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Cardiac output measurement during exercise in COPD: A comparison of dye dilution and impedance cardiography

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Short title: Impedance cardiography for cardiac output in COPD

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Summary

Impedance cardiography (IC) derived from morphological analysis of the thoracic impedance signal is now commonly used for non-invasive assessment of cardiac output (CO) at rest and during exercise. However, in COPD, the two published studies disagree about its accuracy. We therefore compared concurrent CO measurements captured by IC (PhysioFlow^{TM}: CO_{IC}) and by the indocyanine green dye dilution method (CO_{DD}) in patients with COPD. Fifty paired CO measurements were concurrently obtained using the two methods from 10 patients (FEV_1:50.5±17.5%predicted) at rest and during cycling at 25%, 50%, 75% and 100% peak work rate. From rest to peak exercise CO_{IC} and CO_{DD} were strongly correlated (r=0.986, p<0.001). The mean absolute and percentage differences between CO_{IC} and CO_{DD} were 1.08 liters/min (limits of agreement (LoA): 0.05 to 2.11 liters/min) and 18±2%, respectively, with impedance cardiography yielding systematically higher values. Bland-Altman analysis indicated that during exercise only 7 of the 50 paired measurements differed by more than 20%. When data were expressed as changes from rest, correlations and agreement between the two methods remained strong over the entire exercise range (r=0.974, p<0.001, with no significant difference: 0.19 Liters/min; LoA: -0.76 to 1.15 liters/min). Oxygen uptake (VO_2) and CO_{DD} were linearly related: r=0.893 (p<0.001), CO_{DD} = 5.94 x VO_2 + 2.27 liters/min. Similar results were obtained for VO_2 and CO_{IC} (r =0.885, p<0.001, CO_{IC} = 6.00 x VO_2 + 3.30 liters/min). These findings suggest that impedance cardiography provides an acceptable CO measurement from rest to peak cycling exercise in patients with COPD.

Keywords: Exercise, Central hemodynamics, Noninvasive techniques, Thoracic impedance, Lung diseases

Introduction

Measurement of cardiac output (CO) in patients with Chronic Obstructive Pulmonary Disease (COPD) is important for comprehensively investigating the pathophysiological mechanisms of exercise intolerance, as well as the efficacy of rehabilitative exercise training interventions.

For many years, a number of invasive techniques such as the direct Fick, thermodilution and dye dilution methods have been used for measuring CO during exercise (Warburton *et al.,* 1999a). The direct Fick method requires trained personnel and blood sampling from both pulmonary and systemic arteries to perform what is regarded as the standard technique - if meticulously carried out- (Darovic, 1995). Requiring discrete blood samples, it is a discontinuous method. Despite its extensive use in clinical settings, the thermodilution method, which requires a systemic but not pulmonary arterial catheter, is reported to yield a consistent overestimation of CO, both at low values and during vigorous exercise compared to the direct Fick method (van Grondelle *et al.,* 1983; Russell *et al.,* 1990; Esprersen *et al.,* 1999) This occurs because unknown quantities of thermal indicator may be lost from the injectate before it enters the circulation and/or through the vessel wall, or because of the temperature difference between pulmonary blood and the injectate (Mackenzie *et al.,* 1986). This method is also discontinuous, because each measurement requires a separate injection of cold tracer.

The dye dilution technique, which also requires an arterial catheter, is more suited to use during exercise, since it is relatively easier to use than the direct Fick method and is more accurate than thermodilution (Russell *et al.,* 1990). However, in addition to the arterial cannula, dye dilution requires post-hoc data analysis involving deconvolution of the main dye appearance curve from its smaller recirculation curve. It also is a discontinuous method as each estimate requires a separate injection of dye, precluding rapid repetition of measurements.

Impedance cardiography is relatively newer as a method for measuring cardiac output, is completely noninvasive, and also virtually continuous. If reliable, it would, for these reasons, offer major advantages over earlier methods. It relies on thoracic impedance waveform analysis to determine stroke volume, which, when multiplied by heart rate recorded from the inbuilt ECG signal, provides CO (Charloux et al., 2000). This method requires only the application of (six) surface electrodes, and CO can, if desired, be measured on a beat-to-beat basis or averaged over selected time periods (Charloux *et al.,* 2000; Bour & Kellett, 2008).

