



Accuracy and Precision of the COSMED K5 Portable Analyser

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The main aims of this study were to determine the accuracy of the portable metabolic cart K5 by comparison with a stationary metabolic cart (Vyntus CPX), to check on the validity of Vyntus CPX using a butane combustion test, and to assess the reliability of K5 during prolonged walks in the field. For validation, measurements were consecutively performed tests with both devices at rest and during submaximal exercise (bicycling) at low (60 W) and moderate intensities (130–160 W) in 16 volunteers. For the reliability study, 14 subjects were measured two times during prolonged walks (13 km, at 5 km/h), with the K5 set in mixing chamber (Mix) mode. Vyntus measured the stoichiometric RQ of butane combustion with high accuracy (error <1.6%) and precision (CV <0.5%), at VO_2 values between 0.788 and 6.395 L/min. At rest and 60 W, there was good agreement between Vyntus and K5 (breath-by-breath, BxB) in VO_2 , VCO_2 , RER, and energy expenditure, while in Mix mode the K5 overestimated VO_2 by 13.4 and 5.8%, respectively. Compared to Vyntus, at moderate intensity the K5 in BxB mode underestimated VO_2 , VCO_2 , and energy expenditure by 6.6, 6.9, and 6.6%, respectively. However, at this intensity there was an excellent agreement between methods in RER and fat oxidation. In Mix mode, K5 overestimated VO_2 by 5.8 and 4.8%, at 60 W and the higher intensity, respectively. The K5 had excellent reliability during the field tests. Total energy expenditure per Km was determined with a CV for repeated measurements of 4.5% (CI: 3.2–6.9%) and a concordance correlation coefficient of 0.91, similar to the variability in VO_2 . This high reproducibility was explained by the low variation of $\text{F}_{\text{E}}\text{O}_2$ measurements, which had a CV of 0.9% (CI: 0.7–1.5%) combined with a slightly greater variability of $\text{F}_{\text{E}}\text{CO}_2$, V_{E} , VCO_2 , and RER. In conclusion, the K5 is an excellent portable metabolic cart which is almost as accurate as a state-of-art stationary metabolic cart, capable of measuring precisely energy expenditure in the field, showing a reliable performance during more than 2 h of continuous work. At high intensities, the mixing-chamber mode is more accurate than the BxB mode.

Keywords: oxygen uptake, ergometry exercise, metabolic cart, validity, reliability

INTRODUCTION

Nowadays, oxygen uptake (VO_2), carbon dioxide production (VCO_2), and substrate oxidation are mostly determined using stationary metabolic carts. For more specific measurements, particularly in the field, low-weight portable devices are more practical. Essentially, portable metabolic carts allow the measurement of the same variables as stationary metabolic carts with similar or slightly

lower accuracy; however, the reliability of portable carts seems lower (Brehm et al., 2004; Schrack et al., 2010). Portable devices operate on a breath-by-breath basis (BxB), requiring the assessment of the tidal volume of each breath and the expiratory fractions of O₂ (F_EO₂) and CO₂ (F_ECO₂), which must be aligned in time for further calculations, by accounting for the respective delay times (Beaver et al., 1973; Noguchi et al., 1982).

The accuracy of portable and stationary metabolic carts working on a BxB mode, depends to a large extent on the exact determination of the delay times (Overstreet et al., 2017). Most modern stationary metabolic carts have remarkably reduced delay times, and some, like the Vyntus CPX (Jaeger-CareFusion) have delay times for O₂ and CO₂ analysis almost matching mass spectrometers (Clemensen et al., 1994). Short delay times are necessary to avoid errors in BxB analysis at high respiratory frequencies, i.e., at high exercise intensities (Overstreet et al., 2017). Underestimation of delay time results in overestimations of F_EO₂, resulting in underestimation of VO₂ (Beaver et al., 1973; Noguchi et al., 1982; Hughson et al., 1991). Conversely, overestimation of delay time results in underestimation of O₂ and overestimation of VO₂ (Beaver et al., 1973; Noguchi et al., 1982; Hughson et al., 1991). This limitation can be overcome by the use of a mixing chamber, where a representative micro-sample of each breath is temporally stored and mixed with previous samples before analysis (Overstreet et al., 2017). A new portable metabolic cart (COSMED K5) has been marketed with the option of measuring using either BxB or using a micro-proportional sampling averaging method. However, the accuracy and reliability of the COSMED K5 remains unknown.

Therefore, the purpose of this study was to determine the accuracy of COSMED K5 by comparison with a stationary metabolic cart at rest and during submaximal cycling exercise. Another aim was to measure the reliability of K5 for the assessment of energy expenditure during prolonged walks in the field. Walking rather than running was chosen to avoid potential artifacts due to mask displacement and to reduce thermal strain, so the subjects will not need to stop to remove the mask and drink. Since the validity of the Vyntus CPX remains unknown, a final aim was to determine the validity of Vyntus CPX using a butane combustion test.

MATERIALS AND METHODS

Participants

Two different studies were carried out to assess validity and reliability on two different groups separately. Sixteen Caucasian physically active volunteers (3 women and 13 men), between 19 and 32 years old, volunteered to participate in the validation study (Table 1). Another fourteen Caucasian physically active volunteers (3 women and 11 men), between 20 and 43 years old, agreed to participate in the reliability study (Table 1). All volunteers provided their written consent after being informed about the risks and benefits of the study, which was approved by the ethical committee of the University Hospital Dr. Negrin (Ref. 140187). All subjects were requested not to exercise and to refrain from drinking alcohol and beverages containing caffeine

TABLE 1 | Descriptive characteristics of K5 validation subjects (resting metabolic rate and exercise tests).

Parameter	Validation study (n = 16)		Reliability study (n = 14)	
	Mean ± SD	Range	Mean ± SD	Range
Age (years)	23.3 ± 3.4	19.0 – 32.0	25.4 ± 6.5	20.9 – 43.1
Weight (kg)	72.3 ± 10.3	61.0 – 96.3	70.6 ± 10.6	55.9 – 89.3
Height (cm)	175.4 ± 7.4	162.2 – 185.0	174.2 ± 7.6	163.8 – 188.3
BMI (kg/m ²)	23.4 ± 2.5	20.7 – 29.1	23.1 ± 2.2	19.7 – 27.2

Values are means ± standard deviation (SD). BMI, body mass index.

or taurine during the 48 h preceding the tests, as well as to eat a similar dinner the night before the tests.

