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ORIGINAL

Effect of FiO_2 in the measurement of VO_2 and VCO_2 using the E-COXV metabolic monitor☆

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Abstract
Objective: We evaluated the effect of changes in FiO_2 on the bias and accuracy of the determination of oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) using the E-COVX monitor in patients with mechanical ventilation.
Design: Descriptive of concordance.
Setting: Intensive Care Unit.
Patients or participants: Patients with mechanical ventilation.
Interventions: We measured $\dot{V}O_2$ and $\dot{V}CO_2$ using the E-COVX monitor. Values recorded were the average in 5 min. Two groups of 30 patients. We analyzed: 1) the reproducibility in the measurement of $\dot{V}O_2$ and $\dot{V}CO_2$ at FiO_2 0.4, and 2) the effect of the changes in FiO_2 on the measurement of $\dot{V}O_2$ and $\dot{V}CO_2$. Statistical analysis was performed using Bland and Altman test.
Variables of main interest: Bias and accuracy.
Results: 1) FiO_2 0.4 reproducibility: The bias in the measurement of $\dot{V}O_2$ and $\dot{V}CO_2$ was 1.6 and 2.1 mL/min, respectively, and accuracy was 9.7 to −8.3% and 7.2 to −5.2%, respectively, and 2) effect of FiO_2 on $\dot{V}O_2$: The bias of $\dot{V}O_2$ measured at FiO_2 0.4 and 0.6 was −4.0 mL/min and FiO_2 0.4 and 0.8 was 5.2 mL/min. Accuracy between FiO_2 0.4 and 0.6 was 11.9 to −14.1%, and between FiO_2 0.4 and 0.8 was 43.9 to −39.7%.
Conclusions: The E-COVX monitor evaluates $\dot{V}O_2$ and $\dot{V}CO_2$ in critical patients with mechanical ventilation with a clinically acceptable accuracy until FiO_2 0.6.

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PALABRAS CLAVE
Consumo de oxígeno;
Dióxido de carbono;
Intercambio pulmonar de gases;
Ventilación mecánica;
Paciente crítico;
Reproducibilidad de resultados

Efecto de la FiO_2 sobre la medición del VO_2 y la VCO_2 con el monitor metabólico E-COVX

Resumen
Objetivo: Valorar el efecto de la FiO_2 sobre el sesgo y la precisión en la medición del consumo de oxígeno ($\dot{V}O_2$) y la producción de dióxido de carbono ($\dot{V}CO_2$) con el monitor E-COVX en pacientes con ventilación mecánica.
Diseño: Descriptivo de concordancia.
Ámbito: Unidad de Cuidados Intensivos.
Pacientes o participantes: Pacientes con ventilación mecánica.
Intervenciones: Se midieron el $\dot{V}O_2$ y la $\dot{V}CO_2$ con el monitor E-COVX. Los valores de $\dot{V}O_2$ y $\dot{V}CO_2$ fueron el promedio de 5 min. Dos grupos de 30 pacientes. Se analizó: 1) la reproducibilidad de la medición del $\dot{V}O_2$ y la $\dot{V}CO_2$ con una FiO_2 de 0,4, y 2) el efecto de los cambios en la FiO_2 sobre el $\dot{V}O_2$ y la $\dot{V}CO_2$. Análisis estadístico por el método de Bland y Altman.
Variables de interés principales: Sesgo y precisión.
Resultados: 1) Reproducibilidad a una FiO_2 de 0,4: los sesgos en la medición del $\dot{V}O_2$ y la $\dot{V}CO_2$ fueron de 1,6 y 2,1 mL/min, respectivamente, y los errores en la precisión fueron de 9,7 a −8,3% y de 7,2 a −5,2%, respectivamente, y 2) efecto de la FiO_2 sobre el $\dot{V}O_2$: el sesgo del $\dot{V}O_2$ medido a una FiO_2 de 0,4 y 0,6 fue de −4,0 mL/min y a FiO_2 de 0,4 y 0,8, de 5,2 mL/min. La precisión entre FiO_2 de 0,4 y 0,6 fue de 11,9 a −14,1%, y entre FiO_2 de 0,4 y 0,8, de 43,9 a −39,7%.
Conclusiones: El monitor E-COVX mide el $\dot{V}O_2$ y la $\dot{V}CO_2$ en pacientes críticos con ventilación mecánica con un sesgo y una precisión clínicamente aceptables hasta una FiO_2 de 0,6.

