



Original article

Indirect calorimetry in critically ill mechanically ventilated patients: Comparison of E-sCOVX with the deltatrac



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SUMMARY

Background & aims: Indirect calorimetry is recommended to measure energy expenditure (EE) in critically ill, mechanically ventilated patients. The most validated system, the Deltatrac® (Datex-Ohmeda, Helsinki, Finland) is no longer in production. We tested the agreement of a new breath-by-breath metabolic monitor E-sCOVX® (GE healthcare, Helsinki, Finland), with the Deltatrac. We also compared the performance of the E-sCOVX to commonly used predictive equations.

Methods: We included mechanically ventilated patients eligible to undergo indirect calorimetry. After a stabilization period, EE was measured simultaneously with the Deltatrac and the E-sCOVX for 2 h. Agreement and precision of the E-sCOVX was tested by determining bias, limits of agreement and agreement rates compared to the Deltatrac. Performance of the E-sCOVX was also compared to four predictive equations: the 25 kcal/kg, Penn State University 2003b, Faisy, and Harris–Benedict equation.

Results: We performed 29 measurements in 16 patients. Mean EE-Deltatrac was 1942 ± 274 kcal/day, and mean EE-E-sCOVX was 2177 ± 319 kcal/day ($p < 0.001$). E-sCOVX overestimated EE with a bias of 235 ± 149 kcal/day, being 12.1% of EE-Deltatrac. Limits of agreement were -63 to $+532$ kcal/day. The 10% and 15% agreement rates of EE-E-sCOVX compared to the Deltatrac were 34% and 72% respectively. The bias of E-sCOVX was lower than the bias of the 25 kcal/kg-equation, but higher than bias of the other equations. Agreement rates for E-sCOVX were similar to the equations. The Faisy-equation had the highest 15% agreement rate.

Conclusion: The E-sCOVX metabolic monitor is not accurate in estimating EE in critically ill mechanically ventilated patients when compared to the Deltatrac, the present reference method. The E-sCOVX overestimates EE with a bias and precision that are clinically unacceptable.

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1. Introduction

Assessment of energy expenditure (EE) is important to guide nutrition in critically ill patients. The most accurate method to measure EE in mechanically ventilated patients, is by indirect calorimetry [1]. Indirect calorimetry measures oxygen consumption (VO_2) and carbon dioxide production (VCO_2), and EE is calculated using the Weir Formula [2]. The Deltatrac® metabolic monitor (Datex, Helsinki, Finland) is considered as gold standard indirect

calorimeter in mechanically ventilated patients. It was clinically validated in this patient population in the mid-nineties and has been extensively used since [3]. Unfortunately, its production has ceased and support on existing devices has recently stopped. This leaves clinicians and researchers interested in pulmonary gas exchange and metabolic monitoring resorting to alternative devices. In recent years, several new devices have been developed. These devices use breath-by-breath analysis of pulmonary gas exchange and VO_2 and VCO_2 . However, their accuracy, especially in critically ill mechanically ventilated patients is not yet established [4–7]. Extensive validation in this specific patient group is necessary, since over- or underestimation can lead to harmful over- or underfeeding.

The E-sCOVX metabolic monitor (GE healthcare, Helsinki, Finland) is a relatively new, compact, easy to use breath-by-breath

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device that can be integrated in the mechanical ventilator module or can be used as a stand-alone monitor. Accuracy was good when tested *in vitro* and in the non-critically ill [8–10]. In a previous study by Sundstrom-Rehal et al., the agreement of E-sCOVX and Quark RMR (Cosmed, Rome, Italy), with the Deltatrac was tested in mechanically ventilated patients. Both devices overestimated EE to a clinically relevant and unacceptable level. During the writing stage of the article, the authors discovered that the mechanically ventilators they used in the study do not have bias flow, while the E-sCOVX assumes a certain inspiratory dead space caused by continuous bias flow. They discussed that the absence of bias flow in their ventilators may have induced overestimation of EE because of interference with the breath-by-breath analysis [5]. Furthermore, they performed 20-min measurements, which may be too short to reach a stable metabolic resting state. Therefore, a new validation study was necessary to determine the accuracy of E-sCOVX in critically ill, mechanically ventilated patients.