General Procedures

Subjects reported to the laboratory between 7:00 and 9:30 A.M., following a 12-h overnight fast. Upon arrival, their body weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively. Measurements were performed while subjects wore light clothes and no shoes using a balance scale (Seca, Hamburg, Germany) calibrated using certified calibration masses of class M1 (Scheck, Germany).

The validity of the COSMED K5 was determined by comparison with the Vyntus CPX (Jaeger-CareFusion, Höchberg, Germany) both at rest and during submaximal exercise on a cycle ergometer (Corival, Lode, Netherlands). Both metabolic carts were equipped with relatively new (less than 3 months old) oxygen fuel cells). Before the measurements both devices were warmed up for a minimum of 15 min calibrated with high-grade calibration gases provided by the manufacturers and by pumping gas with a 3 L calibration syringe through the flow meters, following the recommendations of the manufacturers. Mask size was individually fitted prior to the first test and the same size was maintained for subsequent trials.

Validation Study

For this purpose, subjects were instrumented with the Vyntus or COSMED facemask, in random order. The Vyntus was operated BxB and the COSMED K5 in BxB and mixing chamber modes. After arrival, subjects rested awake in the supine position during the next 60 min on a comfortable laboratory stretcher provided with a pillow, while their resting metabolic rate (RMR) was determined with both metabolic carts. Subjects were instructed to lie motionless and avoid talking during the measurement, which was carried out in a well-ventilated room while maintaining a quiet environment. The ergospirometric values recorded between the 20th and 30th min were averaged and used as representative of the metabolic cart tested first. During the following 5 min the device was changed in case the measurements started with the Vyntus, or switched from BxB to mixing chamber if the first device tested was the COSMED K5 and then to Vyntus. Thus, 10 min periods were collected with each device, with the first measurements starting after at least 20 min of comfortable rest in the supine position. A new full calibration (gas and flow) was done before switching systems.

Then the volunteers performed two bouts of exercise on the cycle ergometer at 60 W for 10 min, followed by 6 min at 130 W (women) or 160 W (men), keeping the pedaling rate at 80 rpm. These intensities were chosen to test the K5 at a low exercise intensity eliciting VO_2 values similar to those observed during brisk walking (i.e., ~ 6 km/h) (van der Walt and Wyndham, 1973), as well to a moderate exercise intensity eliciting a VO_2 value close to the $\text{VO}_{2\text{max}}$ observed in sedentary populations (Edvardsen et al., 2013). To reduce potential carry-over effects when changing from one metabolic cart to the other and to allow the assessment of substrate oxidation by indirect calorimetry, the highest load was chosen to elicit RER values close to 1.00. This sequence was repeated in random order while data were collected with the Vyntus, the COSMED K5 set on the BxB and mixing-chamber modes allowing a 20-min rest period between the bouts. Seat and handlebar adjustments were fit to the subject specifications and remained unchanged during all bouts.

Reliability Study

The reliability of the COSMED K5 was assessed by measuring ergospirometric variables and the energy expenditure during prolonged walks (13 km), which were repeated two times at least 4 days apart, with the device set in the mixing chamber mode. These tests were performed at the same time of day on non-raining days, and subjects were requested to wear similar clothing and the same walking shoes for the two trials. The walking route was relatively flat; including land and concrete sidewalks sections. The walking speed was maintained close to 5 km/h, using a Garmin Forerunner 210 (Garmin International Inc., Olathe, KS, United States) with GPS. The heart rate was measured with a Garmin Sensor connected to the K5. All subjects were weighted immediately before and after walking (SECA 869, Hamburg, Germany) while wearing all equipment and clothes. The scale was calibrated with certified calibration masses of class M1.

Energy Expenditure

Energy expenditure was calculated from VO_2 and VCO_2 data, assuming a negligible contribution of protein oxidation as previously reported (Peronnet and Massicotte, 1991).

Validation of Vyntus CPX by Burning Butane

The combustion of butane ($2 \text{C}_4\text{H}_{10} + 13 \text{O}_2 \rightarrow 8 \text{CO}_2 + 10 \text{H}_2\text{O} + \text{heat}$) has a respiratory quotient of 0.615 (8/13). Thus, we built an air-tight Plexiglas box (70 cm \times 50 cm \times 50 cm) with two 3.05 cm circular openings. One opening was connected to a 3-L calibration syringe (Hans Rudolf, Shawnee, KS) and in the other the turbine of the Vyntus with the sample lines for gas analysis was placed. Inside the Plexiglas box, a small butane burner was ignited while a 5 liter stainless steel cooking pot was placed on top filled with 0.5 L of water and ice up to the top, to dissipate the heat generated by the butane combustion. Three different burning intensities were used to simulate low, medium and very high exercise intensity. Within 5 s after the ignition of the butane burner, air was pumped in and out continuously

using the calibration syringe, adjusting the stroke rate between 15 and 80 strokes/min until an almost “steady state” was reached, as reflected by the $\text{F}_{\text{E}}\text{O}_2$ and $\text{F}_{\text{E}}\text{CO}_2$. The pumping rate was then maintained for 2 min. Butane combustion data were averaged every 10 s to determine the precision of the metabolic cart, and the coefficient of variation (CV) determined for a set of 5–6 consecutive averages with steady ventilation. The ventilation was considered steady when consecutive values differ by less than 10%. Some variability in ventilation was unavoidable since the air was pumped manually, although always by the same operator.