Introduction

The main interest of measuring oxygen consumption (VO_2) and the production of carbon dioxide (VCO_2) in critical patients subjected to mechanical ventilation (MV) is to calculate energy expenditure by applying the formula of Weir.[1] Recent studies have shown that a calorie supply capable of compensating the losses resulting from energy expenditure shortens the duration of mechanical ventilation, reduces the nosocomial infection rate, facilitates physical recovery and reduces mortality.[2–5] The measurement of VO_2 and VCO_2 also has other applications, however. In effect, the measurement of VO_2 allows us to assess the relationship between oxygen transport and VO_2[6] or determine the respiratory effort of a given ventilatory mode with respect to some other mode.[7] The measurement of VCO_2 in turn allows us to measure the physiological dead space.[8]

However, the precise measurement of VO_2 and VCO_2 in the critical patient subjected to mechanical ventilation poses a series of problems including the need for a fraction of inspired oxygen (FiO_2) above that of room air, particularly in the acute phase of the disease; airway gas leakage due to the positive pressure of the ventilator; and the presence of water vapor in the expired gas.[1,9–11] Of these problems, FiO_2 is the most important, since error in the measurement of the concentrations of inspired and expired oxygen in order to determine VO_2 is amplified when FiO_2 is incremented.[12]

The measurement of respiratory gas exchange in patients under mechanical ventilation has been facilitated by the development of automated systems capable of measuring VO_2 and VCO_2 on a breath-to-breath basis. In this regard, some studies have reported that the M-COVX and E-COVX monitors can be used in patients subjected to mechanical ventilation and with a need for high FiO_2 (<0.85), with an error acceptable to clinical practice.[13–15]

The present study was carried out to evaluate the effect of FiO_2 upon precision in the measurement of VO_2 and VCO_2 using the E-COVX metabolic monitor in critical patients subjected to mechanical ventilation.

Material and methods

Patients

The study included patients admitted to the Intensive Care Unit (ICU), intubated and subjected to mechanical ventilation, who were receiving sedatives (midazolam or propofol) and/or analgesics (morphine or fentanyl) in continuous perfusion. Measurements were made of VO_2 and VCO_2, with the calculation of resting energy expenditure (REE). The study was carried out in the morning, with the patient under resting conditions, the headrest raised 30 degrees, and after two or more days of mechanical ventilation. All the patients were ventilated in volume control mode with $FiO_2 \leq 0.4$. Before indirect calorimetry measurement, we checked the pressure of the balloon of the endotracheal tube and the absence of air leakage. Indirect calorimetry measurement was carried out during the administration of enteral, parenteral or mixed nutrition, with a calorie supply of 15–30 kcal/kg/day. The nutrition was administered continuously and was not interrupted, since the increase in VO_2 and VCO_2 is constant and with a value of about 3%.[16] During at least 30 min before the measurements we performed no tracheal aspirations, physiotherapy, postural changes, body hygiene measures, radiological studies or catheter insertions.[17,18]

The following conditions were regarded as study exclusion criteria: hemodynamic instability (defined as the need to modify vasoactive drug doses or variations >20% in arterial pressure and/or heart rate); a respiratory frequency of over 35 rpm; the need for $FiO_2 > 0.4$; a body temperature of under 36 °c or over 38 °C; a sedation level as determined with the Richmond Agitation-Sedation Scale[19] of over −3; patients with bronchopleural fistulas; and patients subjected to renal replacement therapy.

The study was approved by the hospital research committee. Since the study involved a monitoring technique, the need for informed consent was not considered necessary.

E-COVX metabolic monitor

The E-COVX metabolic monitor (GE Healthcare/Datex-Ohmeda, Helsinki, Finland) is a noninvasive system equipped with a paramagnetic analyzer for oxygen, an infrared analyzer for CO_2, and a pneumotachograph for measuring inspired and expired volumes. The pneumotachograph and gas sampling ports were located in a disposable connector called D-Lite sensor (GE Healthcare Finland Oy, Helsinki, Finland), placed between the heat and humidity exchanger (Edith Flex®, GE Healthcare Finland Oy, Helsinki, Finland) and the Y-piece of the ventilator circuit, in order to avoid water accumulation.[14] A connector with a dead space of 15 ml (the manufacturer recommended a dead space of 5 ml) was placed between the D-Lite sensor and the Y-piece. The purpose of this dead space was to avoid contamination of the expired gas with the continuous air flow of the ventilator, which was set to minimum (2 l/min).