The aim of the present study was to test the agreement of the E-sCOVX with the gold standard method up to now (Deltatrac) in critically ill mechanically ventilated patients, in the presence of bias flow and during longer measurement periods.

The secondary aim was to compare the performance of E-sCOVX to commonly used predictive equations.

2. Methods

This was a prospective cohort study performed over a two-month period in the mixed intensive care unit of the VU University medical center in Amsterdam, the Netherlands. Patients who were mechanically ventilated for more than 24 h, and able to undergo indirect calorimetry were eligible. Patients were excluded if they were hemodynamically and/or respiratory unstable, or failed to meet accuracy criteria for indirect calorimetry; being a fraction of inspired oxygen of ≥ 0.6 , air leakage, a positive end expiratory pressure of ≥ 15 cm H₂O. Also patients with a respiratory rate above 35 per minute were excluded because, according to the manufacturer of the E-sCOVX, a respiratory rate below 35/min is required to ensure its accuracy. Patients could be measured more than once, provided that the interval between measurements was at least 24 h.

2.1. Ethical statement

Indirect calorimetry is standard in our intensive care unit, and we used coded patient data. Therefore, the medical ethics committee of our hospital waived the need for written informed consent (METC-201379).

Deltatrac and E-sCOVX measurements were performed simultaneously (see Fig. 1). After a 5-min stabilization period, the measurements were performed over two hours. Minute-to-minute readings of VO₂, VCO₂, RQ and EE by both devices were recorded and averaged. During temporary disconnection from the ventilator (i.e. during suctioning and nebulizing), the Deltatrac measurement was paused and restarted after equilibration. The corresponding E-sCOVX values were discarded.

Prior to this study an alcohol-burning test was performed to test the gas sensors of the Deltatrac, and to calibrate the constant flow generator. Results were good. Prior to each measurement the Deltatrac was warmed up and calibrated according to the manufacturer's instruction.

In our intensive care unit we use SERVO-i mechanical ventilators (Maquet, Rastatt, Germany), which have a standard bias flow of 2 L/minute. This bias flow facilitates the detection of a breathing effort by the patient, and thereby improves synchronization of the ventilator to the patient.

Deltatrac II MBM -200 metabolic monitor (Datex, Helsinki, Finland):

The device is connected to the expiration port of the ventilator. All the expiratory gas is collected in the mixing chamber and drawn through the fixed flow generator that entrains air at a total constant flow rate. Sampling takes place every minute. The inspired gas is sampled to measure the FiO₂ (see Fig. 1). The oxygen content of the inspired and expired air is measured with a paramagnetic field and CO₂ content with an infrared CO₂ sensor. Volumetric measurements are made by the constant flow air dilution system that measures the exhaled gas volume. Inspiratory volumes are calculated using the Haldane transformation.

2.2. E-sCOVX

A connector with gas sampling ports and a flow sensor (D-lite®) is connected between the endotracheal tube and the ventilator tubing. The gas module samples continuously 120 ml/min of gas side stream. It has a paramagnetic sensor that measures the O₂ content, and an infrared sensor to measure the CO₂ content (see Fig. 1). The flow measurement is based on the pressure drop across a turbulent flow restrictor. As a result of the side stream principle, the measurement of gas concentrations and flow are not simultaneous. The flow signal is recorded with almost no delay (<10 ms), while it takes about 1.5 s for the gas to travel through the sample line to the module where the O₂ and CO₂ concentrations are measured. This transport time delay is not constant. The module synchronizes the flow measurement with the gas concentrations. Additionally, the Haldane transformation is applied to avoid the need of absolute accuracy of the volume measurements.

