VCO_2 including the food quotient

The estimated mean $EEVCO_2$, including the food quotient, was 2120 kcal/24 h compared with an estimated mean EE from indirect calorimetry of 1624 kcal/24 h, resulting in a significant bias of 496 kcal (95% 451–542; $p < 0.001$). Bias and precision, as visualized by the limits of agreement, are shown in the Bland–Altman plot in Fig. 3C. Reliability was good, with an absolute intraclass correlation coefficient of 0.610 (95% CI 0.550–0.661, $p < 0.001$). The 10% accuracy rate was 9.2%, with $EEVCO_2$ including the food quotient overestimating and underestimating the EE in respectively 90.6% and 0.2% of cases.

3.2.3. Performance of predictive equations

In a post-hoc analysis we evaluated the performance of four commonly used predictive equations for EE: The World Health Organization and Food and Agriculture Organization (WHO/FAO) [18], Penn State [19], Harris-Benedict [20] and the American College of Chest Physicians (ACCP) [21]. The results are shown in supplement 2.

4. Discussion

We prospectively compared the performance of the $EEVCO_2$ with the EE measured by indirect calorimetry, using 414 paired measurements among 31 adult critically ill patients. The performance of the $EEVCO_2$ in this study was poor, shown by a large bias of 511 kcal and a low 10% accuracy rate of 7.0%. Reliability between $EEVCO_2$ and EE by indirect calorimetry was good, suggesting that there may be a systematic error causing the $EEVCO_2$ to be significantly higher. However, precision was low, reducing the accuracy of the $EEVCO_2$ regardless of whether a systematic error could be corrected for or not.

Two previous prospective studies have compared the $EEVCO_2$ with the EE measured by indirect calorimetry and found

Table 1
Baseline characteristics.

Characteristics	Data
Number of patients	31
Male, n (%)	18 (58.1)
Female, n (%)	13 (41.9)
Age, year, median (IQR)	69 (55–79)
Height, cm, (mean ± SD)	172.8 (10.9)
Weight, kg, median (IQR)	84 (75–100)
BMI, kg/m^2, median (IQR)	27.9 (25.9–32.4)
APACHE II score, mean (±SD)	19.2 (7.8)
SOFA score, mean (±SD)	5.3 (2.0)
ICU admission diagnosis, n (%)	
Sepsis	11 (35.5)
Respiratory insufficiency	10 (32.3)
Cardiovascular	4 (12.9)
Post-surgery	3 (9.7)
Endocrine/Metabolic	1 (3.2)
Neurologic	1 (3.2)
Post-cardiac arrest	1 (3.2)
Length of ICU stay, days, median (IQR)	13 (8–22)
Length of mechanical ventilation, days, median (IQR)	7.8 (3.9–16.3)
Length of stay hospital, days, median (IQR)	22 (14–41)
ICU mortality, n (%)	3 (9.7)
Hospital mortality, n (%)	4 (13.0)
NUTRIC score on admission (mean ± SD)	6.1 ± 2.1

IQR = interquartile range; SD = standard deviation; BMI = body mass index; APACHE = Acute Physiology And Chronic Health Evaluation; SOFA = Sequential Organ Failure Assesment; ICU = intensive care unit; NUTRIC score = Nutrition Risk in Critically ill score.

Table 2
Clinical, nutritional and ventilatory characteristics during measurements.

Measurements, n	414
Clinical characteristics	
ICU day of evaluation, days, median (IQR)	4.3 (2.2–9.2)
Body temperature, °C, median (IQR)	37.5 (37.0–37.9)
Heart rate, beats/min, median (IQR)	88 (78–103)
Vasopressor use, n (%)	28 (35.4)
Nutritional characteristics	
Type of nutrition, n (%)	
Enteral, n (%)	75 (94.9)
Parenteral, n (%)	2 (2.5)
Combination enteral and parenteral, n (%)	2 (2.5)
Non-nutritional energy intake, kcal/24 h, median (IQR)	108 (0–264)
Glucose intake, kcal/24 h, median (IQR)	48 (0–204)
Propofol intake, kcal/24 h, median (IQR)	0 (0–0)
Citrate intake, kcal/24 h, median (IQR)	0 (0–0)
Nutritional energy intake, kcal/24 h, median (IQR)	1524 (876–1818)
Carbohydrate intake, kcal/24 h, median (IQR)	600 (348–780)
Protein intake, kcal/24 h, median (IQR)	336 (204–480)
Fat intake, kcal/24 h, median (IQR)	396 (228–516)
Total nutritional intake, kcal/24 h, median (IQR)	1572 (1020–2016)
Ventilator Settings	
PEEP, cmH_2O, median (IQR)	8 (6–8)
FiO_2, %, median (IQR)	34 (30–39)
Minute volume, L/min, median (IQR)	10.2 (8.2–12.0)
Respiratory rate, breaths/min, median (IQR)	21 (16–26)
Tidal volume, ml, median (IQR)	494 (427–602)
$ETCO_2$, kPa, mean (±SD)	5.7 (±0.72)

ICU = intensive care unit; IQR = interquartile range; PEEP = positive end-expiratory pressure; FiO2 = fraction of inspired oxygen; ETCO2 = end-tidal carbon dioxide; SD = standard deviation.

