

Reproducibility of Inert Gas Rebreathing Method to Estimate Cardiac Output at Rest and During Cardiopulmonary Exercise Stress Testing

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Bibliography

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ABSTRACT

The present study evaluated reproducibility of the inert gas rebreathing method to estimate cardiac output at rest and during cardiopulmonary exercise testing. Thirteen healthy subjects (10 males, 3 females, ages 23–32 years) performed maximal graded cardiopulmonary exercise stress test using a cycle ergometer on 2 occasions (Test 1 and Test 2). Participants cycled at 30-watts/3-min increments until peak exercise. Hemodynamic variables were assessed at rest and during different exercise intensities (i. e., 60, 120, 150, 180 watts) using an inert gas rebreathing technique. Cardiac output and stroke volume were not significantly different between the 2 tests at rest 7.4 (1.6) vs. 7.1 (1.2) liters min⁻¹, p=0.54; 114 (28) vs. 108 (15) ml beat⁻¹, p=0.63 and all stages of exercise. There was a significant positive relationship between Test 1 and Test 2 cardiac outputs when data obtained at rest and during exercise were combined (r=0.95, p<0.01 with coefficient of variation of 6.0%), at rest (r=0.90, p<0.01 with coefficient of variation of 5.1%), and during exercise (r=0.89, p<0.01 with coefficient of variation 3.3%). The mean difference and upper and lower limits of agreement between repeated measures of cardiac output at rest and peak exercise were 0.4 (–1.1 to 1.8) liter min⁻¹ and 0.5 (–2.3 to 3.3) liter min⁻¹, respectively. The inert gas rebreathing method demonstrates an acceptable level of test-retest reproducibility for estimating cardiac output at rest and during cardiopulmonary exercise testing at higher metabolic demands.

Introduction

Cardiac output is an important parameter of the cardiovascular system function, which provides an indication of systemic oxygen delivery and tissue perfusion. Changes in cardiac function are commonly reported in response to exercise training and pharmacological interventions [5]. Therefore, methods that can accurately detect hemodynamic changes in response to a clinical intervention are desirable. Cardiopulmonary exercise testing is recommended in evaluation of cardiorespiratory fitness and exercise tolerance in athletes, general population and patients [2–5]. Cardiac output measurement during stress testing helps define physiological adaptive mechanisms in response to an intervention. Additionally, it can improve risk stratification and management of patients with coronary artery disease, heart failure and those undergoing elective cardiac and non-cardiac surgeries [5–8].

To date, there is no consensus on the best method for measuring cardiac output. In addition to being accurate, reproducible, safe, and easy to perform, new technologies in medicine should also be non-invasive. Currently available methods (i. e., pulse contour, esophageal Doppler, carbon dioxide rebreathing, bioimpedance) rely on various assumptions and have limitations that restrict their routine use in medical practice [9–13]. Cardiac magnetic resonance imaging is currently accepted as the non-invasive gold standard method for cardiac output assessment [14, 15]. However, this technique is expensive, time consuming and not applicable in daily practice [36].

A non-invasive approach for cardiac output measurement at rest and during cardiopulmonary exercise stress testing is inert gas rebreathing (Innocor, Innovision, Denmark) [1]. In principle, it functions by measuring the rate of clearance of a physiologically inert gas from the pulmonary capillary circulation, which is directly proportional to pulmonary blood flow [9]. If the inert gas completely diffuses into the pulmonary capillary circulation (i. e., in the absence of significant pulmonary shunt flow) pulmonary blood flow equals total cardiac output [36]. Previous studies have reported promising results for monitoring cardiac output using this method when compared with the invasive gold standard thermodilution [19, 20], and more recently, cardiac magnetic resonance imaging the non-invasive gold standard [15, 21].

The 2 most important features of any clinical test are validity and reproducibility. A common method of assuring a reproducible response to cardiopulmonary exercise testing is to have the patient perform 2 exercise tests on separate days, at the same time of the day; a test is considered reproducible, if functional capacity of the cardiorespiratory system (i. e., peak oxygen uptake) is within 10% on both days [26].

Reproducibility of inert gas rebreathing method was subject to limited number of previous clinical investigations [17, 23]. However, these investigations have been focused on a reproducibility of measurements obtained in patients with limited functional capacity. To obtain a better insight into performance of the inert gas rebreathing method, ideally the study design will involve assessment of cardiac output at different levels of metabolic demand. Therefore, we designed the present study with the aim of assessing test-retest reproducibility of inert gas rebreathing method at rest and different stages of graded cardiopulmonary exercise testing in healthy volunteers.