2.3. Predictive equations

Performance of the E-sCOVX was also compared to frequently used predictive equations: The ACCP-25 kcal/kg-equation [11], the PSU 2003b-equation [12], the Faisy-equation [13] and the Harris Benedict-equation multiplied by a stress factor of 1.15 [14]. This stress factor is based on an earlier study that showed the lowest bias for HB+15% in our Intensive Care unit (ICU) population [15].

2.4. Statistical analysis

Descriptive data are reported as mean (standard deviation (SD)), median (25th–75th percentile), or number (percentage) where appropriate. Continuous variables were compared with the unpaired T-test or Mann–Whitney U test as appropriate, and proportions by the Chi square test. Correlations were calculated using Pearson's test and strength of correlation was expressed as *r*. The agreement between E-sCOVX and Deltatrac was assessed by determining bias and precision. The bias was calculated as the mean difference of EE-E-sCOVX and the EE-Deltatrac. Precision was quantified as the limits of agreement (bias \pm 2SD), and Bland–Altman plots were constructed to graphically represent bias and precision [16]. To quantify agreement, the percentage error (PE) of the limits of agreement, as compared with the population mean, was calculated as was proposed by Critchley and Critchley [17]. The agreement between E-sCOVX and Deltatrac was further quantified in 10% and 15% agreement rates, which are defined as the proportion of measurements that had a less than 10% or 15% difference in EE when compared to the Deltatrac.

2.5. Sample size calculation

Sample size was calculated for a 1-sample mean comparison and based on results of a previous study comparing the Deltatrac

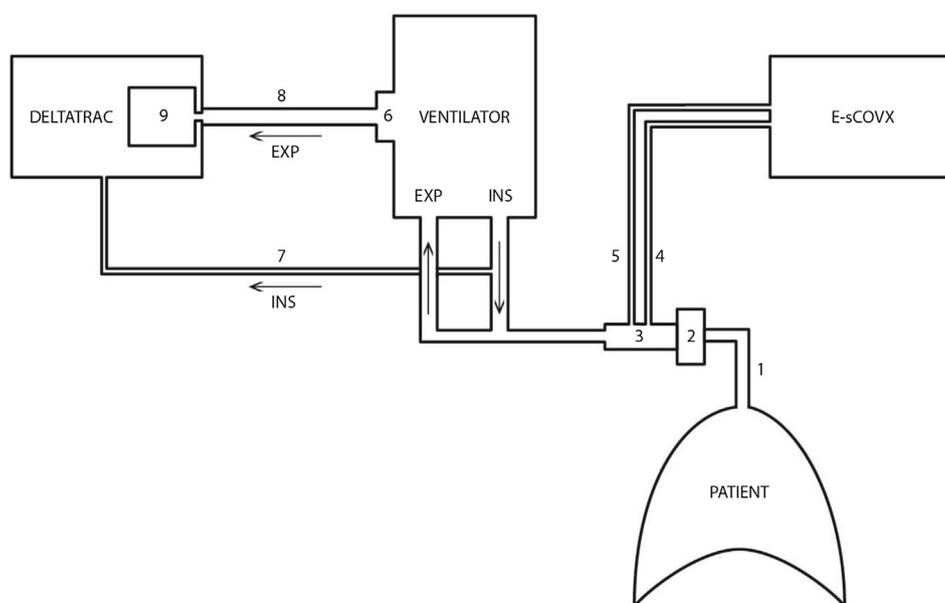


Fig. 1. Illustration showing the connection of the E-sCOVX and the Deltatrac to the mechanical ventilator and tubing, and the different gas sampling points. 1: Endotracheal tube, 2: Filter, 3: D-lite[®]-connector with gas sampling ports and flow sensor, 4: Spirometry tubing, 5: Gas sampling line, 6: Expiratory outlet of the ventilator, 7: Inspired gas sampling line, 8: Connection between ventilator and Deltatrac, 9: Mixing chamber.

and the E-sCOVX. Assuming a mean EE Deltatrac of 2000 kcal/day, a mean EE E-sCOVX of 2200 kcal/day and a standard deviation of ± 200 kcal/day [5]. For an α of 0.05 and a power of 0.90, a sample size of at least 22 measurements is sufficient.