Table 3
Energy expenditure, VCO_2, VO_2 and respiratory quotient.

	mean ± SD	median (IQR)
VCO_2 (mL/min)		
Calorimetry		193 (166–218)
Ventilator		249 (210–273)
VO_2 (mL/min)		
Calorimetry		220 (195–255)
Respiratory quotient		
Calorimetry	0.8676 ± 0.0657	
Food quotient		0.8691 (0.8546 –0.8871)
Energy expenditure (kcal/24 h)		
Calorimetry		1544 (1359–1778)
VCO2- and food quotient-derived		1967 (1705–2268)
VCO2 and respiratory quotient 0.86		2035 (1724–2239)

VCO_2 = carbon dioxide consumption; VO_2 = oxygen consumption; SD = standard deviation; IQR = interquartile range; The median energy expenditure and median food quotient, without correction for repeated measures, are reported in this table in addition to the estimated mean energy expenditure and estimated mean food quotient in the results section.

significantly higher 10% accuracy rates of 61% and 89% and smaller biases, but one of these studies [9] had a small sample size of only 18 measurements. $EEVCO_2$ was also found to be more precise in one study compared with our results [10], but not reported in the other study [9]. Reliability was not reported in either study [9,10].

The significant bias and low 10% accuracy rates in our study are either due to the inaccuracy of the VCO_2 measurements by the ventilator, the RQ estimation or inaccuracy of the Quark RMR metabolic monitor. The inaccuracy of the VCO_2 derived from the ventilator can be due to calibration errors, rapid or irregular breathing, and patient-ventilator dyssynchrony. Inaccuracy of the Quark RMR metabolic monitor may also be due to calibration errors or a large variability (>10%) in VCO_2 and VO_2 during the measurement. The differences in accuracy rates and biases between the studies may be explained by the use and calibration of different mechanical ventilators and metabolic monitors. The higher precision may be explained by the differences in duration of the measurements, which was 24 h in the study by Stapel and coworkers and 10 min in our study [10].

In addition, one retrospective study compared $EEVCO_2$ derived from the mechanical ventilator with the EE from indirect calorimetry and found a 5% accuracy of 11–18% and 15% accuracy of 37–43% depending on the value of the fixed RQ that was used (between 0.80 and 0.89) [22].

4.1. Use of the food quotient as a substitute of RQ

We found a very poor correlation between the food quotient and the RQ, as shown by the intraclass correlation coefficient of 0.148 (95% CI 0.053–0.240, $p = 0.001$). Food quotient is the RQ estimated from the oxidation of the administered nutrients or total caloric intake; therefore, only the exogenous energy sources are taken into account. A possible explanation for our results is that endogenous substrate utilization accounts for a large part of energy expenditure in the early phase of critical illness and cannot be estimated by nutritional intake [23]. Our findings are in line with previous studies reporting no correlation between the food quotient and RQ, nor improvement of the performance of the $EEVCO_2$ when the food quotient is used instead of a fixed RQ value [10,24].

4.2. Strengths & weaknesses

Although the study population was small, a large amount of paired repeated measurements could be analyzed in this study, improving the overall statistical power. Multiple aspects of $EEVCO_2$ were analyzed, including bias, precision, 10% accuracy rates, and reliability, providing a complete picture of its performance.

Our study has several limitations. A steady-state, whereby there is less than 10% variation in oxygen consumption and CO_2 production over a 5-min interval, was not possible in a certain amount of measurements, leading to the exclusion of multiple measurements from the analysis. A second limitation is the generalizability of the study as only one type of mechanical ventilator and one type of indirect calorimeter were used.