In order to reduce systematic error in the volume measurements, the E-COVX monitor uses the Haldane transformation to calculate both VO_2 and VCO_2. Systematic error occurs in all the measurements and is inherent to the apparatus itself or to the measurement process. In contrast, random error is accidental, not controllable and can be reduced by increasing the sample size. The Haldane transformation consists of measuring the inspiratory volume and estimating the expiratory volume, since the latter is dependent upon the temperature (assumed to be 35 °C) and humidity (assumed to be 100%) of the expired gas.

The signals from the pneumotachograph and gas analyzers were synchronized in order to allow breath-to-breath gas exchange estimates. The results corresponding to VO_2 and VCO_2 were expressed each minute as an average of the last 60 s. The measurements of VO_2 and VCO_2 were recorded only when the patient was metabolically stable (defined as a variation of $\leq$5% in 10 consecutive values).[20,21] The volumes were corrected to standard conditions of temperature, pressure and dryness.

The E-COVX monitor is ready for use 5 min after being turned on, and automatic calibration is performed. The system calibrations are made every 6 months according to the instructions of the manufacturer, who reports a precision of ±10% for FiO_2 <0.7 and a respiratory frequency of <35 rpm.

Study protocol

Two groups of 30 patients each were studied sequentially and on a non-consecutive basis: in the first group, we assessed the reproducibility of the measurements of VO_2 and VCO_2 at $FiO_2 = 0.4$, while in the second group we evaluated the effect of the changes in FiO_2 upon the measurements of VO_2 and VCO_2. Each VO_2 and VCO_2 value in the study corresponded to the average of 5 min.[20,22]

In the first group, 30 min after turning on the E-COVX monitor and with the ventilator set to $FiO_2 = 0.4$, we recorded body temperature and the VO_2 and VCO_2 values corresponding to 5 min. Data recording was repeated 30 min later in order to establish the reproducibility of the VO_2 and VCO_2 measurements at $FiO_2 = 0.4$.

In the second group, 30 min after turning on the E-COVX monitor and with the ventilator set to $FiO_2 = 0.4$, we likewise recorded body temperature and the VO_2 and VCO_2 values corresponding to 5 min. The ventilator was then modified to $FiO_2 = 0.6$, and after 30 min we again recorded body temperature and the VO_2 and VCO_2 values corresponding to 5 min. Lastly, the process was repeated at $FiO_2 = 0.8$.

Statistical analysis

The descriptive data included the number and percentage corresponding to categorical variables, and the mean and standard deviation or median and interquartile range (IQR) in the case of continuous variables. The Kolmogorov–Smirnov test was used to assess normal distribution of the data. We used the Student *t*-test or the Friedman test in application to continuous variables, and the χ^2 test or the Fisher exact test in the case of categorical variables. The Bland and Altman method[23] was used to determine bias (mean difference between two measurements) and precision as the limits of agreement (twice the standard deviation of the difference between two measurements). Bias (or accuracy) assesses the similarity between the mean values of repeated measurements. Precision (reproducibility or variability) refers to the difference between repeated measurements and assesses the degree of dispersion. In addition, we evaluated absolute agreement between the repeated measurements of VO_2 and VCO_2 using the intraclass correlation coefficient (ICC) with the corresponding 95% confidence interval (95%CI). The error between two measurements was expressed as a percentage of the limits of agreement with respect to the mean value of the two measurements. *A priori*, an error of < 20% was considered acceptable.[24] Statistical significance was considered for $p < 0.05$. The data were analyzed using the SPSS, version 19.0 statistical package (SPSS Inc., Chicago, IL, USA).

Results

There were no demographic, clinical or metabolic activity differences (measured by indirect calorimetry) between the two groups (Table 1).

Table 1 Demographic and clinical characteristics, and indirect calorimetry results of the two groups of patients.

