

Study full title: Comparison of cardiac output estimates by bioreactance and inert gas rebreathing methods during cardiopulmonary exercise testing

Study short title: Bioreactance and inert gas rebreathing cardiac outputs

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Running title: Bioreactance vs. Inert gas rebreathing cardiac output

Abstract

Purpose. The present study assessed the agreement between cardiac output estimated by inert gas rebreathing and bioreactance methods at rest and during exercise.

Methods. Haemodynamic measurements were assessed in 20 healthy individuals (11 females, 9 males; aged 32 ± 10 years) using inert gas rebreathing and bioreactance methods. Gas-exchange and haemodynamic data were measured simultaneously under rest and different stages (i.e. 30, 60, 90, 120, 150, and 180 watts) of progressive graded cardiopulmonary exercise stress testing using a bicycle ergometer.

Results. At rest, bioreactance produced significantly higher cardiac output values than inert gas rebreathing (7.8 ± 1.4 vs. 6.5 ± 1.7 L/min, $p=0.01$). At low-to-moderate exercise intensities (i.e. 30-90W), bioreactance produced significantly higher cardiac outputs compared with rebreathing method ($p<0.05$). At workloads of 120W and above, there was no significant difference in cardiac outputs between the two methods ($p=0.10$). There was a strong relationship between the two methods ($r = 0.82$, $P=0.01$). Bland-Altman analysis including rest and exercise data showed that inert gas rebreathing reported 1.95 l/min lower cardiac output than bioreactance, with lower and upper limits of agreement of -3.1 to 7.07 l/min. Analysis of peak exercise data showed a mean difference of 0.4 L/min (lower and upper limits of agreement of -4.9 to 5.7 l/min) between both devices.

Conclusion: Bioreactance and inert gas rebreathing methods show acceptable levels of agreement for estimating cardiac output at higher levels of metabolic demand. However, they cannot be used interchangeably due to strong disparity in results at rest and low-to-moderate exercise intensity.

Keywords: Cardiac Output, Exercise testing, Gas rebreathing, Bioreactance

Introduction

Cardiac output is an important measure of cardiac function. It is a measure of the amount of blood pumped out of the heart each minute. Cardiac output assessment at rest and during exercise can provide important information about cardiac function and performance (Jhanji et al. 2008). The average cardiac output for a healthy adult is approximately 5-6 L/min (Hall 2010). This value can increase up to four fold in untrained individuals, and in trained athletes, cardiac output may increase seven fold (Hall 2010).

Cardiac output measurement provides an indication of systemic oxygen delivery and global tissue perfusion (Marik 2013; Wasserman et al. 2000). In patients with heart failure cardiac output obtained during stress testing, coupled with blood pressure, is the strongest predictor of mortality and functional capacity (Roul et al. 1995; Williams et al. 2001; Lang et al. 2009; Bain et al. 1990). Furthermore, monitoring of haemodynamics during surgical procedures reduces time to hospital discharge (Gan et al. 2002; Venn et al. 2002).

The first method for cardiac output evaluation was proposed in 1870 by Adolf Fick (Hoff & Scott 1948), which has since led to the development of more precise and sophisticated methods. Pulmonary artery catheters which use a bolus thermodilution method was introduced a century later (Swan et al. 1970). This was the first clinical device which enabled bedside cardiac output measurement and is now regarded as the invasive gold standard for cardiac output measurement alongside the Fick's technique (Critchley et al. 2010). However, the use of these techniques and their wide clinical applications have been limited due to their invasive nature, cost, need for specialist expertise and the risks of arrhythmia, infection, complications of central line insertion and morbidity, (Harvey et al. 2006; Sandham et al. 2003; Hamilton & Huber 2002). Due to the aforementioned limitations of these 'gold

standard' methods for cardiac output measurements, investigators have tried to identify new technologies that may assist in monitoring cardiac output.