Two studies in patients with COPD have compared impedance cardiography -derived from thoracic impedance waveform analysis- against the direct Fick method during cycling. Charloux *et al.,* (2000) demonstrated clinically acceptable agreement between these methods during exercise of moderate intensity. They reported that during exercise only 6.2% of CO values obtained by impedance cardiography differed from the reference Fick method by more than 20% (which is considered to indicate the clinically acceptable difference between two CO evaluation methods, Stetz *et al.,* 1982; La Mantia *et al.,* 1990). In contrast, Bougault *et al.,* (2005), found that impedance cardiography overestimated CO by 25-31% compared to the Fick method during maximal exercise in COPD, thus precluding the use of IC under these conditions. Consequently the acceptability of impedance cardiography during cycling exercise in patients with COPD is still uncertain, and the resolution of this uncertainty requires additional comparisons.

Because of this conflicting evidence and the increasing use of impedance cardiography in clinical studies, we analyzed, and here present, data obtained from an exercise study we conducted in COPD patients in which impedance cardiography and dye dilution had been concurrently applied (Vogiatzis *et al.,* 2010). The primary purpose of that study was to examine respiratory muscle blood flow at rest and during exercise in COPD. However, as we required cardiac output measurements (by the established dye dilution method) in that study, we saw the opportunity to also measure cardiac output by impedance cardiography and compare the two. Accordingly, the purpose of the present report is to compare cardiac output obtained by both methods across the full range of (cycling) exercise intensity in patients with COPD. We wish to fully and clearly disclose that the dye dilution data appear in the 2010 paper, Figure 4, panel B (Vogiatzis *et al.,* 2010), while impedance cardiography data do not appear anywhere in that, or in any other, report. With this disclosure, we reason that it is necessary to bring back those dye dilution data in order to accomplish direct comparison with the impedance cardiography values. We have also brought back VO_2 from the same study to allow the relationship between cardiac output and VO_2 to be examined for both methods. It would not be possible to perform that comparison without so doing.

Materials and methods

Study participants and experimental procedures

As originally reported in greater detail (Vogiatzis *et al.,* 2010), 10 clinically stable patients [2 females, mean±SD: FEV_1:50.5 ± 17.5% predicted, age, 60 ± 7 years, weight 77 ± 18 kg, body surface area 1.90 ± 0.24m^2] with COPD but without cardiac disease classified by the Global Initiative for Chronic Obstructive Lung Disease (GOLD, 2016) as spirometric stages II (n = 4) and III (n = 3) and IV (n=3) were studied. Patients demonstrated reduced exercise capacity (peak work rate 73 ± 42 watts (mean±SD) which was 41 ± 19 %predicted; and peak oxygen uptake 15 ± 4 ml/kg/min (39 ± 13%predicted).

After resting measurements, all patients were studied while cycling at 25%, 50%. 75% and 90-100% of their peak work rate, each level sustained for 2-5 min. This protocol therefore yielded 5 comparisons per subject, so that a total of 50 simultaneous paired measurements of CO by impedance cardiography and dye-dilution were available for comparison.

Cardiac output measurements

Procedures for determination of CO by the dye-dilution method (CO_{DD}) are described in the on-line supplement to Vogiatzis *et al.,* (2010). For impedance cardiography, a commercially available signal-morphology device, (PhysioFlow™ PF05; Manatec Biomedical, Macheren, France) was used for determining stroke volume and heart rate, and from this, CO (CO_{IC}). A detailed technical description of this method can be found elsewhere (Charloux *et al.,* 2000; Bougault *et al.,* 2005; Tonelli *et al.,* 2011; Ferreira *et al.,* 2012). After careful skin preparation that included shaving, application of a mildly abrasive gel (Nuprep, www.dowaver.com) and then cleaning (by alcohol), six electrodes (Physioflow™ PF5; Manatec Biomedical, Macheren, France) were placed according to the manufacturers' instructions in effect at the time, as shown in Figure 1 of Nasis *et al.,* (2015): two on the neck on the left side (one vertically above the other over the carotid artery above the supraclavicular fossa); two anteriorly in the xiphoid region; and two in locations corresponding to the V1 and V6 positions used for conventional ECG monitoring (Bougault *et al.,* 2005). After the subject had rested for 15 minutes, the system was auto-calibrated (a nominal, one-time, initial 30 second procedure as recommended by the manufacturer).