	Group 1 (n = 30)	Group 2 (n = 30)	*p*-value
Male sex, n (%)	20 (66.7)	20 (66.7)	1.0
Age in years, mean ± SD	53 ± 16	55 ± 13	0.55
Weight in kg, mean ± SD	81 ± 19	83 ± 19	0.71
Height in cm, mean ± SD	171 ± 10	169 ± 10	0.42
Body mass index in kg/m^2, mean ± SD	27.6 ± 4.8	28.7 ± 5.3	0.40
Type of patient, n (%)			0.59
Trauma	12 (40.0)	9 (30.0)	
Medical	14 (46.7)	18 (60.0)	
Surgical	4 (13.3)	3 (10.0)	
Indirect calorimetry, mean ± SD			
Temperature, °C	36.5 ± 0.9	36.6 ± 0.9	0.86
REE, kcal/day	1.917 ± 396	1.907 ± 396	0.92
REE, kcal/kg/day	24.4 ± 5.3	23.5 ± 4.7	0.52
REE, %	116 ± 20	116 ± 21	0.93
RQ	0.71 ± 0.07	0.72 ± 0.07	0.87

SD: standard deviation; REE: resting energy expenditure; RQ: respiratory quotient.

Table 2 Reproducibility of the measurements of VO_2 and VCO_2 at $FiO_2 = 0.4$.

	First measurement FiO_2 0.4	Second measurement FiO_2 0.4	Difference first – second measurement	*p*-value
Temperature, °C	36.5 ± 1.0	36.5 ± 0.9	0.1 ± 0.4	0.28
VO_2, mL/min	284 ± 60	283 ± 61	1.6 ± 13.1	0.51
VCO_2, mL/min	202 ± 42	200 ± 40	2.1 ± 6.7	0.10

FiO_2: fraction of inspired oxygen; VO_2: oxygen consumption; VCO_2: production of carbon dioxide.
Data expressed as mean ± standard deviation.

Reproducibility of VO_2 and VCO_2 at $FiO_2 = 0.4$

There were no significant differences in body temperature, VO_2 or VCO_2 between the first and second indirect calorimetry measurements at $FiO_2 = 0.4$ (Table 2). The biases between the two measurements of VO_2 and VCO_2 were 1.6 and 2.1 mL/min, respectively (Table 2). The precision for VO_2 was 27.8 to −24.6 mL/min, which represents a percentage error of 9.7 to −8.3%, versus 15.5 to −11.3 mL/min for VCO_2, which represents a percentage error of 7.2 to −5.2% (Fig. 1). The ICC (95%CI) for VO_2 was 0.98 (0.95–0.99), and 0.98 (0.97–0.99) for VCO_2.

Effect of the variation of FiO_2 upon the measurement of VO_2 and VCO_2

There were no significant differences in the values corresponding to body temperature, VO_2 or VCO_2 measured at $FiO_2 = 0.4$, 0.6 and 0.8 (Table 3).

The bias of the VO_2 values measured at $FiO_2 = 0.4$ and 0.6 was −4.0 mL/min, while at $FiO_2 = 0.4$ and 0.8 the bias was 5.2 mL/min (Table 3). The precision of the measurements of VO_2 between $FiO_2 = 0.4$ and 0.6 was 32.2 to −40.2 mL/min, which represents a percentage error of 11.9 to −14.1%. In turn, the precision of the measurements of VO_2 between $FiO_2 = 0.4$ and 0.8 was 117.2 to −106.8 mL/min, which represents a percentage error of 43.9 to −39.7% (Fig. 2). The ICC (95%CI) for VO_2 measured at $FiO_2 = 0.4$ and 0.6 was 0.95 (0.90–0.98), versus 0.70 (0.46–0.85) for VO_2 measured at $FiO_2 = 0.4$ and 0.8.

The bias of the values of VCO_2 measured at $FiO_2 = 0.4$ and 0.6 was −0.5 mL/min, while at $FiO_2 = 0.4$ and 0.8 the bias was −0.2 mL/min (Table 3). The precision of the measurements of VCO_2 between $FiO_2 = 0.4$ and 0.6 was 19.5 to −20.5 mL/min, which represents a percentage error of 9.3 to −9.9%. In turn, the precision of the measurements of VCO_2 between $FiO_2 = 0.4$ and 0.8 was 27.6 to −28.0 mL/min, which represents a percentage error of 12.4 to −13.2% (Fig. 2). The ICC (95%CI) for VCO_2 measured at $FiO_2 = 0.4$ and 0.6 was 0.97 (0.94–0.99), versus 0.95 (0.90–0.98) for VCO_2 measured at $FiO_2 = 0.4$ and 0.8.