Currently, a number of less invasive and non-invasive monitoring devices are available. These techniques have previously been reviewed in detail elsewhere (Marik 2013), and include pulse contour analysis, oesophageal doppler, CO₂ rebreathing, thoracic bioimpedance and bioreactance. Regrettably, whilst these techniques reduce the risk to patients, their acceptability have been limited by inaccuracy and reliability (Critchley et al. 2010; Booth et al. 2008). The ideal cardiac output monitor should be valid, reliable, reproducible, non-invasive, cheap and should have a fast response time (de Waal et al. 2009). Two novel, non-invasive methods for cardiac output monitoring that have received increased clinical and research attention over the previous years are inert gas rebreathing and, bioreactance methods (Agostoni et al. 2005; Jakovljevic et al. 2014)

Rebreathing methods are based on the principle that exchange rates of physiological or non-physiological gases can be determined from analysis of alveolar gas exchange. Based on this assumption, it is possible to calculate pulmonary capillary blood flow, which constitutes total cardiac output in the absence of intrapulmonary shunt (Agostoni et al. 2005; Christensen et al. 2000). Previous studies have reported that a novel inert gas (nitrous-oxide, (N₂O) rebreathing method is valid and reliable for estimating cardiac output under rest and stress testing conditions (Agostoni et al. 2005; Christensen et al. 2000; Gabrielsen et al. 2002; Jakovljevic, Seferovic, et al. 2012). Additionally, it was demonstrated that inert gas rebreathing outperforms other rebreathing methods (Jakovljevic et al. 2008).

The bioreactance method is based on electrical signal processing technology and estimates cardiac output by analysing the frequency of relative phase shift of electronic current applied across the thorax. (Jakovljevic et al. 2014). Its validity and reproducibility have also been

reported in previous investigations (Marik 2013; Keren et al. 2007; Squara et al. 2009; Maurer et al. 2009; Jones et al. 2015). It has also been reported that bioactance outperforms traditional bioimpedance, particularly during exercise stress testing (Jakovljevic, Moore, et al. 2012).

There is only one study that previously compared bioactance and inert gas rebreathing methods (Elliott et al. 2010). However, the study was performed in trained athletes making its applicability to the generally population limited. In addition the authors reported that there were discrepancies in the results between the two methods. There is a need for further investigation on the performance of both methods, particularly under stress testing. Therefore the aim of this study was to compare cardiac output values obtained by bioactance and inert gas rebreathing methods at rest and cardiopulmonary stress to assess their agreement.

Methods

This was a single centre, observational, direct comparison study between inert gas rebreathing and bioactance method for monitoring cardiac output at rest and during different levels of exercise.

Participants

Ethical approval for this study was provided by the Ethical Committee North-East of England - Tyne and Wear South. Twenty healthy individuals (11 females and 9 males) participated in the study which was conducted at the Clinical Research Facility. All participants performed < sixty minutes of moderate to vigorous activity per week, were non-smokers, normotensive, free from any cardiac and respiratory disorders and on no medication 3 months prior to study commencement, as determined during screening and consent. Subjects were instructed to

abstain from eating for a >2 h before each test and from vigorous exercise 24 h prior to the test. Subjects were also instructed not to consume alcohol or caffeine containing foods and beverages on test days. Upon arrival at the laboratory participants were asked to lay in a supine position for 10 min. Blood pressure was measured in duplicate in the brachial-artery of participant's non dominant arm. Participants then completed a standardised health screening questionnaire and undertook a resting electrocardiogram (ECG). All procedures were according to Declaration of Helsinki. Participants were informed of the benefits and potential risks of the study and they subsequently provided a written informed consent.

Study protocol and measurements

Cardiac output was recorded using bio-reactance and inert gas rebreathing techniques simultaneously at rest and during exercise. In addition, theoretically calculated arterial-venous oxygen difference and consequently cardiac output were also calculated for a given oxygen uptake using equation previously suggested by Stringer and colleagues (Stringer et al. 1997):

$$C(a-vDO_2) = 5.72 + 0.105 \times \% VO_{2max}$$

Where C (a-vDO₂) is arterial venous oxygen difference and % VO₂ max is the percentage of measured maximal oxygen uptake. Gas analysis (e.g. oxygen consumption, ventilation, and respiratory exchange ratio) were measured using the Innocor device (Innovision, Denmark) and exercise was performed on an electro-magnetically controlled semi-recumbent bicycle ergometer (Corival, Lode, Groningen, Netherlands). The test comprised three minutes rest period and progressive exercise of six steady-state stages each lasting 3 min (30, 60, 90, 120, 150 and 180W). Cardiac output was monitored continuously using bioreactance method, whereas rebreathing maneuver was performed at the end of three minute stage. Exercise 12-lead ECG was monitored using Custo Diagnostic system (SunTech Medical Inc. NC, USA).