Data were then recorded at 1 second intervals and stored on a disk in Excel for off-line analysis. Verification of signal quality was performed according to the manufacturers' instructions and as reported later by Ferreira *et al.,* (2012). The Physioflow™ software includes real-time indication of signal quality (expressed in percentage values i.e., 0-100%). In this study data points were excluded when signal quality was less than 90% as performed in previous studies published by our group (Vassilopoulou *et al.,* 2012; Nasis *et al.,* 2015; Louvaris *et al.,* 2015). The reason for <90% signal quality is motion artefacts induced by exercise and exaggerated ventilatory responses to exercise, or poor skin contact with electrodes (Edmunds *et al.,*1982; Warburton *et al.,* 1999b). Data were smoothed using a 5-point moving average (Savitzky & Golay, 1964). The values were then time-aligned with the data captured by the dye-dilution method (CO_{DD}). The value of CO_{IC} used for comparison with the dye dilution estimate was the average of all smoothed values obtained over a 30-second period at rest and over a 15-second period during exercise, time periods corresponding to the typical duration of the dye curves in each case. A representative example of both raw and smoothed data for CO_{IC} is shown in Figure 1.

Statistical analysis

Data are presented as means ± SEM. We chose SEM (standard error of the mean) rather than SD (standard deviation) because the comparison of interest is between the two methods' mean values. Pearson's correlation coefficient (r) was used to establish associations between measurements. Two-way ANOVA with repeated measures and post-hoc comparisons were used to identify statistically significant differences across cycling work rates between the two methods. Analysis of agreement between the two methods was performed by using Bland-Altman analysis. Limits of agreement were defined as ±1.96 x standard deviation of the difference between the two methods, corresponding to 95% confidence intervals. The level of statistical significance was set at $P < 0.05$. All statistical analyses were performed using the SPSS statistical software (v. 20 IBM SPSS Statistics, Chicago, IL, USA).

Results

Central hemodynamic responses at rest and exercise

CO measured by both methods reached a plateau at 75% of WRpeak (Figure 2a). There were significant differences in absolute values of CO between CO_{IC} and CO_{DD} at rest and during exercise ($p<0.001$, Figure 2a) secondary to stroke volume that was consistently higher with impedance cardiography (as compared to stroke volume calculated by dye-dilution CO divided by heart rate, $p<0.001$, Table 1). Specifically, mean CO_{IC} at rest was 5.0±0.4 liters/min and increased to 9.8±0.9 liters/min at 100% WRpeak whilst CO_{DD} increased from 4.1±0.4 (rest) to 8.4±1.0 liters/min (at

100%WRpeak, Figure 2a). Therefore, an approximately 1 l/min systematic difference was observed between methods from rest to maximal exercise, with impedance cardiography giving the higher values. (Figure 2a). Hence, when CO values were expressed as changes from rest, there were no significant differences between the two methods (Figure 2b).

Association between cardiac output by both methods, and between cardiac output and VO_2

The association between all individual absolute values of CO_{IC} and CO_{DD} at rest and during exercise was strong (r=0.986, p<0.001, Figure 3a). Similarly strong correlations were obtained when looking at changes from rest to exercise (r=0.974, p<0.001, Figure 3b). The correlation coefficient between VO_2 and CO_{DD} was r=0.893 (p<0.001), and the regression equation was CO_{DD} = 5.94 x VO_2 + 2.27 liters/min (Figure 4a). The correlation coefficient between VO_2 and CO_{IC} was r=0.885 (p <0.001), and the regression equation was CO_{IC} = 6.00 x VO_2 + 3.30 liters/min (Figure 4b). These two equations also point out that the intercept values are different (by ~1.0 l/min) between the methods while the slopes are essentially the same.