Discussion

The results of our study with the E-COVX metabolic monitor reveal good precision at $FiO_2 = 0.4$ in the measurement of VO_2 and VCO_2. We observed no clinically significant bias in the measurements of VO_2 and VCO_2 over the FiO_2 range of 0.4–0.8. However, precision in the measurement of VO_2 increased on elevating FiO_2 – the situation being clinically inadequate (>20%) with $FiO_2 > 0.6$. Therefore, in clinical practice we should not use the E-COVX monitor to measure

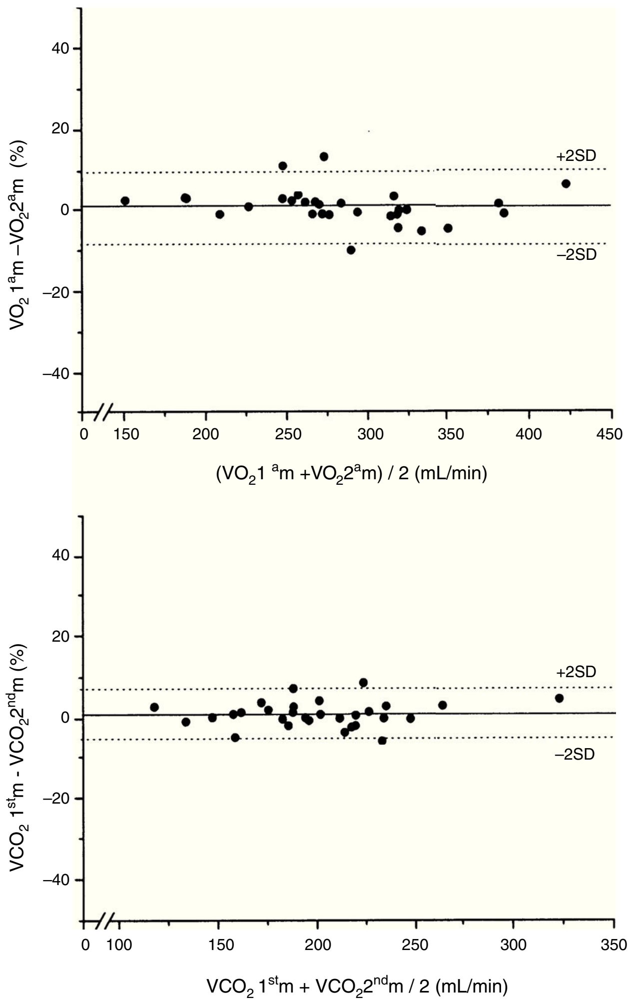

Figure 1 Graphic representation according to Bland and Altman of the percentage differences in the two consecutive values of VO_2 and VCO_2 of each patient measured at $FiO_2 = 0.4$ with respect to the mean value of both measurements in mL/min.

VO_2 in critical patients subjected to mechanical ventilation at $FiO_2 > 0.6$.

The precision of the repeated measurements of VO_2 at $FiO_2 = 0.4$ was 10%, which is consistent with the specifications of the manufacturer, while the precision of VO_2 at $FiO_2 = 0.6$ was about 15%, versus 40% at $FiO_2 = 0.8$. This progressive and exponential error in precision must be attributed to the increase in FiO_2.[25] Such a lack of agreement with VO_2 measured at $FiO_2 = 0.8$ is reflected by the low ICC value of only 0.7, while ICC for the measurements of VCO_2 always remained above 0.95, independently of the FiO_2 setting.

The measurement of VO_2 and VCO_2 in short periods of time can replace prolonged measurements, with the added advantage of reducing the physiological fluctuations.[20,22] This advantage is lost as a result of the sequential design of the study; consequently, precision includes both the physiological variations of metabolism and the true error of the measurements.[13] However, the gradual increase in precision of the measurements of VO_2 with incrementing FiO_2 values, which is not seen with the measurements of VCO_2, supports the idea that the increase in the precision of VO_2 is due to errors in the measurement of the inspired and expired oxygen concentrations.