The test was terminated when the participant was unable to pedal at a cadence of 60 – 70 revolutions per minute or voluntarily terminated the test.

Bioreactance

The bio-reactance system (NICOM, Cheetah Medical, Delaware, USA), is based on an analysis of time-dependent relative phase shifts of an oscillating current that occur when this current traverses the thoracic cavity, as previously described (Keren et al. 2007). The bio-reactance system comprises a radiofrequency generator for creating a high-frequency current that is injected across the thorax. Four dual-surface electrodes are used to establish electrical contact with the body; two were applied over the trapezius muscle on either side of the upper torso and two on the lower posterior torso lateral to the margin of the latissimus dorsi musculature. Signals were applied to and recorded from the left and right sides of the thorax, the signals processed separately and averaged after digital processing. The signal processing unit of the system determines the relative phase shift between the input signals relative to the output signals. This phase shift is due to instantaneous changes in blood flow in the aorta. Cardiac output (QT) was subsequently calculated by:

$$QT = (C \times VET \times \Delta\phi/dt_{\max}) \times HR$$

Where C is a constant of proportionality and VET is ventricular ejection time, which is determined from the bio-reactance and electrocardiogram signals, $\Delta\phi/dt_{\max}$ is the relative phase shift of current and HR is heart rate. The value of C has been optimized in prior studies (Squara et al. 2007) and accounts for patient age, gender and body size. Electrodes and all connecting wires were additionally secured with the tape to ensure minimal movement artifact.

Inert gas rebreathing

The inert gas rebreathing method was performed using the Innocor system (Innovision, Odense, Denmark). The system assumes that alveolar uptake of a blood soluble gas is proportional to pulmonary blood flow in the absence of intrapulmonary shunt. The rebreathing system consists of a three-way respiratory valve unit with a mouthpiece and a rebreathing bag connected to an infrared photo-acoustic gas analyser. Respired gases were sampled continuously from the mouthpiece and analysis of oxygen consumption, respiratory exchange ratio and minute ventilation performed by the infrared photo-acoustic gas analyser. Cardiac output was measured by rebreathing in a closed system (subjects wore face masks that covered mouth and nose for collection of expired air). The closed system contains a gas mixture of 0.5% nitrous oxide, N₂O (blood-soluble gas), 0.1% sulphur hexafluoride, SF₆ (blood-insoluble gas) and 28% O₂ in balanced Nitrogen in a 5 l rubber bag. The gas distribution system controlled the pneumatics for the respiratory valve unit and the filling or emptying of the rebreathing bag. Rebreathing was performed and lasted about 8-12 seconds with a gas volume of 40-60% of the participants' predicted vital capacity. A constant ventilation rate during rebreathing was ensured by having the participant breathe in and out synchronously with a graphical tachymeter on the Innocor screen, which was set up to indicate the breathing frequency of 20 breaths per minute. A constant rebreathing volume was also ensured by requesting the participant to completely empty the rebreathing bag with each inspiration. The Innocor software calculated cardiac output from the rate of uptake of N₂O. N₂O concentration decreases during the rebreathing manoeuvre, with a rate proportional to pulmonary blood flow. This is based on the slope of the regression line through logarithmically transformed expiratory (i.e., alveolar) N₂O concentrations plotted against time after correction for system volume changes using the SF₆ concentration. SF₆ was used to determine the volume of the lungs, and accordingly the volume of air to fill the rebreathing

bag. The first two or three breaths were excluded from the analysis due to initial incomplete gas mixing. Rebreathing determines effective pulmonary blood flow, which constitutes cardiac output in the absence of intra-pulmonary shunt.