Materials and Methods

Participants

Thirteen participants (10 males) who were non-smokers and free from cardiorespiratory, metabolic, and musculoskeletal diseases were enrolled in the study. The study protocol (number 15/NE/0190) was approved by the local research Ethics Committee and all procedures were in accordance with the Declaration of Helsinki and Standards for Ethics in Sport and Exercise Science Research [15]. All participants provided written informed consent. All aspects of the study were conducted at the Clinical Research Facility of the Royal Victoria Infirmary, Newcastle upon Tyne. Participants visited the laboratory on 2 occasions (2 days apart, Test 1 and Test 2) and were instructed to abstain from vigorous exercise 24 h prior to each visit and from eating for at least 2 h prior to each visit. Subjects were also instructed not to consume alcohol or caffeine containing foods and beverages on the test days. Upon arrival at the laboratory, participants were asked to complete a standardized health screening questionnaire. This was followed by a 10-min rest period in supine position when blood pressure and ECG were measured.

Study protocol and measurements

Cardiac output, coupled with gas exchange metabolic and ventilatory data at rest and during exercise was recorded using the Innocor device (Innovision, Odense, Denmark), which uses inert gas rebreathing technique [17, 24]. Exercise testing was performed on an electro-magnetically controlled semi-recumbent bicycle ergometer (Corival, Lode, Groningen, Netherlands). The test comprised a 3-min rest period followed by a progressive exercise test of 6 steady-state stages each lasting 3 min (30, 60, 90, 120, 150 and 180 watts). Rebreathing maneuver and cardiac output recording were performed at rest and at 60, 120, 150 and 180 watts. ECG and blood pressure were monitored throughout exercise using a 12-lead ECG with Custo Diagnostic system (SunTech Medical Inc. NC, USA). The test was terminated when participants were unable to maintain a cadence of 60–70 revolutions per minute, or desired to stop. Peak exercise intensity was regarded as the maximum power output (watts) achieved before exercise was stopped.

Inert gas rebreathing

Inert gas rebreathing is based on the Fick's principle and assumes that the rate of disappearance of a blood soluble gas from the alveoli is proportional to pulmonary blood flow in the absence of an intrapulmonary shunt. The rebreathing system consists of a breathing valve attached to an online infrared photo-acoustic gas analyzer, which measures cardio-metabolic parameters in a closed system containing 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. During rebreathing, the volume of blood soluble gas (N₂O) in the alveoli decreases due to dissolution in the blood, and the concentration of the insoluble gas decreases from the initial value in the bag to a final equilibrium value obtained after a few breaths. The Innocor software calculates cardiac output from the rate of uptake of expiratory (alveolar) N₂O and is extrapolated from the gradient of logarithmically transformed N₂O concentrations plotted against

time. Stroke volume is calculated as the ratio between estimated cardiac output and measured heart rate.

Data analysis

Data analyses were carried out using SPSS version 24.0 (SPSS Inc., Chicago, IL, USA). Data are expressed as mean (SD). Reproducibility of hemodynamic and metabolic variables were calculated using a coefficient of variation (CV) while linear relationships between repeated measures were assessed using Pearson's correlation coefficient (r). CV was calculated as a percentage of within-person SD divided by the within-person average. A CV of $\leq 6\%$ was considered good reproducibility, while CVs of 6–10% and $> 10\%$ was considered acceptable and poor reproducibility, respectively [19]. Additionally, Bland-Altman plots were constructed to evaluate the upper and lower limits of agreements (± 2 SD of mean difference) of cardiac output measured at rest and different intensities of exercise [3]. Cardiac output trending analysis was performed using a polar plot method described by Critchley and colleagues [7].

Results

Physical characteristics of the subjects were: age 27 (23–32) years, weight 69.5 (9.7) kg, height 171 (7) cm, body mass index 23.5 (2.2) kg/m² and body surface area 1.8 (0.2) m². All subjects completed each exercise test without any contraindication and a total of 46 paired rebreathing maneuvers were performed.

There was no significant difference in resting and exercise metabolic and ventilatory variables between Test 1 and Test 2 (► **Table 1**). At rest and at all stages of exercise, there were no significant differences in cardiac output values between Test 1 and Test 2 (► **Fig. 1**).

There were no significant differences between other hemodynamic variables (i. e., heart rate and stroke volume) at rest and during exercise between the 2 tests (► **Table 2**). There was a strong relationship between Test 1 and Test 2 cardiac outputs when all data (rest and exercise) were combined together ($r = 0.95$, $p < 0.01$ ► **Fig. 2**).