Statistical Analysis

Data are reported as the mean (\pm SD), unless otherwise stated. Values were checked for normal distribution using the Shapiro-Wilks test. The agreement between methods was assessed by determining the bias in absolute values and as a percentage of the measured value with the reference method (Vyntus) and the corresponding limit of agreement upper limit of agreement (ULA) = bias + $1.96 \times$ SD; lower limit of agreement (LLA) = bias – $1.96 \times$ SD. In addition, the agreement between methods was further examined by determining the Concordance Correlation Coefficient (CCC; Lin, 1989). The accuracy was evaluated by determining the differences between the mean values obtained with each method using Student *t*-test. The reliability of COSMED K5 measurements was assessed by determining the CV as described by Forkman (2007). Finally, the relationship between VO_2 and VCO_2 during butane combustion at different rates was assessed by the correlation coefficient of Pearson using 10-s averaged data. A *P*-value ≤ 0.05 was considered to be statistically significant. All statistical analyses were performed using IBM SPSS v.21.0 for Mac Computers (IBM, New York, United States).

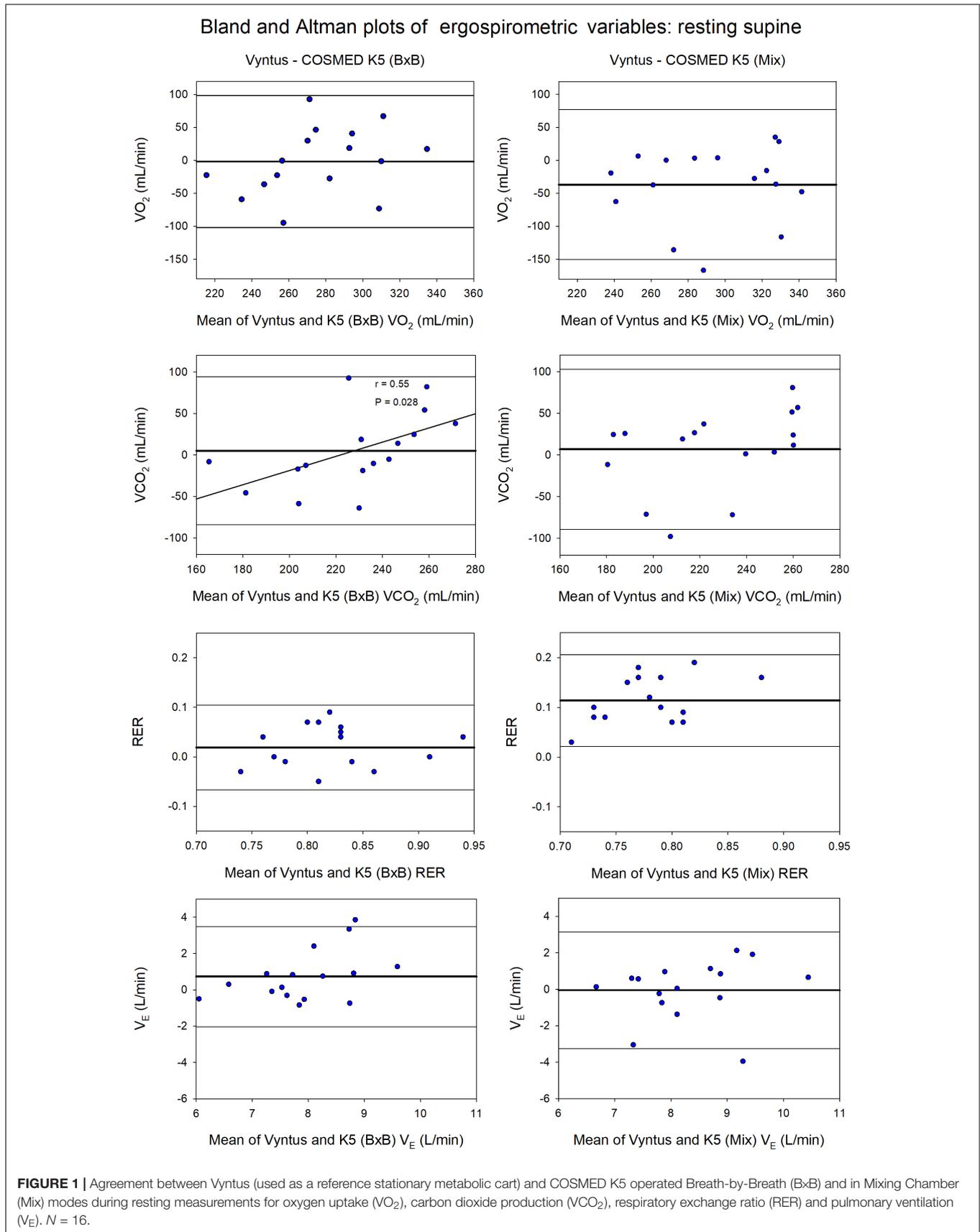
RESULTS

In vitro Validation of Vyntus

We used three different levels of combustion to simulate low, medium, and very high exercise intensities (**Supplementary Table 1**). The corresponding VO_2 values were 0.788, 1.314, and 6.395 L/min and the associated RQ values 0.624, 0.608, and 0.619, respectively. The RQ deviation from the theoretical value for the combustion of butane (0.615) were 1.5, –1.1, and 0.7%, respectively. The CV of RQ for 5–6 consecutive 10 s averaged-intervals with similar ventilation was always below 0.5%. VO_2 during butane combustion was closely related to VCO_2 ($r = 0.9999$).

Accuracy and Precision

During measurements at rest and 60 W Vyntus and COSMED K5 (BxB) reported similar mean VO_2 , VCO_2 , RER, and energy expenditure values (**Supplementary Tables 2, 3** and **Figures 1–4**). Nevertheless, compared to Vyntus, COSMED K5 operated in mixing chamber mode (Mix) overestimated VO_2 by 13.4 and 5.8%, at rest and 60 W, respectively (**Supplementary Table 2**). Both Vyntus and COSMED K5 (Mix) reported similar V_{E} and