3. Results

Between July 2016 and September 2016, we performed 29 measurements in 16 patients. Ten patients were male. The majority of patients were ventilated in pressure support mode (83%). Patient characteristics and ventilator settings are shown in Table 1.

Mean EE-E-sCOVX was higher than EE-Deltatrac, with a bias of 235 ± 149 kcal/day, corresponding to a percentage error of 12.1% of the reference method. EE, VCO_2 and VO_2 measured by E-sCOVX and Deltatrac were significantly correlated. RQ was not.

Mean EE, VCO_2 , VO_2 , and RQ for the Deltatrac and the E-sCOVX, as well as the correlation coefficient (r), the bias, limits of agreement of the E-sCOVX are shown in Table 2. Bland–Altman plots for EE, VCO_2 , VO_2 , and RQ are shown in Fig. 2.

The Bland–Altman plots showed a systematic overestimation of EE, VCO_2 , and VO_2 , measured by the E-sCOVX compared to the Deltatrac. Agreement rates for EE-EsCOVX and the predictive equations are shown in Table 3. The 10% agreement rate of the E-sCOVX was comparable to the 10% agreement rates of the equations. The 15% agreement rate of the Faisy-equation was higher than of the E-sCOVX (76% vs 48%, $p = 0.02$).

3.1. Post hoc analysis

We hypothesized that the large bias of the E-sCOVX could be caused by problems with synchronizing gas sampling, flow and volume measurements in patients with high respiratory rates or irregular breathing patterns. Therefore, we correlated the bias of EE, VCO_2 and VO_2 with respiratory rate for all measurement and for those measured during controlled ventilation only. The bias for EE and VO_2 did not correlate with respiratory rate ($r = 0.192$, $p = 0.32$ and $r = 0.081$, $p = 0.68$ respectively). However, the bias of VCO_2 tended to become higher at higher respiratory rate ($r = 0.330$, $p = 0.08$). The bias of EE in patients on controlled ventilation was not

lower than in patients on support mode (284 kcal/day vs 246 kcal/day, $p = 0.34$).

4. Discussion

The present study in critically ill, mechanically ventilated patients, shows that the E-sCOVX overestimates energy expenditure compared to the Deltatrac. The bias corresponded to 12.1% of EE measured by the reference method, which is more than the 10% deemed acceptable according to a consensus statement [18]. Furthermore, precision of E-sCOVX was low, as indicated by wide limits of agreement. Only one third of the measurements had a less

Table 1
Patient characteristics.

Characteristics	Results
Number of measurements	29
Number of patients	16
Male, n (%)	10 (63)
Female, n (%)	6 (38)
Age, yr (mean \pm SD)	62.2 \pm 22.7
Height, cm	169 \pm 9.7
Weight, kg	88.2 \pm 20.1
BMI, kg/m ² (mean \pm SD)	25.9 \pm 6.3
ICU admission diagnosis	
Trauma, n (%)	5 (31)
Sepsis, n (%)	2 (13)
Respiratory insufficiency, n (%)	2 (13)
Post-cardiac arrest, n (%)	3 (19)
Cardiovascular, n (%)	4 (25)
Total length of stay in ICU, days (median (IQR))	29 (15–58)
Length of stay at day of measurement, days (median (IQR))	9 (6–11)
SOFA score on day of measurement (mean \pm SD)	10 \pm 3
Mechanical ventilation characteristics during measurement	
PS/CPAP, n (%)	24 (83)
PC, n (%)	5 (17)
PEEP, cm H ₂ O, (median (IQR))	8 (5–10)
FiO ₂ , (median (IQR))	0.4 (0.35–0.45)
Minute volume, L/min, (mean \pm SD)	11.3 \pm 2.7
Respiratory rate, breaths/minute, (median (IQR))	23 (19–28)

BMI; body mass index, SOFA; sequential organ failure assessment, PEEP; positive end-expiratory pressure, PS; pressure support, CPAP, continuous positive airway pressure, PC; pressure support, FiO₂; fraction of inspired oxygen, SD; standard deviation, IQR; inter quartile range.