When all data were combined (rest and exercise), coefficient of variation for cardiac output, stroke volume and oxygen consumption were 6.0%, 11.1% and 5.7%, respectively. Coefficients of correlations and variations for resting and each exercise stage's hemodynamic data are presented in ► **Table 2**.

Resting cardiac output (7.4 (1.5) vs 7.1 (1.1) liters min⁻¹) and peak cardiac output 18.7 (3.6) vs 18.2 (4.1) liters min⁻¹) between both tests were not significantly different. The agreement between cardiac output estimates at Test 1 and Test 2 are shown using Bland-Altman analyses (► **Fig. 3a-d**). Rest and peak exercise cardiac outputs between Test 1 and Test 2 showed mean difference and limits of agreement of 0.4 (–1.1 to 1.8 liters min⁻¹, ► **Fig. 3b**) and 0.9 (–0.9 to 2.6 liters min⁻¹, ► **Fig. 3d**). Further analysis including rest and exercise data together demonstrated a mean difference (limits of agreement) of 0.3 (–2.64 to 3.24 liters min⁻¹, ► **Fig. 3a**), while the mean difference of low intensity (60 watts) and higher intensities (120–180 watts) were –0.1 (–5.0 to 4.8 liters min⁻¹) and 0.3 (–2.43–3.02 liters min⁻¹, ► **Fig. 3c**), respectively.

Polar analysis after central exclusion showed a mean polar angle of 3 degrees, radial limits of agreement of less than 19° and a concordance rate of 87%. Centrally occurring data was excluded when change in cardiac output was analyzed. This was because small

changes in cardiac output represent statistical noise, which makes detection of true cardiac output changes difficult. There was also a strong positive correlation between cardiac output and oxygen consumption for both tests ($r > 0.91$, $P < 0.05$) signifying that with increasing metabolic demand there was increased ejection of blood to meet oxygen and nutritional demand of exercise muscles. However, only a moderate positive relationship was seen between peak exercise stroke volume and oxygen pulse although this was not significant ($r = 0.49$, $p = 0.18$).

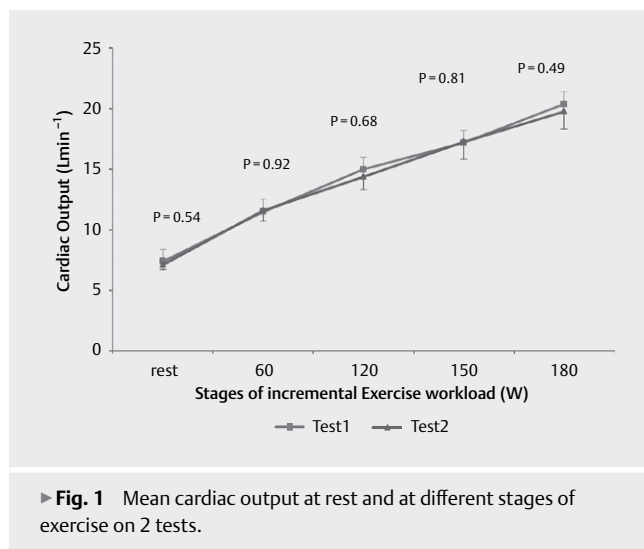
Discussion

The present study assessed the test-retest reproducibility of resting and exercise hemodynamic and metabolic parameters in healthy individuals using inert gas rebreathing. The data show that the inert gas rebreathing method demonstrates acceptable levels of reproducibility in estimating cardiac output. Assessment of pulmonary blood flow and thus cardiac output from uptake of nitric oxide using inert gas rebreathing is safe and feasible. Reproducibility is usually assessed by performing 2 or more tests at different time intervals using a particular technique and maintaining similar testing conditions. A technique is assumed to be reproducible, if the coefficient of variation of that test parameter was within 10% on repeated tests [26]. A limited number of studies reported reproducibility of rebreathing methods for measuring cardiac output in clinical conditions [17, 23–25], and our study provides further evidence of the reproducibility of the inert gas rebreathing method using N₂O as a test gas. In this study, we reported acceptable reproducibility of inert gas rebreathing method in estimating cardiac output with mean CVs of 6.9 and 6.2% for rest and exercise measurements, respectively. These data are consistent with previous studies that have reported reproducibility of resting or peak exercise measurements in heart failure patients with a CV between 3.4 and 11%. [17, 20, 25]. At low exercise intensity, i. e., 60 watts in the present study, reproducibility of cardiac output from inert gas rebreathing was poorer than at rest and at higher exercise intensities (CV, 12.5%). This was possibly due to constant fluctuations in stroke volume, which showed a high CV of 11.9% in response to onset of exercise whereas the heart rate remained fairly stable with a low CV of 3%. Fontana et al. [13] noted that at exercise intensities below 70% of an individual's maximal capacity there was a significant difference in repeated measures of stroke volume. They also suggested better volume reproducibility during higher exercise intensities. This may shed some light on the use of inert gas rebreathing method for clinical cardiopulmonary exercise testing. Based on our current findings and those of Fontana et al. [13], it seems reasonable to suggest that the most reproducible cardiac output results using inert gas rebreathing methods can be obtained at high exercise intensities due to better reproducibility of the stroke volume component of cardiac output. Interpretation of inert gas rebreathing cardiac output data obtained at the beginning of cardiopulmonary exercise testing and low exercise intensities should be considered with caution when suggesting a potential effect of clinical interventions on cardiac function. This is clinically relevant as hemodynamic response to dynamic exercise, especially at high intensities and peak exercise, defines overall function and performance of the heart, and can help explain the mechanisms underlying exercise intolerance [29–31].