Bland and Altman plots of ergospirometric variables: resting supine

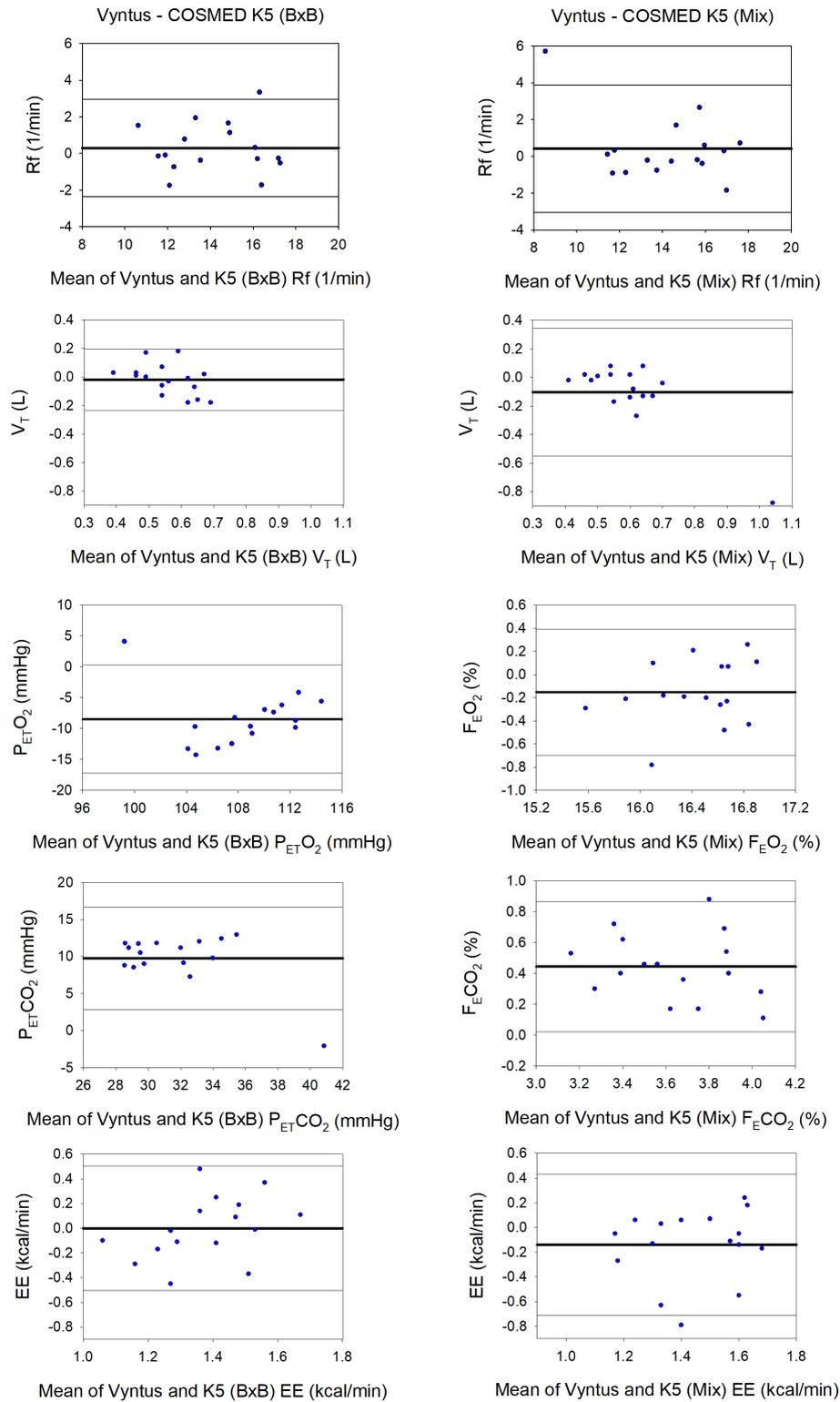


FIGURE 2 | Agreement between Vyntus (used as a reference stationary metabolic cart) and COSMED K5 operated Breath-by-Breath (BxB) and in Mixing Chamber (Mix) modes during resting measurements for respiratory frequency (Rf), tidal volume (V_T), end-tidal O₂ pressure (P_{ET}O₂), end-tidal CO₂ pressure (P_{ET}CO₂), and energy expenditure (EE). *N* = 16.