Table 2
Comparison of EE, VCO₂, VO₂, and RQ as measured by the Deltatrac and the E-sCOVX.

	Mean ± SD	P-value	Bias ± SD (kcal/day) (%-Error of Deltatrac)	Limits of agreement (kcal/day) (%-Error of Deltatrac)	Correlation	
					r	P-value
EE (kcal/day)						
Deltatrac	1942 ± 274		235 ± 149	-63 to +532		
E-sCOVX	2177 ± 319	<0.001	(12.1%)	(-3% to +27%)	0.885	<0.001
VCO ₂ (ml/min)						
Deltatrac	237 ± 36		26.6 ± 26.2	-25.8 to +79		
E-sCOVX	264 ± 49	<0.001	(11.2%)	(-11% to +33%)	0.853	<0.001
VO ₂ (ml/min)						
Deltatrac	282 ± 39		32.1 ± 29.8	-27.5 to +91.7		
E-sCOVX	314 ± 41	<0.001	(11.4%)	(-10% to +33%)	0.725	<0.001
RQ						
Deltatrac	0.85 ± 0.06		-0.04 ± 0.06	-0.16 to +0.08		
E-sCOVX	0.81 ± 0.04	0.003	(4.7%)	(-19% to +9%)	0.362	0.053

EE; energy expenditure, VCO₂; carbon dioxide excretion, VO₂; oxygen consumption, Bias: mean difference of the two measurements (E-sCOVX – Deltatrac); SD: standard deviation; r: Pearson's correlation coefficient.

than 10% difference with the Deltatrac. Both the systematic error (bias) and the random error (precision) of the E-sCOVX are higher than can be clinically accepted. Our results correspond to those of Sundstrom-Rehal et al. They suggested that the absence of bias flow

in their ventilators could contribute to the inaccuracy of the E-sCOVX, because it could interfere with synchronization of gas sampling and flow measurement [5]. We therefore tested the agreement of E-sCOVX using a ventilator with bias flow, and also