Agreement between impedance cardiography and dye-dilution

The differences between the two measurements plotted against their mean value of the Bland-Altman analysis reference are presented in Figure 5. Specifically, at rest and during exercise, the mean difference (CO_{IC}-CO_{DD}) was 1.08 liters/min with limits of agreement of 0.05 liters/min and 2.11 liters/min (Figure 5a). The difference between the two methods exceeded 20% in only 11 out of 50 measurements (4 cases at rest and only 7 during exercise) whilst the mean percentage difference between the two methods was 18 ± 2%. When comparing changes from rest to peak exercise, the mean difference (CO_{IC} -CO_{DD}) was +0.19 liters/min with the limits of agreement of -0.76 liters/min and 1.15 liters/min (Figure 5b) whilst only 8 out of 50 measurements exceeded 20% difference between the two methods. In addition, when comparing changes from rest to peak exercise the mean percentage difference between the two methods (CO_{IC} -CO_{DD}) was ~~reduced to~~ 13 ± 4%.

Discussion

Main findings

The present analysis compared measurements of cardiac output by impedance cardiography against an established, older and invasive method (i.e., dye dilution) in patients with COPD at rest and over a wide range of exercise workloads up to the limit of tolerance. At rest the mean difference between the two methods was ~1.0 l/min (impedance value higher than dye dilution), a difference that remained unchanged during exercise up to the limit of tolerance (Figure 2). We found strong individual correlations between the two methods (Figure 3) accompanied by highly significant and comparable correlations between CO and VO_2 (Figure 4). These positive findings were further supported by the acceptable agreement (Figure 5) between the two methods (mean difference ~1.0 l/min or 18%) under all conditions examined. The results support the use of impedance cardiography in these patients during exercise up to maximal levels.

Prior studies using impedance cardiography in COPD and other diseases

Charloux *et al., (*2000) compared PhysioFlow™ against the direct Fick method in 40 patients with moderate COPD at rest and during low to moderate exercise intensity (between 10-50 watts, which was below patients' ventilatory threshold). They found a mean difference between the two methods of 0.3 liters/min, with only 9.3% of measurements (3 out of 32 measures) differing by more than 20% from the reference method. Of interest, at rest, and in the same range of cardiac output as in the present study, they found that the impedance technique resulted in a slightly higher value than the reference method (Figure 3A of their paper, showing every data point in the 3-5 liters/min range on or above the regression line). Our study expands the Charloux *et al*., (2000) findings by presenting results from rest to the limit of exercise tolerance, and by including patients with more severe COPD. The difference between the two studies is in our results showing a continued difference of ~ 1.0 l/min across the entire exercise range when compared to the chosen standard method.

Bougault *et al.,* (2005) compared cardiac output measured by the PhysioFlow™ device with the direct Fick method in 8 patients with moderately severe COPD during a maximal incremental exercise test and an intermittent work exercise test up to maximal levels. They found a mean difference between the two methods of 3.2 liters/min and 2.5 liters/min, respectively with impedance cardiography yielding the higher values. These differences, especially in the incremental test, may be at least in part explained by lack of a gas exchange steady state, since a steady state is required for proper use of the Fick method (Guyton *et al.,* 1973; Warburton *et al.,* 1999a). That said, the slope of the relationship between cardiac output and VO_2 by the Fick method (5.9 liters/min per liter/min VO_2) was in the usually reported range, while that for the impedance method was unusually high (9.7 liters/min per liter/min VO_2), suggesting a systematic error in their application of the latter method. Note from Figure 5 in the present paper that we found a slope of 6.0 liters/min per liter/min VO_2, essentially the same as their Fick-derived slope value, and a value in accord with the literature based on various measurement methods. Furthermore, Granath *et al.,* (1964) employed the thermodilution method in 27 individuals aged between 61-83 years during exercise in supine and sitting position and reported a slope between CO-VO_2 of 5.8 liters/liter. Julius et al. (1967) used the direct Fick method to measure CO in 18 subjects aged between 50-69 years and in 36 subjects aged between 18-49 years old. They established that the slope of the CO-VO_2 relationship was ~6.0 liters/liter, which was not altered by aging or the level of physical fitness among subjects. Grimby et al., (1966) by using dye dilution method in middle-aged trained subjects reported a slope of 5.2 liters/liter during submaximal and maximal exercise. These findings have been consistently confirmed by a number of investigators using noninvasive techniques for assessing CO such as foreign gas measures methods (i.e., acetylene rebreathing) or indirect Fick methods (i.e, CO_2 rebreathing,) (Faulkner, *et al.,* 1977; Hagberg *et al.,* 1985; McElvaney *et al.,* 1989; Makredis *et al.,* 1990; Proctor *et al.,* 1998). They reported slopes from 4.6 to 6.0 liters/liter in subjects aged between 49-72 years old.