► **Table 1** Reproducibility of metabolic measurements at rest and peak exercise.

Variables	Test 1	Test 2	P value	r	CV (%)
Rest					
VO ₂ (liter min ⁻¹)	0.3 (0.1)	0.3 (0.1)	0.86	0.43	15.9
VO ₂ (ml kg ⁻¹ min ⁻¹)	4.4 (1.7)	4.7 (1.6)	0.69	0.65	15.3
VCO ₂ (liter min ⁻¹)	0.3 (0.1)	0.3 (0.1)	0.83	0.44	17.3
VE (liter min ⁻¹)	10.9 (3.3)	10.9 (2.9)	0.97	0.64	15.4
RER	0.8 (0.1)	0.8 (0.1)	0.65	0.32	4.5
SPO ₂ (%)	97 (1)	98 (1)	0.20	0.52	0.4
Oxygen pulse (ml beat ⁻¹)	4.5 (1.7)	5.0 (1.7)	0.41	0.73	14.0
Peak Exercise					
VO ₂ (liter min ⁻¹)	2.2 (0.5)	2.2 (0.5)	0.88	0.60	8.9
VO ₂ (mlkg ⁻¹ min ⁻¹)	32.5 (6.7)	32.9 (6.2)	0.84	0.95	3.7
VCO ₂ (liter min ⁻¹)	2.3 (0.6)	2.3 (0.4)	0.79	0.38	10.9
VE (liter min ⁻¹)	62 (14)	57 (16)	0.43	0.75	9.8
RER	1.0 (0.1)	1.0 (0.1)	0.26	0.85	3.1
SPO ₂ (%)	95 (3)	97 (2)	0.26	0.60	0.9
Oxygen pulse (ml beat ⁻¹)	19.3 (6.3)	18.6 (6.0)	0.79	0.84	3.2

VE- minute ventilation, VO₂- Oxygen consumption, SPO₂- peripheral oxygen saturation, RER- respiratory exchange ratio VCO₂- carbon dioxide release. Data are expressed as mean (SD)



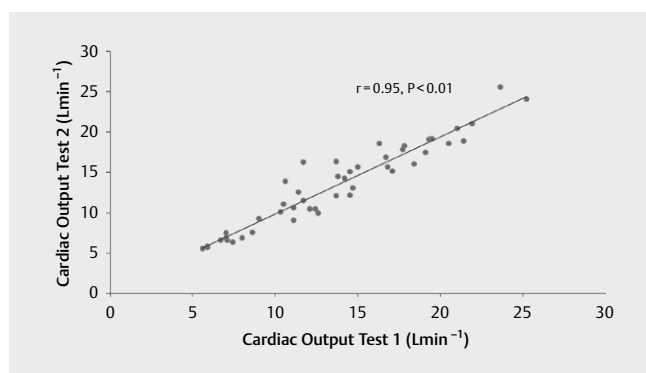
The present results have shown very good reproducibility of inert gas rebreathing method with increased metabolic demand. When cardiac output was analyzed at peak exercise, reproducibility was even better with a 3.3% coefficient of variation. At rest and at low intensity exercise, it is possible that not all parts of the lungs are perfused and also ventilated. This means there is incomplete mixing of gases and possibly a pulmonary shunt that may result in slight variation of cardiac output values as previously suggested [30]. As exercise intensity surpasses the anaerobic threshold, the increase in lung volume and pulmonary blood flow progresses, thereby leading to adequate mixing and uptake of rebreathing gases [2]. Our peak exercise cardiac output result thus corroborates the notion that rebreathing methods are more accurate for monitoring cardiac output during increased metabolic demand and higher exercise intensities