Data Analysis

Data are expressed as mean \pm SD unless otherwise stated. Normality of distribution was evaluated using a Kolmogorov-Smirnov test. One-way analysis of variance with a post hoc (tukey) test was used to assess differences between the bioreactance and inert gas rebreathing and theoretically calculated cardiac output values. Pearson's correlation coefficient was used to evaluate the relationship between cardiac output and oxygen uptake measures taken at different time points. Paired *t*-tests were also used to assess differences between the two methods at different intensities of exercise. Bland-Altman plots were constructed to evaluate the upper and lower limits of agreements (\pm 2SD of mean difference) between bioreactance and inert gas rebreathing methods (Bland & Altman 1986). All statistical analysis was carried out using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Participants were aged 32 ± 10 years, weight 74 ± 10 kg, height 171 ± 8 cm and **body surface area 1.83 ± 0.2 m²** with a maximal oxygen consumption (VO_{2max}) of 2.17 ± 0.7 Lmin⁻¹. In all subjects a stable bio-reactance signal was obtained at rest, whereas 18 out of 20 participants (90%) successfully carried out the rebreathing procedure at rest. Resting cardiac output estimated by bioreactance and inert gas rebreathing methods were significantly different ($P = 0.01$, respectively), which was likely due to the significant difference in stroke volume estimates (Table 1).

During exercise, the inert gas rebreathing method reported lower cardiac output values compared to bioreactance throughout the test and values were significant at low to moderate exercise intensities ($P < 0.001$, Table 1). However at higher intensities (120 – 180 Watts), there was no significant difference between the two methods (Table 2). There was a strong positive relationship between bioreactance inert gas rebreathing cardiac outputs ($r = 0.87$, $p < 0.001$) (Figure 1). Similarly, there was a strong relationship between oxygen uptake and bioreactance and inert gas rebreathing cardiac outputs (Figure 2)

Theoretically estimated arteriovenous oxygen difference and cardiac output at peak exercise were 16.2 ml/dl and 18.0l/min respectively. This did not differ significantly with values estimated from inert gas rebreathing (16.6 ml/dl and 17.1l/min) and bioreactance (15.5ml/dl and 17.9 l/min). Figure 3 shows mean cardiac output values obtained at rest and during exercise using inert gas rebreathing and bioreactance methods and those theoretically calculated using the Stringer's equation.

Bland-Altman analysis including rest and exercise demonstrated that inert gas rebreathing method reported 1.95 l/min lower cardiac output than bioreactance, with lower and upper limits of agreement -3.1 to 7.1 l/min (Figure 4). Further analysis showed that much of the difference occurred during low to moderate exercise intensities (up to 90watts) with the mean difference of 2.7l/min, and lower and upper limits of agreement of -1.6 to 7.0 l/min. At higher intensities (120 -180 watts) the mean difference between both methods was 1.2 l/min, with lower and upper limits of agreement -5.03 to 7.4l/min. Interestingly, when data from peak exercise was analysed, mean difference in cardiac output between both devices was 0.4 L/min (lower and upper limits of agreement of -4.9 to 5.7 l/min).

Discussion

The purpose of the present study was to compare two non-invasive methods for estimating cardiac output i.e. bioreactance and inert gas rebreathing under rest and exercise stress testing conditions. The major findings suggest that inert gas rebreathing method consistently reported lower cardiac output values than bioreactance at rest and during exercise. These differences were particularly emphasized during low to moderate exercise intensities. However, the difference between the two methods was not significantly different at higher and peak exercise intensities. There were strong relationships between the two methods and peak oxygen consumption. However, calculated limits of agreement were wide and unacceptable, suggesting that the two methods cannot be used interchangeably.

The data presented here are consistent with previous studies that have reported lower cardiac output from the inert gas rebreathing when compared with other non-invasive cardiac output measuring devices e.g. pulse contour analysis, (Bartels et al. 2011; Siebenmann et al. 2015). This is probably due to recirculation of N₂O which reduces alveolar-arterial diffusion gradient for N₂O and further attenuate N₂O uptake (Bartels et al. 2011). Furthermore, incomplete mixing of gases at rest and low intensity exercise results in an underestimation of cardiac output (Gabrielsen et al. 2002; Peyton et al. 2005). In contrast to the present findings and previous reports, Elliott et al. (2010) reported a significantly lower cardiac output from bioreactance compared to the inert gas rebreathing when trained athletes were assessed. They reported a systematic bias between both devices at rest and during all exercise intensities. The study design however may have been a limiting factor. Initial exercise intensity of 150W might have warranted substantial body movement to adjust to this intensity at the start of exercise. A recumbent bike which reduces upper body movements would have been a better choice with the bioreactance device as the Velotron ergometer used may have also contributed to the interference/ movement artefacts, underestimated values of heart rate and loss of electrocardiograph signal reported in the study.