Bland and Altman plots of ergospirometric variables: exercise at 60 W

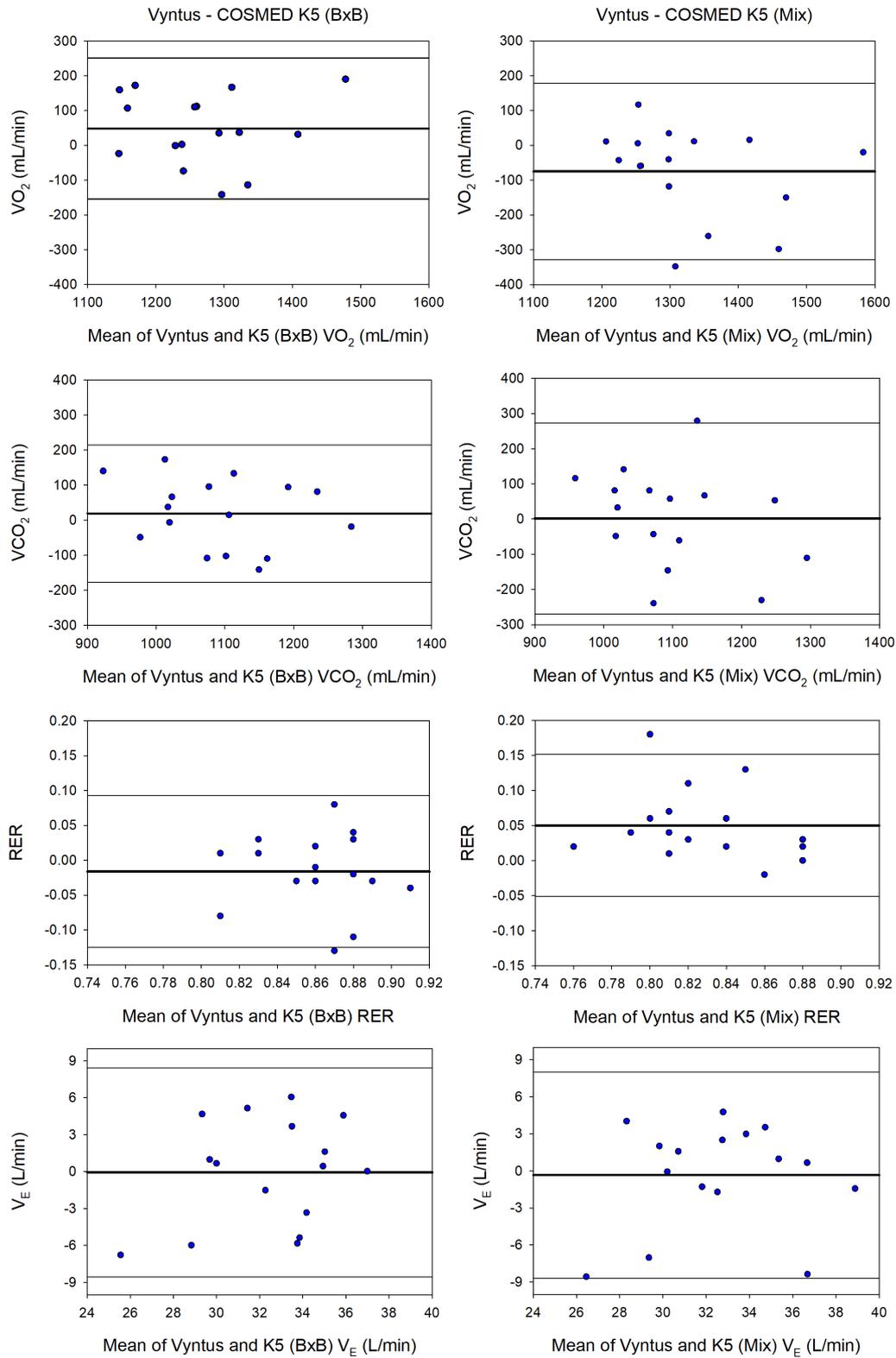


FIGURE 3 | Agreement between Vyntus (used as a reference stationary metabolic cart) and COSMED K5 operated Breath-by-Breath (BxB) and in Mixing Chamber (Mix) modes during low-intensity exercise (60W) for VO_2 , VCO_2 , RER, and pulmonary ventilation (V_E). $N = 16$.

Bland and Altman plots of ergspirometric variables: exercise at 60 W

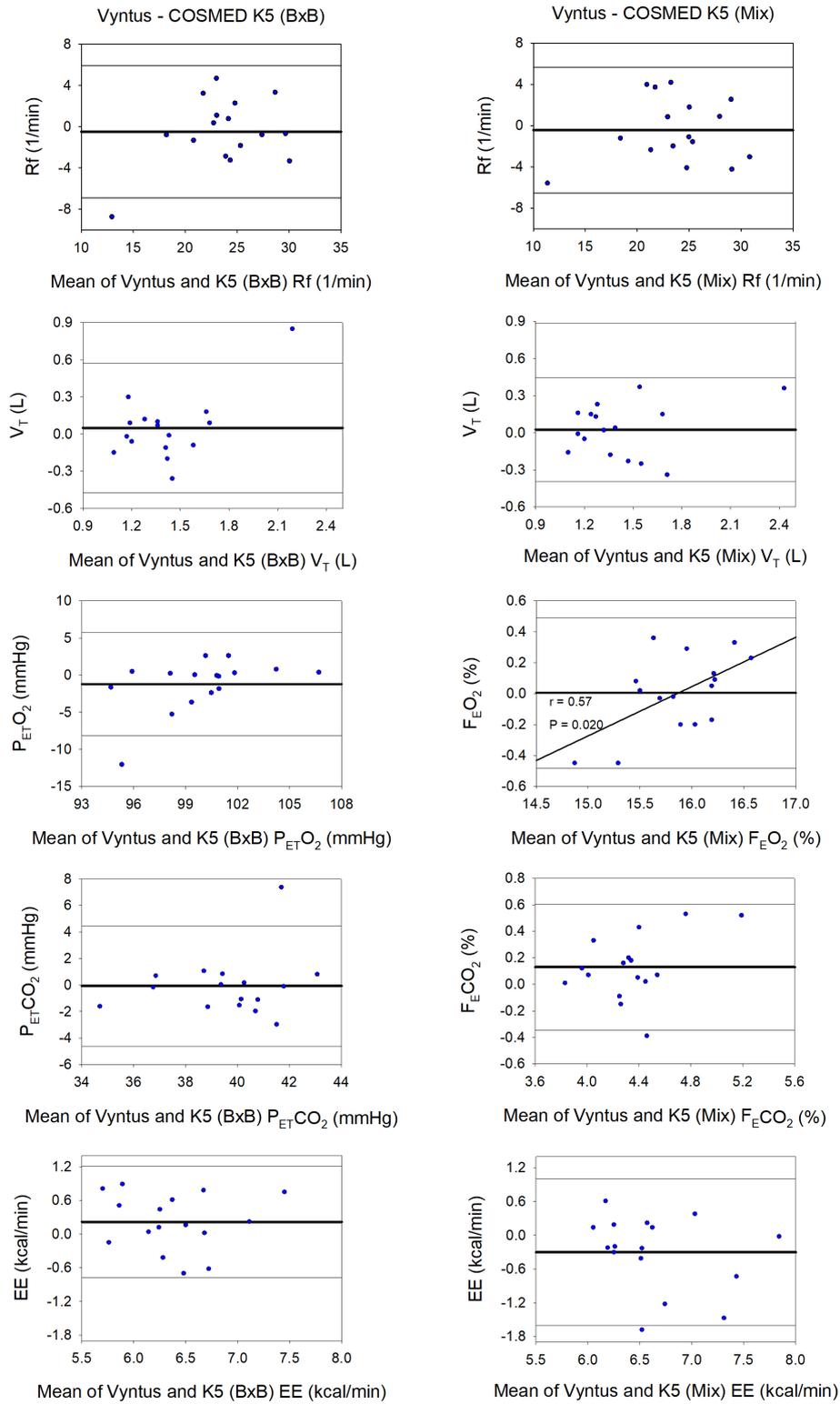
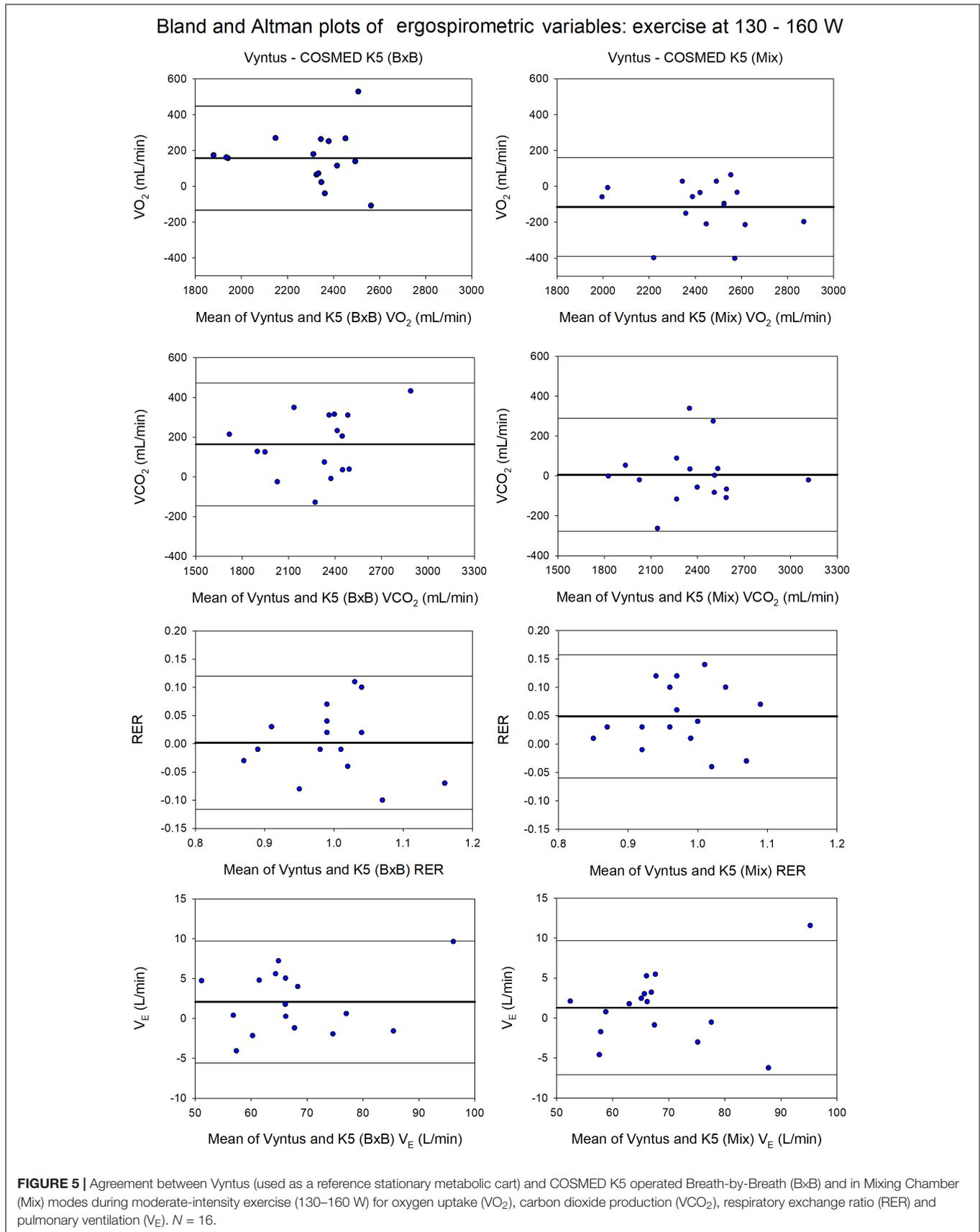