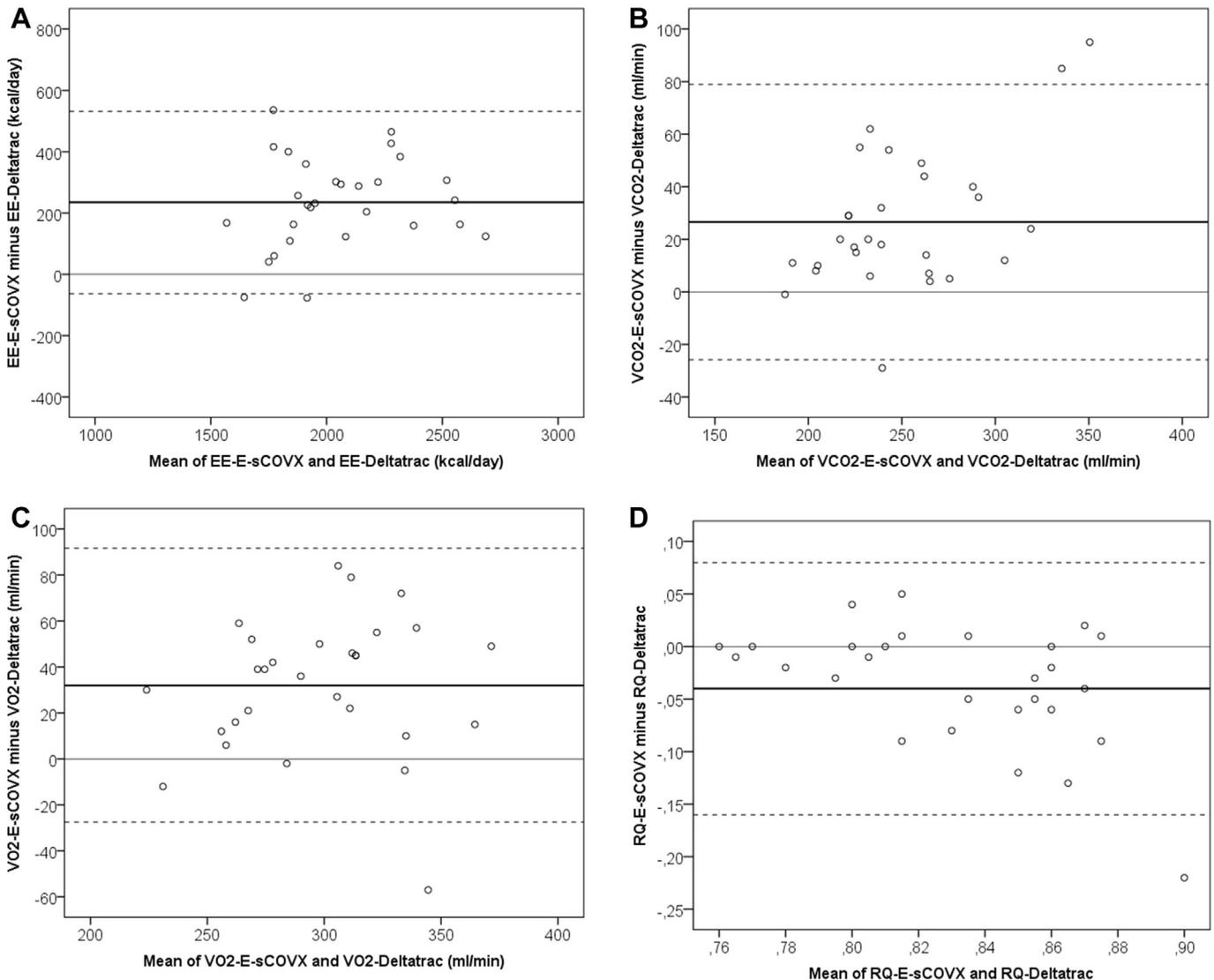


Fig. 2. Bland–Altman plots showing the agreement between the E-sCOVX and the Deltatrac measurements for A. Energy Expenditure (EE) B. Carbon dioxide excretion (VCO₂), C. Oxygen consumption (VO₂), D. Respiratory quotient (RQ), being the ratio of VCO₂ and VO₂.

Table 3

Performance of the E-sCOVX compared to predictive equations, using the Deltatrac as reference method.

	Mean \pm SD (kcal/day)	Bias \pm SD (kcal/day) (%-Error of Deltatrac)	Limits of agreement (kcal/day) (%-Error of Deltatrac)	10% agreement ^a	15% agreement
EE-E-sCOVX	2177 \pm 319	235 \pm 149 (12.1%)	-63 to +532 (-3% to +27%)	31%	48%
EE-25 kcal/kg	1640 \pm 287	-303 \pm 366 (15.6%)	-1035 to +429 (-53% to +22%)	21%	41%
EE-HB15	1860 \pm 333	-82.6 \pm 304 (4.3%)	-691 to +525 (-36% to +27%)	45%	59%
EE-PSU	1878 \pm 319	-64.9 \pm 262 (3.3%)	-589 to +459 (-30% to +24%)	52%	69%
EE-Faisy	2063 \pm 268	121 \pm 245 (6.2%)	-369 to +611 (-19% to +32%)	48%	76% ^b

HB15; Harris–Benedict equation with 15% added, PSU; Penn State University 2003 equation.