A similar study which compared bioreactance with bioimpedance reported no significant difference in resting cardiac output. However, at increasing exercise intensities, a significant disparity between the two methods was reported (Jakovljevic, Moore, et al. 2012). The authors noted differences in technology as a possible factor for this disparity. While bioreactance works on the analysis of beat-by-beat changes in electrical current travelling across the thoracic cavity, bioimpedance is based on the measurement of resistance to the transmission of electrical current in the thorax. Interestingly, the present study showed no significant difference between bioreactance and inert gas rebreathing methods at exercise intensities ≥ 120 watts. This could be explained physiologically by increase in lung volume and blood flow as exercise progressed, thereby leading to adequate mixing and uptake of rebreathing gases (Bartels et al. 2011). Our result thus supports the notion that rebreathing methods are more accurate for monitoring cardiac output during increased metabolic demand and higher exercise intensities (Saur et al. 2009).

In the current study there was a linear increase in oxygen consumption during incremental exercise for both methods, which was proportional to oxygen uptake, as previously suggested (Elliott et al. 2010). Cardiac outputs obtained by bioreactance and inert gas rebreathing demonstrated a strong positive relationship with oxygen consumption. Stringer et al., 1997 (Stringer et al. 1997), demonstrated that if oxygen consumption was measured, arterial venous oxygen difference and cardiac output could be calculated with a high degree of accuracy and this could be a useful surrogate indicator of the accuracy of a cardiac output measuring device (Elliott et al. 2010). Using the Stringer equation, mean peak exercise cardiac output was 18.0l/min. This value was similar to those estimated by bioreactance (17.9 l/min) and inert gas rebreathing (17.1 l/min).

Both cardiac output methods were non-invasive and easy to operate, however, the inert gas rebreathing required a high level of subject – operator coordination and familiarization

procedure before actual measurements. In contrast to inert gas rebreathing, bioreactance provides continuous cardiac output monitoring. Furthermore, it is patient-friendly and does not require a familiarization procedure and therefore may have wider application, especially in different clinical settings where cardiac output monitoring is warranted. In stark contrast the inert gas rebreathing method is not continuous and only provides cardiac output measurements at specific time points during testing, and is less user friendly for patients. However, the inert gas re-breathing is also coupled with gas exchange and respiratory data and thus may provide further insight into cardiovascular pathology underlying diminished functional capacity in many clinical conditions presented with exercise intolerance (Farina et al. 2014). Furthermore, it could also be used as previously suggested in settings where bioreactance electrical signal can potentially be diminished due to interference with cardiac devices i.e. patients implanted with left ventricular assist device (Jakovljevic et al. 2010; Jakovljevic, Seferovic, et al. 2012).

In the present study the following limitations should be considered. First, the gold standard method for cardiac output assessment was not included. Applying any of the gold standards to this study could have raised ethical concerns as there would have been increased risk to the study's healthy population due to its invasive nature. However, both techniques have been previously validated against the invasive gold standard methods i.e. thermo-dilution and Fick's techniques. Results revealed acceptable levels of agreement between bioreactance and inert gas rebreathing with these invasive methods (Rich et al. 2013; Agostoni et al. 2005; Gabrielsen et al. 2002; Christensen et al. 2000). Secondly, in four subjects we experienced gas leakage during rebreathing due to inappropriate mask fitting but this was corrected immediately. The rebreathing maneuver is a discontinuous process and requires extra effort during exercise which may pose significant challenge in clinical groups.