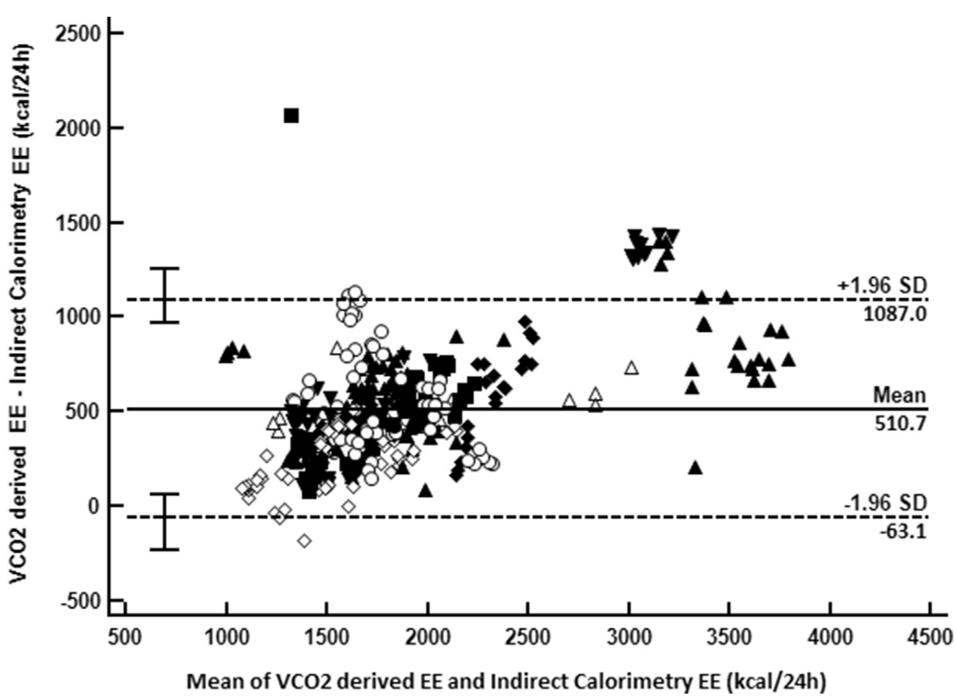

Fig. 2. Bland-Altman plot of $EEVCO_2$ and EE by IC. Similar symbols indicate separate measurements in the same patient. Abbreviations: $EEVCO_2$: energy expenditure calculated with ventilator-derived carbon dioxide production, EE: energy expenditure, IC: indirect calorimetry, SD: standard deviation, kcal: kilocalories.