We have no technical explanation for the findings by Bougault *et al.,* (2005) noting that we used the same version of the Physioflow™ system as did they. However, they did not provide methodological details regarding how they used the PhysioFlow™ system or how they analyzed the data (i.e., smoothing procedure, if any; data sample frequency, etc) nor did they report whether they followed the manufacturer's instructions for using specific electrodes, subject calibration, software for data analysis, information for skin preparation and signal quality inspection, as we report here (see methods).

In support of our findings, a study by Bogaard *et al.,* (1997) in 19 patients with moderate COPD compared a different impedance cardiography device (i.e., IPG-104 impedance;Mini-Lab; Detroit, MI) against the CO_2 re-breathing method during steady-state exercise, ranging from light intensity to the limit of tolerance. They reported similar results to ours - that the overall correlation during exercise between the two methods was strong (r=0.92), with few measurements falling outside the limits of agreement of 20%. The mean CO difference between impedance cardiography and the reference method was only 0.01 liters/min with limits of agreement of 2.56 liters/min.

In summary, in examining the three published studies and our present data, two of the published studies and our data set report adequate agreement with standard methods at rest and during exercise in patients with COPD, while the remaining published study did not, without apparent explanation. Our study is novel in providing comparisons using the Physioflow™ system over the entire exercise range from rest to maximal.

The PhysioFlow™ system has also been investigated in patients with chronic heart failure (CHF) or pulmonary arterial hypertension (PAH) at rest and during exercise against different reference methods (Tordi *et al.,* 2004; Kemps *et al.,* 2008; Tonelli *et al.,* 2011; Ferreira *et al.,* 2012; Tonelli *et al.,* 2013). These studies also reported adequate agreement with standard methods used simultaneously.

The difference between cardiac output by dye dilution and by impedance cardiography in the present study

As the results of our study show (Figure 2a), impedance cardiography yielded values 1 l/min higher than did dye dilution over the entire range from rest to maximal exercise. The question that this poses is, which method was likely more accurate? Using the regression equations of cardiac output against VO_2 in Figure 4 for both methods, at a normal resting VO_2 of 300 ml/min, cardiac output by impedance cardiography would be 5.1 liters/min while that by dye dilution would be only 4.1 liters/min. A similar calculation from the Charloux *et al.,* (2000) paper (their Figure 2) estimates cardiac output at this VO_2 would be 6.3 liters/min, while that from Bogaard e*t al* (their Figure 5) estimates cardiac output would be 4.7 liters/min. Taken together with the relatively high body mass of the subjects in our study of 77.0 kg, these calculations suggest that the impedance-based values in our study may be more accurate than those derived from dye dilution.

Strengths, Limitations and Conclusions

While the present study is limited by small sample size (10 patients), the group spans the COPD severity and exercise capacity spectrum (i.e., GOLD stages II-IV and WRpeak 11 to 69% predicted), and the measurements cover the entire range of exercise from none to maximal, such that we were able to accumulate 50 paired cardiac output measurements. Cardiac output is well-known to be an important contributor to exercise capacity, but has proven difficult to measure in clinical exercise testing because the usual methods (dye dilution, direct Fick, thermodilution, CO_2 rebreathing) are technically complex and mostly invasive as well as being limited to discrete rather than essentially continuous measurements that require often substantial analysis of raw data before the result is known. Impedance cardiography on the other hand is noninvasive, requires only the placement of skin electrodes thus saving valuable time for operators, and gives an essentially continuous readout of cardiac output. With the unexplained exception of one study described above, our study and those that preceded it together suggest that impedance cardiography is well suited to (clinical) exercise testing settings in patients with COPD.

Conflict of interest

The authors state explicitly that there are no conflicts of interest in connection with this article and have no relevant financial disclosures, particularly in connection with the manufacturer of the impedance cardiography system used in the study.

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Figures

Figure 1. Representative example of cardiac output by impedance cardiography in an individual subject, from rest to maximal exercise. Values were recorded at 1 second intervals. A 5-point moving average was implemented to smooth (red dots) the raw data (black dots).