In conclusion, bioreactance and inert gas rebreathing methods provide different cardiac output estimates particularly at rest and during lower intensities of exercise, and therefore cannot be used interchangeably. Technological differences are likely to explain discrepancies in cardiac output estimates between the bioreactance and inert gas rebreathing cardiac outputs. Future studies are warranted to assess performance of bioreactance and inert gas rebreathing methods against the gold standard procedure in broader clinical settings.

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Conflict of interest: None

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Tables

Table 3.1. Comparison of haemodynamic variables by bioreactance and inert gas rebreathing methods under resting condition and low to moderate exercise intensity.

	REST ^a				30W ^b				60W ^c				90W ^d			
	BR	IGR	TCO	P	BR	IGR	TCO	P	BR	IGR	TCO	P	BR	IGR	TCO	P
CO (l/min)	7.8±1	6.5±2	4.8±1	0.01	12.4±2	9.8±3	10.6±2	0.01	13.8±3	10.7±2	12.7±2	<0.01	14.6±3	12.3±2	14.5±3	<0.01
CI (l/m²/min)	4.4 ±1	3.5 ±1		<0.01	6.8±1	5.3±1		<0.01	7.6±1.2	5.8±1.1		<0.01	8.0±1.2	6.7±1.0		<0.01
SV (ml)	104± 14	90±28		0.06	134±23	114±29		0.06	133±31	105±29		0.01	117±29	104±30		0.10
HR (b/min)	76 ±12	76±13		0.89	95±10	95±13		0.99	109±10	108±11		0.78	128 ±10	128±11		0.97

BR- bio-reactance; IGR- Inert gas rebreathing; TCO- theoretically calculated cardiac output; CO- cardiac output; CI- Cardiac index; SV- Stroke Volume; HR- Heart rate; Data presented as mean (SD). Subjects ^an=18, ^bn=14, ^cn=16, ^dn=19, for which concurrent data were available. P value presented for paired t-test of Bioreactance vs Inert gas Rebreathing .

Table 3.2 Comparison of haemodynamic variables by bioreactance and inert gas rebreathing methods during higher intensity exercise

	120W ^e				150W ^f				180W ^g			
	BR	IGR	TCO	P	BR	IGR	TCO	P	BR	IGR	TCO	P
CO (l/min)	15.9±2.4	14.7±3.2	17.8±3	0.20	18.1±2.7	17.6± 3.2	19.5±3	0.54	21.6± 3.3	18.5 ± 2.6	20.9±3	0.10
CI (l/m²/min)	8.6± 0.9	7.9± 1.6		0.10	9.8± 1.1	9.3± 1.6		0.34	10.9± 1.5	9.2 ± 1.8		0.07
SV (ml)	116±26	115±49		0.96	140±37	122± 23		0.15	124±23	119± 30		0.70
HR (b/min)	147±11	147±11		1.00	159±16	158±15		0.88	173±14	172±15		0.77

BR- Bioreactance; IGR- Inert gas rebreathing CO- cardiac output; TCO- theoretically calculated cardiac output; CI- Cardiac index; SV- Stroke Volume;

HR-Heart rate; Data presented as mean ± SD. Subjects ^en=18, ^f n=15, ^g n=7, for which concurrent data were available. P value presented for paired t-test of

Bioreactance vs Inert gas Rebreathing.