Our results contrast with those of other studies that found the measurement of VO_2 with the M-COVX monitor at FiO_2 settings of up to 0.7 and 0.8 to be clinically acceptable.[13–15] These studies are based on the notion that the E-COVX monitor measures VO_2 and VCO_2 on a breath-to-breath basis for 5 min, which would be the equivalent to about 100 measurements (5 min at 20 rpm). According to the theoretical study of Ultman and Bursztein,[12] random error in the measurement of VO_2 would be gradually reduced by incrementing the number of measurements. Accordingly, precision is considered to be ±10% when $FiO_2 < 0.65$, versus ±15% when $FiO_2 > 0.65$ and < 0.85.[25]

The results of our study referred to the precision of the measurement of VO_2 are consistent with the idea that any error in the measurement of oxygen concentration in the inspired and expired gas is amplified when FiO_2 is increased.[9,11] An error of 1% in the measurement of FiO_2, at $FiO_2 = 0.4$, results in an error of 15% in the measurement of VO_2. At $FiO_2 = 0.8$ or higher, the same error of 1% results in an error of ≥100%, and because of this we did not perform measurements with $FiO_2 > 0.8$. On the other hand, the measurement of REE in patients subjected to mechanical ventilation at $FiO_2 > 0.6$ remains difficult and should not be made. As expected, the precision in the measurement of VCO_2 showed minimum changes with increments of FiO_2.[12]

The mean respiratory quotient (RQ = 0.72) observed in our series of patients was lower than expected. The RQ in patients subjected to mechanical ventilation under the effects of sedoanalgesia and with enteral, parenteral or mixed nutrition including carbohydrates (50%), lipids (30%) and proteins (20%), should be between 0.8 and 0.9. The most likely explanation for the low RQ would be systematic error in measuring VCO_2. In this sense, Meyer et al.[26] recorded a VCO_2 value with the M-COVX monitor of under 17.6% with respect to the Deltatrac II system. The low RQ could also be due to overestimation of VO_2, but this would give rise to a

Table 3 Bias and precision of the measurement of VO_2 and VCO_2 at $FiO_2 = 0.4$, 0.6 and 0.8.

	FiO_2 0.4	FiO_2 0.6	FiO_2 0.8	Difference 0.6–0.4	Difference 0.8–0.4	*p*-value
Temperature, °C	36.6 ± 0.9	36.6 ± 0.9	36.6 ± 0.8	0.0 ± 0.3	0.0 ± 0.4	0.99
VO_2, mL/min	283 ± 60	279 ± 58	288 ± 83	−4.0 ± 18.1	5.2 ± 56	0.90
VCO_2, mL/min	201 ± 41	201 ± 42	201 ± 47	−0.5 ± 9.8	−0.2 ± 13.9	0.88

FiO_2: fraction of inspired oxygen; VO_2: oxygen consumption; VCO_2: production of carbon dioxide.
Data expressed as mean ± standard deviation.