Figure 2. (a). Group mean absolute values of cardiac output measured by impedance cardiography and dye dilution at rest and during cycling (b). Relative changes from rest in cardiac output measured by impedance cardiography and dye dilution. Data are presented as mean ± SEM. Asterisks denote significant differences from values at 100% of WRpeak. Cross denotes significant difference between the two methods, P=0.031. (Cardiac output data by dye dilution reproduced from Vogiatzis *et al.,* 2010).

Figure 3. Correlation between (a) absolute values of cardiac output measured by impedance cardiography and dye dilution during cycling (50 pairs) and (b) relative changes from rest in cardiac output measured by impedance cardiography and dye dilution during cycling (40 measured pairs). Linear regression equations and correlation coefficients are shown. (Cardiac output data by dye dilution reproduced from Vogiatzis *et al.,* 2010).

Figure 4. Correlation between oxygen uptake (VO_2) and absolute values of cardiac output measured by (a) dye-dilution (b) impedance cardiography (50 pairs). Linear regression equations and correlation coefficients are shown. (VO_2 data reproduced from Vogiatzis *et al.,* 2010).

Figure 5. Bland-Altman plots comparing (a) cardiac output measured by impedance cardiography and dye dilution at rest and during cycling trials (50 pairs) and (b) relative changes form rest in cardiac output measured by impedance cardiography and dye dilution in (40 pairs). (Cardiac output data by dye dilution reproduced from Vogiatzis *et al.,* 2010).

Table 1. Central hemodynamic characteristics at rest and during exercise

Characteristics	Rest	25%WRpeak	50%WRpeak	75%WRpeak	100%WRpeak
HR IC, beats/min	74±4	89±5	98±6	109±8	112±7
ΔHR IC, beats/min	-	15±2	25±3	34±4	37±4
HR ECG, beats/min	75±4	90±6	100±6	110±7	112±6
ΔHR ECG, beats/min	-	15±3	26±4	35±5	38±4
SV IC, ml/beat	67.8±5.1*	87.4±6.2*	95.8±7.9*	90.1±8.2*	87.6±7.3*
ΔSV IC, ml/beat	-	20.4±2.5	28.1 ±3.4	23.1±3.7	20.1±3.1
SV DD, ml/beat	54.4±4.2	75.7±6.6	83.7±7.1	78.5±7.6	74.8±6.2
ΔSV DD, ml/beat	-	21.1±2.1	29.1±3.1	24.1±3.3	20.4±3.0
SBP (mmHg)	122±3	148±5	156±7	161±9	170±11
DBP (mmHg)	82±3	84±3	85±4	87±3	90±3
MAP(mmHg)	97±3	106±3	109±3	115±4	117±4
SpO_2, (%)	95.5±0.6	94.2±0.8	93.0±1.0	92.6±1.3	92.2±1.1

Data are presented as mean and SEM for 10 subjects. WRpeak, peak work rate, IC, impedance cardiography (PhysioFlow^{TM}); ECG, electrocardiography, DD, Dye dilution method; HR, heart rate; Δ,changes from rest, SV, stroke volume; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial blood pressure; SpO_2, arterial oxygen saturation measured by pulse oximetry. Asterisks denote significant differences between SV IC and SV DD, P values range between 0.010 and 0.020.

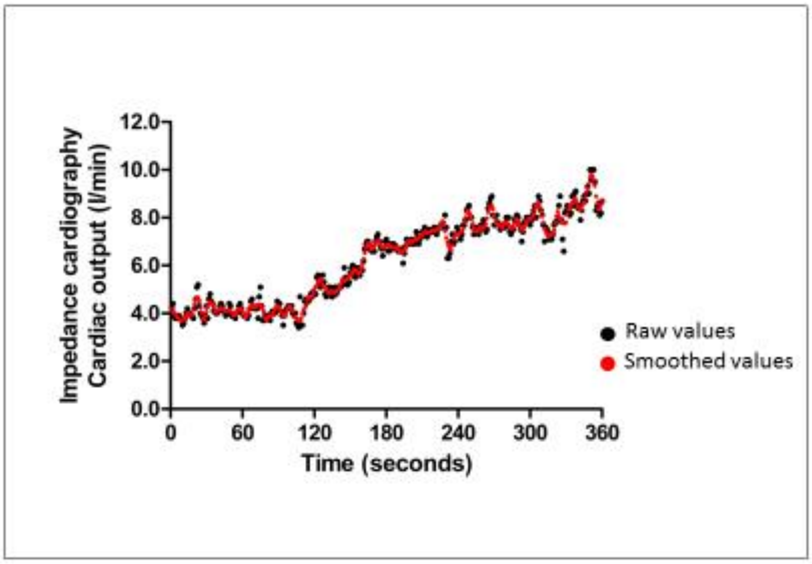


Figure 1.