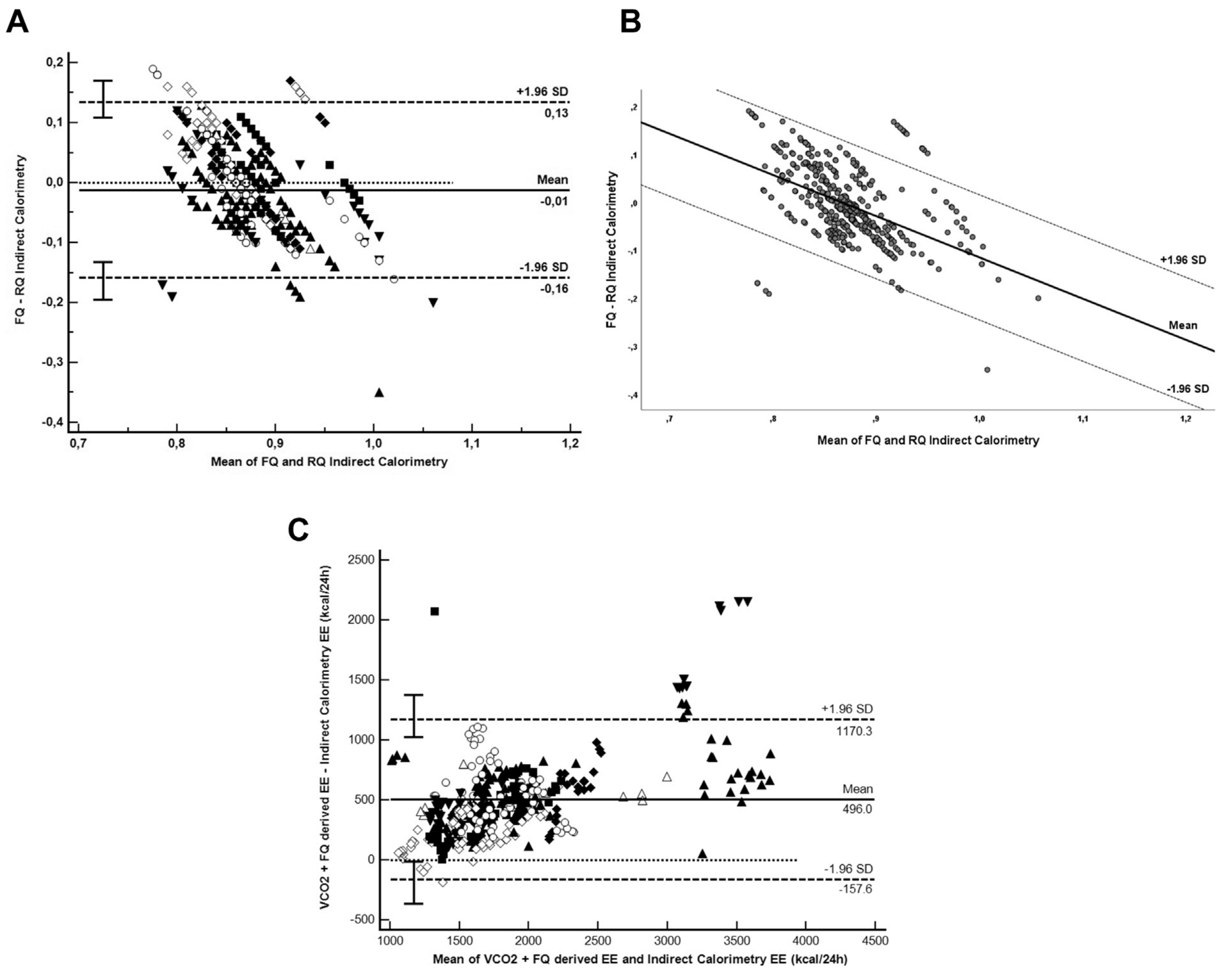

Fig. 3. A: Bland-Altman plot of FQ and RQ by IC. B: Bland-Altman plot of FQ and RQ by IC with regression based limits of agreement. C: Bland-Altman plot of $EEVCO_2$ adjusted for FQ and EE by IC. Similar symbols indicate separate measurements in the same patient. Abbreviations: RQ: respiratory quotient, IC: indirect calorimetry, $EEVCO_2$: energy expenditure calculated with ventilator-derived carbon dioxide production, EE: energy expenditure, IC: indirect calorimetry, SD: standard deviation, FQ: food quotient.

4.3. Clinical implications

Based on our results, we cannot recommend $EEVCO_2$ as a substitute for EE measured by indirect calorimetry. $EEVCO_2$ may over- or underestimate EE in a large proportion of patients, and when nutritional goals are based on this, it may inflict harm. In addition, the food quotient should not be used as a substitute for the RQ as they are not correlated in critically ill patients.

When indirect calorimetry is not feasible or available, alternatives should be used to estimate EE. In patients with pulmonary artery catheters, VCO_2 and VO_2 can be measured and used to calculate EE, and this is, however, a select population. The performance of the $EEVCO_2$ may be increased with higher accuracy of (V) CO_2 detection and analysis in mechanical ventilators as well as a standard calibration of the mechanical ventilators with indirect calorimeters. Predictive equations are available but not accurate. New techniques, including isotopic CO_2 breath measurement and wearable bracelets and waistbelts are being developed, but are not available yet [25].

5. Conclusions

EE VCO_2, compared with indirect calorimetry, overestimates actual energy expenditure. Although reliability is acceptable, bias is significant, and precision and the accuracy rates are unacceptably low when the VCO_2 method is used. Including food quotient into the $EEVCO_2$ equation does not improve the accuracy nor the agreement of the $EEVCO_2$. Predictive equations, although inaccurate, may even predict energy expenditure better compared with the VCO_2-method. Indirect calorimetry remains the gold standard method.

Authorship contribution

Dr. Van Zanten had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and designing: Koekkoek, Xiaochen, Van Zanten.

Acquisition of data: Koekkoek, Xiaochen.

Statistical analysis and interpretation of data: Koekkoek, Xiaochen, Van Zanten.

Drafting the manuscript: Koekkoek.

Critical revision of the manuscript for important intellectual content: Koekkoek, Van Zanten, Van Dijk.

Administrative, technical or material support: Xiaochen, Koekkoek, Van Zanten.

Study supervision: Koekkoek, Van Zanten.

Funding sources

There was no funding source for this work.

Declaration of competing interest

Arthur van Zanten reported that he had received honoraria for advisory board meetings, lectures, and travel expenses from Amomed, Baxter, Danone-Nutricia, Dim-3, Fresenius Kabi, Lyric, Mermaid and Nestle -Novartis. Inclusion fees for patients in nutrition trials were paid to the local ICU research foundation. The remaining authors have disclosed that they do not have any conflicts of interest.

Acknowledgments

The authors wish to thank Linda M. Peelen (epidemiologist, Julius Centre, UMC Utrecht, The Netherlands) for her support with statistical analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2020.07.005.

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