^a 10% agreement rates were not significantly different between methods.^b The 15% agreement rate of EE-Faisy was significantly higher than the 15% agreement rate of EE-E-sCOVX ($p = 0.02$).

performed longer measurements. However, these measures did not improve the agreement of the E-sCOVX with the Deltatrac.

In the present study, we also compared the performance of the E-sCOVX to that of the predictive equations. Although the equations EE-HB15, EE-PSU and EE-Faisy had a bias below 10%, their precision was poor. It has repeatedly been shown that equations are inaccurate in critically ill patients and should not be used to guide nutrition [15,19,20]. In the present study the E-sCOVX did perform better than the 25 kcal/kg-equation, but was not better than the other equations.

In accordance with other studies in mechanically ventilated patients, we confirmed that breath-by-breath methods seem to overestimate EE compared to the Deltatrac [4–7].

Explanation for the inaccuracy of breath-by-breath methods in mechanically ventilated patients could be inaccuracies resulting from synchronizing flow and volume during gas sampling for analysis. In contrast, the Deltatrac has a large mixing chamber and collects all expired air thus avoiding difficult spirometry measurements. Critically ill mechanically ventilated patients may exhibit rapidly changing breathing patterns, especially in assisted ventilator modes. In the presence of rapid breathing or a short breathing cycle the synchronization of flow and volume becomes less accurate. We tried to reduce this cause of error by including patients only if breathing frequency was below 35 per minute. Although we did not find a correlation between respiratory rate and increasing bias of EE, the bias of VCO₂ tended to be higher in patients with higher breathing frequency. We did not find lower bias in patients on controlled ventilation compared to assisted modes. However, this was not an aim of the present study and the sample size was probably too small for such a post-hoc analysis.

Another explanation for overestimation of E-sCOVX compared to the Deltatrac could be a consequence of the simultaneous measurements. A small volume of air (120 ml/min) is sampled by the E-sCOVX and is not collected in the mixing chamber of the Deltatrac. Leading to lower VCO₂ and VO₂ values and thus lower EE. In contrast, the Deltatrac samples a small volume of air (150 ml/min) for the FiO₂ from the inspiratory tubing, distal from the sampling point of the E-sCOVX. This volume is therefore not measured by the E-sCOVX. However, these volumes account for only 1% of the mean minute volume in our patients. Therefore, sampling cannot explain the large errors. Since the sampling of the E-sCOVX is continuous and fixed (120 ml/min), a higher respiratory rate does not have an effect on the bias as a result of the simultaneous measurement. In our patients, there was a correlation between RR and minute volume. Higher minute volumes even reduce the effect on bias as a result of the simultaneous measurements because the fraction of volume that is not collected by Deltatrac becomes even smaller at higher minute volumes.

In 2006 Singer et al. performed a similar study, testing the agreement between MCOVX (an earlier version of the E-sCOVX) with Deltatrac and Evita. In the discussion, Singer et al. address the issue of simultaneous or sequential measurement. The authors performed all measurements simultaneous. Mean minute

ventilation of their patients was 10.1 l/min, with sampling of 200 ml/min being 3% of the minute volume. Prior to the start of the study, the authors tested the influence of sampling 3%, and found no significant variation in minute volume as measured by the Deltatrac or in the VO₂ or VCO₂ measurements [21].

Thirdly, we should not overlook the old-timer status of our Deltatrac that was used as reference. The device was tested and recalibrated by alcohol-burning just before the study. Nonetheless, it is possible that inaccuracies occurred during the 2-h measurement period.

The Deltatrac is no longer in production and the need for an alternative device that is cheap, easy to use, and accurate is high. Advantage of the E-sCOVX and other breath-by-breath devices is that they are easy to use and can be used for continuous measurement. This method also allows rapid measurements and conception of small devices.