Figures

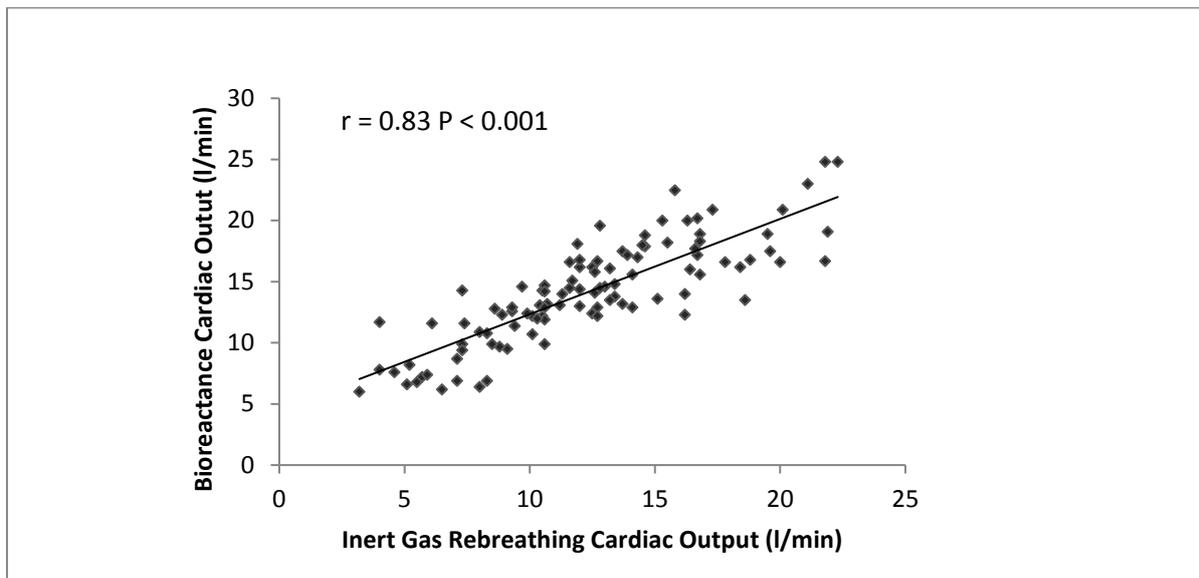


Figure1 Relationship between bioreactance and Inert gas rebreathing cardiac outputs.

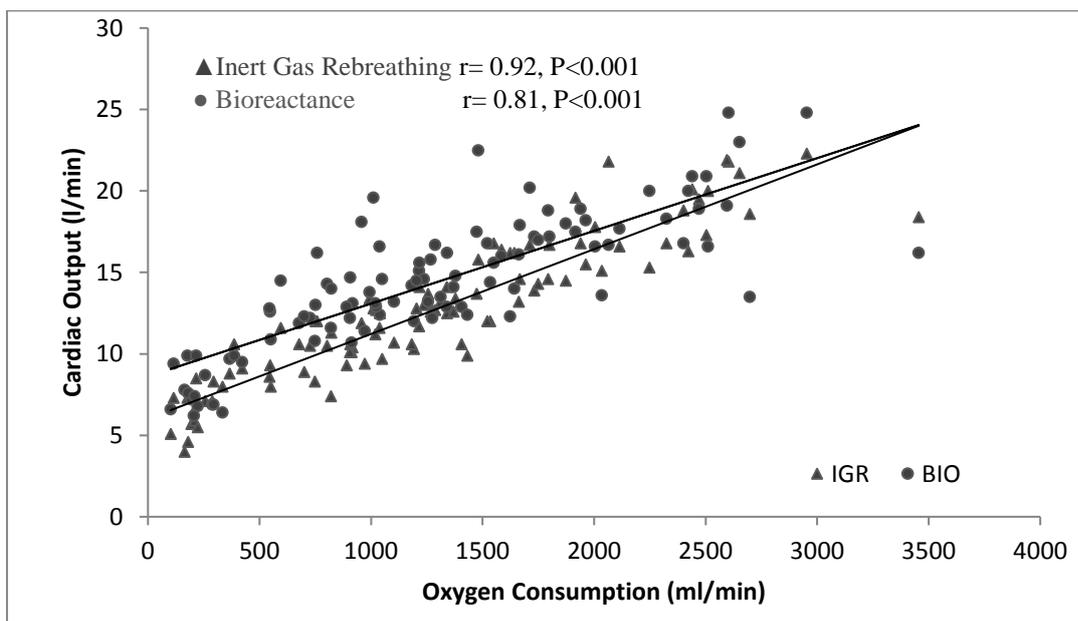


Figure2 Relationship between Bioreactance and Inert gas rebreathing cardiac outputs to oxygen consumption.