FIGURE 4 | Agreement between Vyntus (used as a reference stationary metabolic cart) and COSMED K5 operated Breath-by-Breath (BxB) and in Mixing Chamber (Mix) modes during low-intensity exercise for respiratory frequency (Rf), tidal volume (V_T), end-tidal O₂ pressure (P_{ET}O₂), expiratory O₂ fraction (F_EO₂), end-tidal CO₂ pressure (P_{ET}CO₂), expiratory CO₂ fraction (F_ECO₂), and energy expenditure (EE). *N* = 16.



Bland and Altman plots of ergospirometric variables: exercise at 130 - 160 W

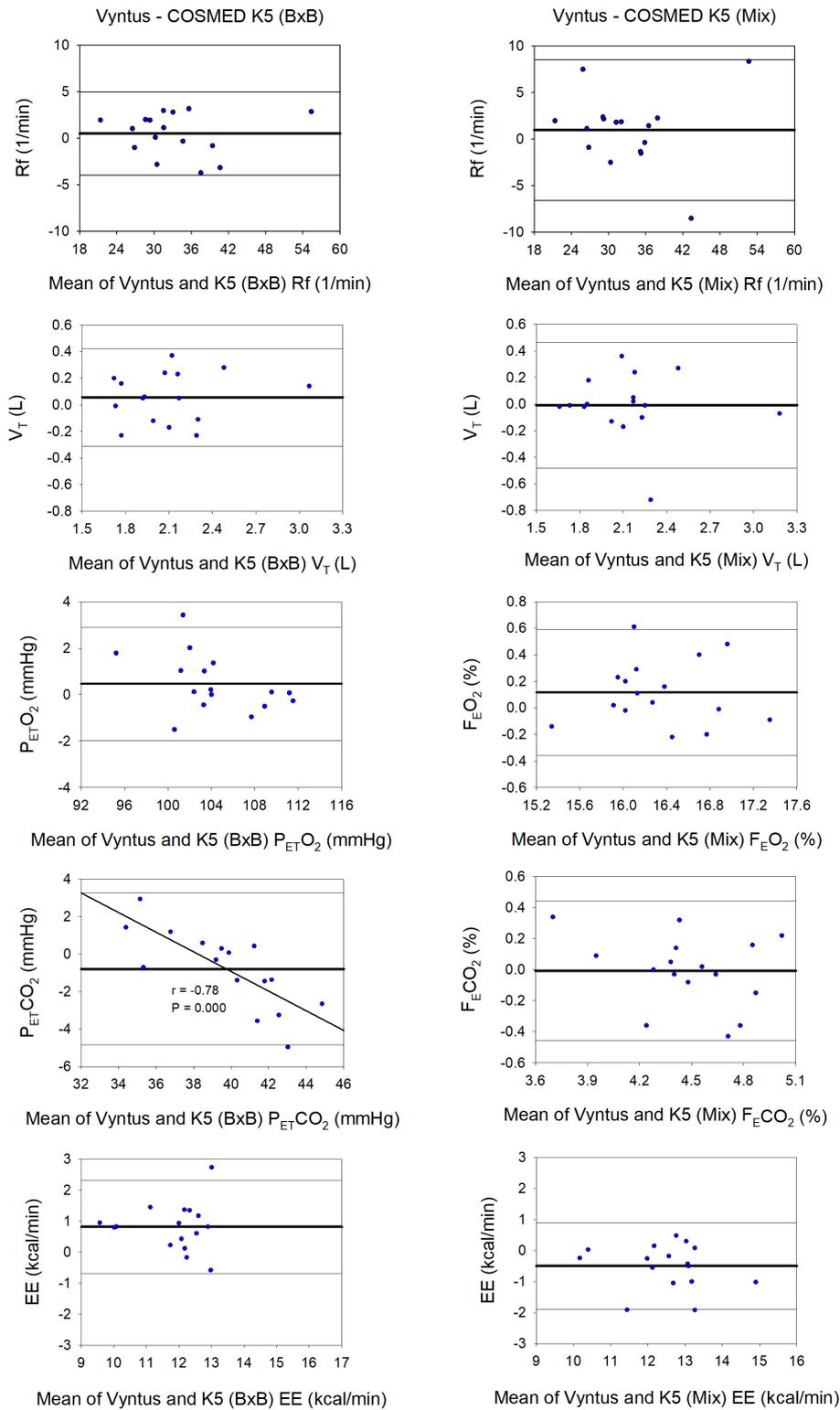


FIGURE 6 | Agreement between Vyntus (used as a reference stationary metabolic cart) and COSMED K5 operated Breath-by-Breath (BxB) and in Mixing Chamber (Mix) modes during moderate-intensity (130–160 W) exercise for respiratory frequency (Rf), tidal volume (V_T), end-tidal O_2 pressure ($P_{ET}O_2$), expiratory O_2 fraction ($F_{E}O_2$), end-tidal CO_2 pressure ($P_{ET}CO_2$), expiratory CO_2 fraction ($F_{E}CO_2$), and energy expenditure (EE). $N = 16$.

VCO₂ values. Consequently, COSMED K5 (Mix) underestimated RER by 13.8 and 5.8%, at rest and at 60 W, respectively.

At the highest intensity (130 W and 160 W in women and men, respectively) COSMED K5 (B×B) underestimated VO₂ and VCO₂ by 6.6 and 6.9%, respectively, due to a 3.0% underestimation of V_E (B×B) combined with 1.8% F_EO₂ overestimation and 5.1% F_ECO₂ underestimation by COSMED K5 (B×B) (**Supplementary Table 3** and **Figures 5, 6**). This resulted in a 6.6% underestimation of energy expenditure by COSMED K5 (B×B). Nevertheless, there was an excellent agreement between methods in RER and fat oxidation, while COSMED underestimated carbohydrate oxidation by 6.9% (**Supplementary Table 3**).

COSMED K5 (Mix) overestimated VO₂ during exercise by 5.8 and 4.8%, at 60 W and the highest intensity, respectively. Consequently, COSMED K5 (Mix) overestimated energy expenditure by 4.1%. Since VCO₂ was accurately measured during exercise by COSMED K5 (Mix), COSMED K5 (Mix) underestimated the RER by 5.8 and 4.8%, at 60 W and the highest intensity, respectively, causing a marked overestimation of fat oxidation (**Supplementary Table 3**).

COSMED K5 Breath-by-Breath Compared With the Mixing Chamber Mode

Compared to B×B, the mixing chamber mode overestimated VO₂ by 12.7% at rest (**Supplementary Table 4**). This bias in the assessment of resting VO₂ is mostly explained by a 10.4% V_E overestimation in Mix mode. However, VCO₂ was accurately measured due to the compensation of the overestimation of V_E by an underestimation of F_ECO₂ in Mix mode. Consequently, the RER was underestimated by 11.8% and energy expenditure by 10.1% in Mix mode.

During exercise the Mix mode the K5 overestimated VO₂ by 9.9 and 12.3% at 60 W and the highest load, respectively (**Supplementary Table 5**). This was explained by a 2.2 and 2.4% F_EO₂ underestimation, respectively. At 60 W, there was no bias in the assessment of VCO₂, but it was overestimated by 7.1% at the highest intensity by the Mix mode, resulting in 7.5 and 4.7% underestimation of the RER at 60 W and the highest load, respectively. Consequently, the Mix mode overestimated energy expenditure by 8.3 and 11.5% at 60 W and highest load, respectively.

Reliability

The COSMED K5 had excellent reliability during the field tests (**Supplementary Table 6**), despite small changes in walking speed, starting weight, and environmental conditions (**Supplementary Table 7**). Total energy expenditure per Km was determined with a CV for repeated measurements of 4.5% (CI: 3.2–6.9%) and a CCC of 0.91, similar to the variability of VO₂. This high reproducibility was explained by the low variation of F_EO₂ measurements, which had a CV of 0.9% (CI: 0.7–1.5%) combined with a slightly greater variability of F_ECO₂, V_E, VCO₂, and RER.

DISCUSSION

In the present investigation, the Vyntus CareFusion metabolic cart was used as the reference method. Although Vyntus is a relatively new metabolic cart and no data about its validity against the Douglas bag method is available, its precedent Oxycon Pro was proven to be valid (Foss and Hallen, 2005). Moreover, this has been confirmed for the Vyntus when cross-calibrated against the Vmax29 (Carlomagno et al., 2015). Our butane combustion tests have also shown that the Vyntus CPX can measure the stoichiometric respiratory quotient of butane combustion at low and very high O₂ flow with unprecedented accuracy and precision. Besides, the present investigation shows that the new COSMED K5 portable ergospirometer is an instrument that reproduces accurately the values obtained with the Vyntus metabolic cart at rest and during low-intensity exercise when operated in the B×B mode. We have also demonstrated that the COSMED K5 is highly precise at low-intensity exercise even during more than 2 h of continuous operation.