However, these instruments require stable breathing patterns as seen in the anesthesia setting and appear unreliability in critically ill patients. Recently, the Q-NRG indirect calorimeter (Cosmed, Rome, Italy) has become available. It was developed by the ICALIC-project group, a collaboration of experts in nutrition, with financial support from The European Society of Intensive Care Medicine and the European Society of Parenteral and Enteral Nutrition. The Q-NRG indirect calorimeter is specifically developed for use in the ICU and has been designed to be accurate, easy to use, compact, and affordable [1]. The device has a micro-mixing chamber (2 ml), which reduces time stabilization of gas concentrations and VO₂, VCO₂ variability, and seems reliable under conditions of an FiO₂ up to 0.7 and PEEP levels up to 10 cm H₂O. Accuracy was tested in the in-vitro setting with promising results [22]. The Q-NRG is currently being tested in a multicenter clinical validation study ([ClinicalTrials.gov](https://clinicaltrials.gov) Identifier: NCT02024958). We are eagerly awaiting the results of this trial.

Up to now, there are no studies showing that the prescription of nutrition based on the energy expenditure measurements improves patient outcome. One of the reasons may be that it is not known yet whether prescribing the amount of energy expended is the optimal way of feeding, especially not in the early phase. In that phase, matched feeding may result in overfeeding due to inflammation-driven endogenous energy [23]. One recent randomized controlled trial (EAT-ICU) prescribed nutrition according to measured energy and did not find benefit [24]. However, the study prescribed 100% of measured energy from day 1, and EE measurements were performed with the Quark RMR metabolic monitor that has shown to be inaccurate in critically ill patients [4,6,7]. Nevertheless, metabolic monitoring in mechanically ventilated patients has other interests as well. EE provides information on the metabolic status of the patient. For example, a rising EE may indicate emerging sepsis before clinically otherwise detectable while decreasing EE may indicate recovery. Most importantly, metabolic monitoring is crucial for further understanding of the consequences of nutrition on patient outcome. Any future study on

timing and dosing of nutrition should include monitoring of EE because the dosing of nutrition based on equations, as done in recent large randomized controlled trials, is notoriously unreliable. Furthermore, measuring EE can help to prevent overfeeding, which should be avoided as there is increasing evidence for its association with mortality [25,26]. On the other hand, during rehabilitation and mobilization EE can be much higher than predicted by the equations. In that phase, monitoring EE may prevent underfeeding.

4.1. Strengths and limitations

Strength of our study is the measurement period of two hours. Other studies comparing different indirect calorimetry devices measured for 10–30 min only, which, in some patients may have been too short to reach steady state. Furthermore, the simultaneous measurement provides the best comparison and excludes true differences as a result of physiological changes.

Another strength is that we measured in the critically ill population (mean SOFA-score of 10 on the day of measurement). Validation in these patients is especially important because breathing patterns in this population differ from those in the anesthesia setting, in which the present device was validated [8].

Sample size was small but adequate. We even had more measurements than strictly needed. The main limitation of the study is that the reliability of the reference method may be doubted. However, the device has a mixing chamber, which seems crucial for intensive care patients and it was calibrated before the study.

5. Conclusion

In critically ill mechanically ventilated patients the E-sCOVX metabolic monitor overestimates energy expenditure when compared to the Deltatrac. The E-sCOVX is not accurate and its use is therefore not recommended in critically ill patients. Because maintenance of the Deltatrac is not supported anymore, we are eagerly looking for a new and reliable device.

Statement of authorship

SS, PW, HO designed the study. SS obtained the data. SS, PW, HO analyzed the data. All authors contributed to the drafting of the manuscript. HO had responsibility for the final content. All authors read and approved the final manuscript.

Conflict of interest

SS received research support from Nestlé and Astellas. PW received speaker fees and research grants from Nutricia, Baxter, Fresenius, and Nestle. HO received congress support and speaker fees from Fresenius, Nutricia, Baxter/Gambro, and Abbott; and research support from Fresenius.

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