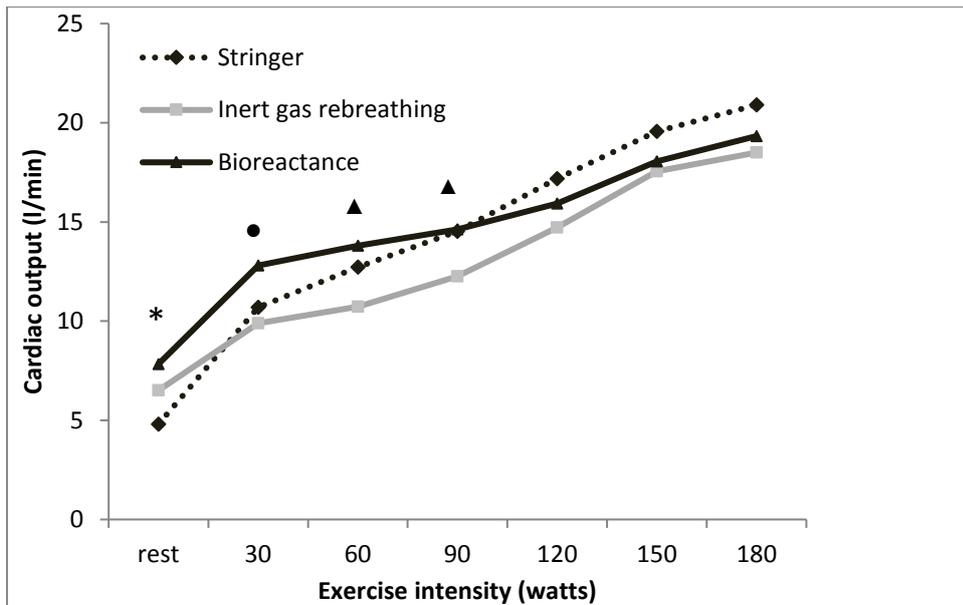


Figure3 Comparison of cardiac output estimated using theoretically calculated cardiac output (Stringer et al., 1997 [29]), bioreactance and inert gas rebreathing methods at rest and during different exercise intensities. * $P < 0.05$ Stringer vs rebreathing vs bioreactance; • $P < 0.05$ Stringer vs Bioreactance, ▲ $P < 0.05$ Stringer vs inert gas rebreathing.

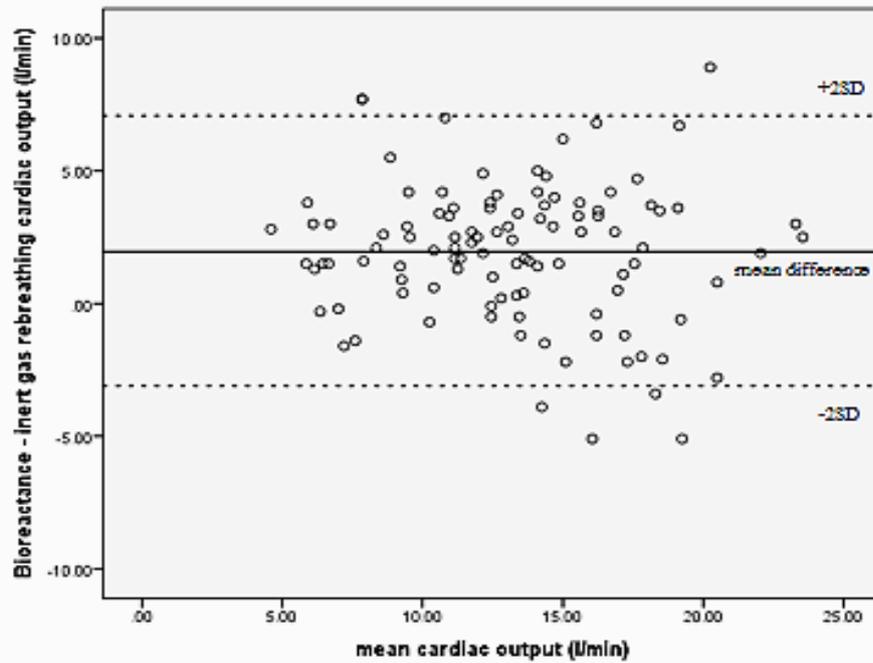


Figure 4 Bland-Altman plot to demonstrate limits of agreement between bioreactance and inert gas rebreathing cardiac outputs measured at rest and during exercise. The solid line represents the mean bias (mean difference) and the dashed lines represent lower and upper limits of agreement.