In the B×B mode, the COSMED K5 measures resting and low-intensity exercise (approximately 5 METs) VO₂, VCO₂, RER, and energy expenditure with an accuracy similar to that of the Vyntus metabolic cart, which has been recently marketed by the CareFusion company as a new metabolic cart based on its predecessors JAEGER Oxycon Pro and SensorMedics™ Vmax™ Encore. Nevertheless, at a higher exercise intensity equivalent to approximately 9 METs, COSMED K5 underestimates by 6–7% VO₂ and VCO₂, mostly due to underestimation of V_E and a small bias in the assessment of F_EO₂ and F_ECO₂.

Inclusion of a mixing chamber mode is the main innovation incorporated in the COSMED K5 compared to its predecessor (K4B²). In a stationary metabolic cart, the addition of a mixing chamber allows to mix the expiratory gases from 3–6 breaths (depending on the size of the mixing chamber and the tidal volume). This allows for a more accurate assessment of the F_EO₂ and F_ECO₂. Nevertheless, in a portable device the size of the mixing chamber is limited and only a fraction (proportional micro-sample) of the tidal volume is aspirated into the chamber for mixing with precedent breaths. However, our results demonstrate that at rest and during low exercise intensity, the mixing chamber is less accurate than the B×B mode. Since there was a good agreement in V_E and VCO₂ between the mixing chamber and the B×B modes of the COSMED K5, the divergence here observed in VO₂ between these two modes is likely due to the impact that the assumption of a fixed F_IO₂ (0.209) has on the calculation of VO₂. At higher exercise intensities, the tidal volume increases and the impact of the facemask dead space on the F_IO₂ is reduced, i.e., the actual F_IO₂ becomes closer to the assumed by the COSMED K5 (0.209) reducing the bias in the assessment of VO₂ at the highest exercise intensity. Our data also demonstrate that in the mixing chamber mode, the COSMED K5 measured the F_EO₂ with similar accuracy as Vyntus, while in the B×B mode it overestimated the F_EO₂ obtained with the Vyntus. Thus, when the aim of the study is to measure VO₂ or substrate oxidation at high exercise intensities the mixing

chamber mode is preferable. In contrast, measuring the resting RER with the COSMED K5 set in mixing chamber mode yields RER values close to 0.70, a value that is too low for subjects that have been fasting only overnight (Compher et al., 2006). Thus, at rest and during low intensity exercise the BxB mode is more accurate.

Our data also indicate that the COSMED K5 performs at least as well as its predecessor COSMED K4B² (Doyon et al., 2001; McLaughlin et al., 2001; Pinnington et al., 2001; Eisenmann et al., 2003; Duffield et al., 2004; Mc Naughton et al., 2005), while the addition of the mixing chamber mode allows more accurate assessments at high-intensity exercise.

Precision of COSMED K5

The precision of COSMED K5 was determined by using the mixing chamber mode during prolonged low intensity exercise in the field. Our data demonstrate that the COSMED K5 can assess VO₂ and energy expenditure during prolonged walking with a CV below 5%, i.e., performing at a similar level of precision as stationary metabolic carts (Carter and Jeukendrup, 2002; Crouter et al., 2006). It should be taken into consideration that this low CV was obtained despite small changes in body weight, environmental conditions, walking speed, and weight loss during the walks. Thus, even lower CVs may be achievable with the K5 under better controlled environmental conditions as during test carried out in laboratories. This level of precision exceeds that reported for its predecessor the K4B² for repeated walking measurements in separate days during treadmill walking (Darter et al., 2013; Howe et al., 2014) as well as during incremental exercise (Schrack et al., 2010; Brisswalter and Tartaruga, 2014).

Accuracy and Precision of Vyntus CPX (Butane Combustion Tests)

Combustion of fuels like ethanol (Cooper et al., 1991; Rising et al., 2015), methanol (Damask et al., 1982; Miodownik et al., 1998), propane (Melanson et al., 2010; Rising et al., 2015; Ismail, 2017), and butane (Nunn et al., 1989; Joosten et al., 2000) are considered gold-standard methods to validate indirect calorimeters. A common feature of precedent propane and butane combustion studies has been the use of only low combustion rates. In the present investigation we have used a similar methodology but using a broad range of combustion rates eliciting VO₂ values spanning across the physiological VO₂ values reachable by humans with varied fitness levels. In addition, our simulation generated respiratory variables mostly within the physiological range for humans. Importantly, our data

indicate that the Vyntus CPX metabolic cart is exceptionally accurate and precise measuring the stoichiometric RQ of butane combustion. This is only possible when VO₂ and VCO₂ are computed correctly from the inspired and expired O₂ and CO₂ fractions, even at high breathing frequencies (highest butane combustion rate) and despite differences in incurrent and excurrent airstreams (see **Supplementary Table 1**).

In summary, our data indicate that the COSMED K5 is an excellent portable metabolic cart which is almost as accurate as a state-of-art stationary metabolic cart, capable of measuring precisely energy expenditure in the field and showing a reliable performance during more than 2 h of continuous work. The mixing-chamber option allows for more accurate assessment of VO₂ during exercise at relatively higher intensities, but is less accurate at low exercise intensities, and should not be used to measure resting energy expenditure.

AUTHOR CONTRIBUTIONS

JC, DM-A, and IP-S conceived and designed the experiments. IP-S, MM-R, CF, SP-R, VG-A, JJ-H, and DM-A performed the pre-testing, experimental preparation, and data collection. IP-S, SP-R, CF, and JC analyzed the data. IP-S and JC wrote the first draft of the manuscript. All co-authors edited and proofread the manuscript and approved the final version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fphys.2018.01764/full#supplementary-material>

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