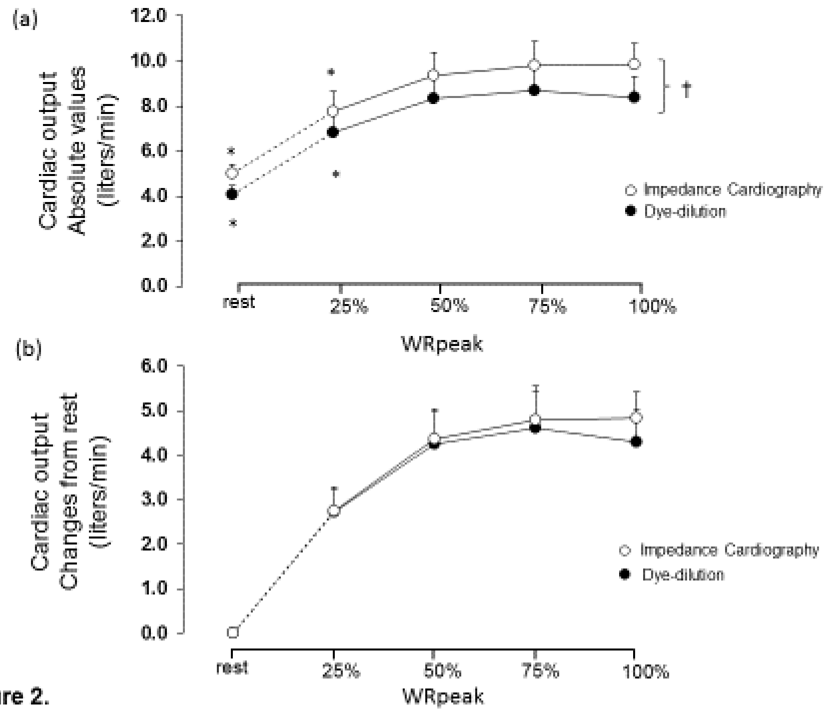


Figure 2.

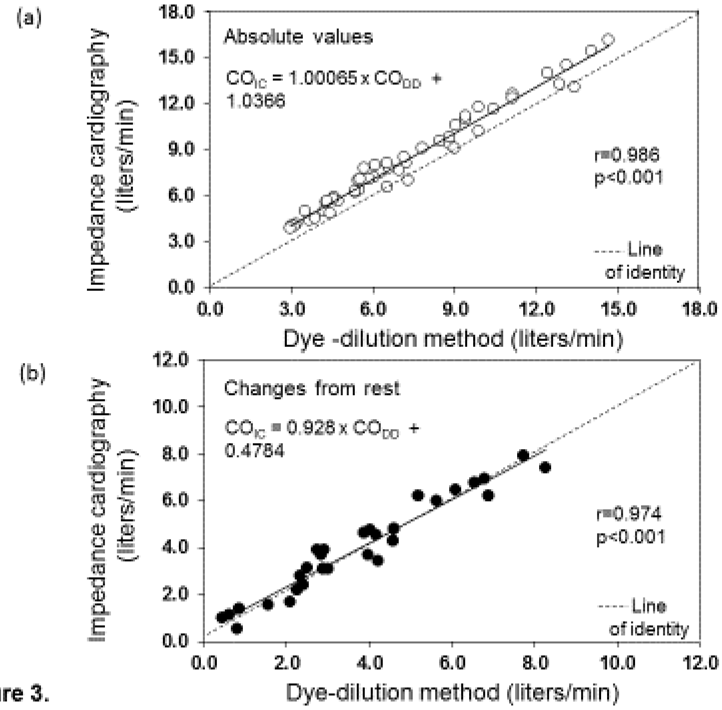


Figure 3.