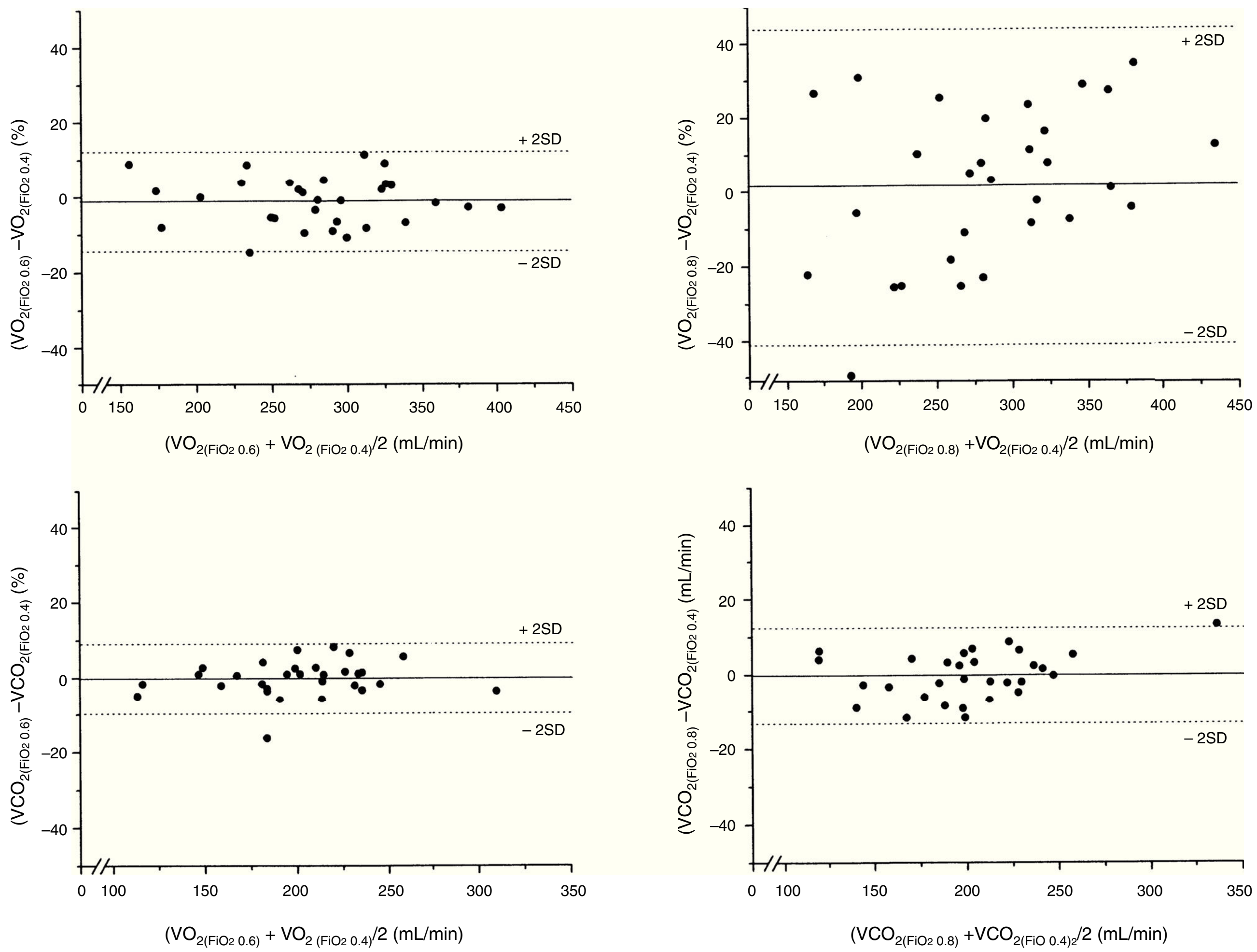

Figure 2 Graphic representation according to Bland and Altman of the percentage differences in the two consecutive values of VO_2 and VCO_2 of each patient measured at $FiO_2 = 0.4$ and 0.6 and at $FiO_2 = 0.4$ and 0.8 with respect to the mean value of both measurements in mL/min.

high REE value which we did not observe, since in the formula of Weir for calculating REE, the VO_2 multiplying factor is 3.9, versus 1.1 in the case of VCO_2.[1] The mean REE of our 60 patients was similar to that recorded in other studies in patients with similar demographic characteristics using other measurement methods.[5,27]

The underestimation of VCO_2 has little impact upon measurement of the REE, but precludes the correct interpretation of RQ in assessing the metabolic substrates. Furthermore, it disables calculation of the physiological dead space. A possible source of systematic error is the continuous flow of the ventilator (Engström Carestation), which could dilute the expired gas. However, and despite increasing the dead space between the D-Lite and the ventilator to 15 ml (the recommended value being 5 ml), we observed no increase in RQ.

The main limitation of our study, apart from its sequential design, is the fact that the measurements of VO_2 and VCO_2 were not compared with another indirect calorimetry method, such as the Douglas bag, particularly for checking the values of VCO_2.

In conclusion, the E-COVX metabolic monitor measures VO_2 in critical patients subjected to mechanical ventilation with clinically acceptable precision to a FiO_2 setting of 0.6. The measurement of VCO_2 is not affected by FiO_2.

Authorship

Mireia Ferreruela: data collection, preparation and review of the manuscript.

Joan Maria Raurich: literature search, data collection, study design, data analysis, preparation and final review of the manuscript.

Juan Antonio Llompart-Pou: preparation and final review of the manuscript.

Asunción Colomar: data collection, preparation and review of the manuscript.

Ignacio Ayestarán: data collection, preparation and review of the manuscript.

Conflicts of interest

The authors declare that they have no conflicts of interest in this study.

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