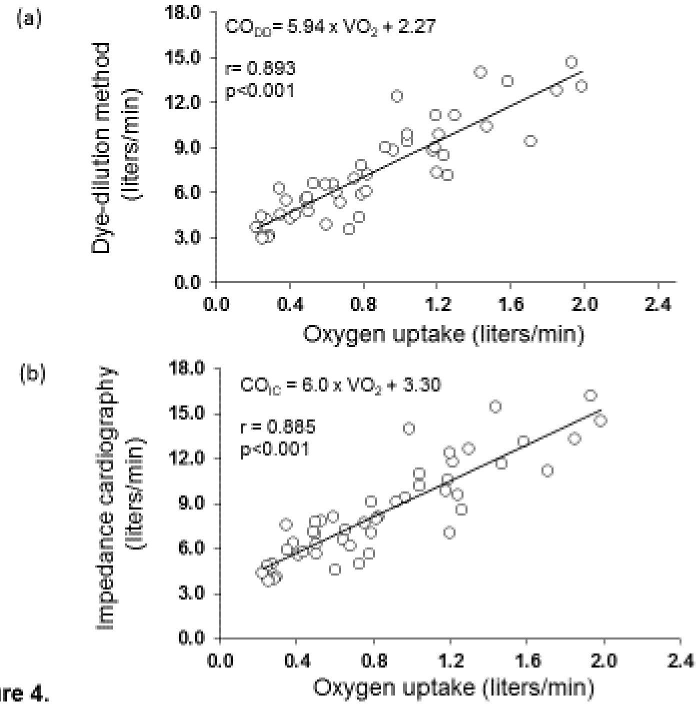
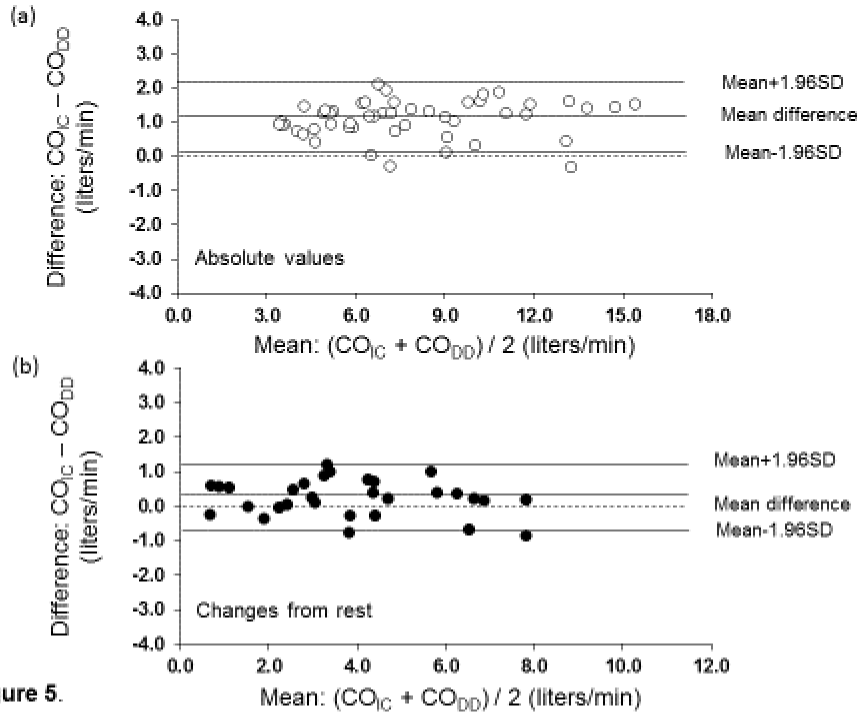


Figure 4.

559 **Figure 5**.


(a)
Difference: CO_IC – CO_DD (liters/min)
Mean+1.96SD
Mean difference
Mean-1.96SD
Absolute values
Mean: (CO_IC + CO_DD) / 2 (liters/min)
(b)
Difference: CO_IC – CO_DD (liters/min)
Mean+1.96SD
Mean difference
Mean-1.96SD
Changes from rest
Mean: (CO_IC + CO_DD) / 2 (liters/min)