[35]. Although there is a paucity of data on reproducibility of inert gas rebreathing during different exercise intensities, our findings are in agreement with one previous study conducted in patients with heart failure demonstrating low CV and acceptable reproducibility [19]. Only one study [1] has investigated the reproducibility of cardiac output measured by inert gas rebreathing at rest and during different stages of graded exercise. Unlike the present study which showed better reproducibility as exercise intensity increased, Agostoni et al. reported a CV ranging between 9 and 11% for all exercise intensities. However, testing was done on heart failure patients. It has been previously suggested that resting cardiac output values in healthy adults may range between 4 and 8 l/min [40]. Values similar to ours have previously been reported by Fontana et al. [13] and Reutershan et al. [33]. It is possible that the rebreathing technique may require increased metabolic demand and consequently slightly increased values of cardiac output at rest, as previously suggested [27]. This may be due to the increased breathing frequency required, which increases oxygen demand from respiratory muscles and in turn increases cardiac output [18]. Other studies have reported an underestimation of cardiac output by the N₂O rebreathing technique compared to other techniques at rest and during exercise [36, 37], with > 30% of recorded values lower than what was considered possible [39]. This is possibly due to recirculation of N₂O [20], which could reduce the alveolar-arterial diffusion gradient for N₂O and attenuate further N₂O uptake [23].

Similarly, data presented here show good reproducibility of metabolic variables at rest and exercise. Metabolic parameters showed very good reproducibility throughout exercise. Reproducibility of peak oxygen consumption per body weight was 3.7%, which is similar to previous studies using non-invasive gas exchange measurement systems [25, 40]. Bland-Altman analysis for both cardiac output and metabolic data show low mean differences between Test 1 and Test 2 and acceptable limits of agreement. Although Bland-Alt-

► **Table 2** Reproducibility of hemodynamic measurements at rest and different exercise intensities.

Variables	Test 1	Test 2	P	r	CV (%)
Rest					
CO (liter min ⁻¹)	7.4 (1.6)	7.1 (1.2)	0.54	0.90	6.9
HR (beats min ⁻¹)	65 (7)	68 (10)	0.72	0.85	4.9
SV (ml beat ⁻¹)	114 (28)	108 (15)	0.63	0.61	13
VO ₂ (ml kg ⁻¹ min ⁻¹)	4.4 (1.7)	4.7 (1.6)	0.69	0.65	15.3
60 watts					
CO (liter min ⁻¹)	11.5 (1.9)	11.6 (2.6)	0.92	0.49	12.5
HR (beats min ⁻¹)	99 (10)	99 (8)	0.96	0.83	3
SV (ml beat ⁻¹)	122.3 (34.2)	122.1 (32.4)	0.99	0.45	11.9
VO ₂ (ml kg ⁻¹ min ⁻¹)	14.3 (1.6)	13.7 (1.9)	0.59	0.65	7.9
120 watts					
CO (liter min ⁻¹)	15.0 (3)	14.4 (3)	0.68	0.87	6.3
HR (beats min ⁻¹)	138 (20)	138 (19)	0.99	0.96	1.9
SV (ml beat ⁻¹)	132 (44)	134 (38)	0.94	0.85	5.9
VO ₂ (ml kg ⁻¹ min ⁻¹)	23.4 (4)	25 (5)	0.47	0.92	5.3
150 watts					
CO (liter min ⁻¹)	17.2 (4)	17.3 (4)	0.81	0.77	4.3
HR (beats min ⁻¹)	145 (19)	147 (23)	0.88	0.98	2.3
SV (ml beat ⁻¹)	126 (35)	123 (43)	0.89	0.86	5.1
VO ₂ (ml kg ⁻¹ min ⁻¹)	27 (4)	26 (5)	0.76	0.83	5.6
180 watts					
CO (liter min ⁻¹)	20.4 (2.3)	19.8 (2.6)	0.49	0.92	3.8
HR (beats min ⁻¹)	163 (15)	160 (17)	0.86	0.99	1.4
SV (ml beat ⁻¹)	135 (25)	132 (25)	0.89	0.92	4.8
VO ₂ (ml kg ⁻¹ min ⁻¹)	35 (1.7)	33.4 (0.9)	0.15	0.75	3.4
CO – cardiac output, HR – Heart Rate, SV – Stroke Volume, VO ₂ – Oxygen Consumption, r: correlation coefficient, CV – coefficient of variation. Data are expressed as mean (SD)					

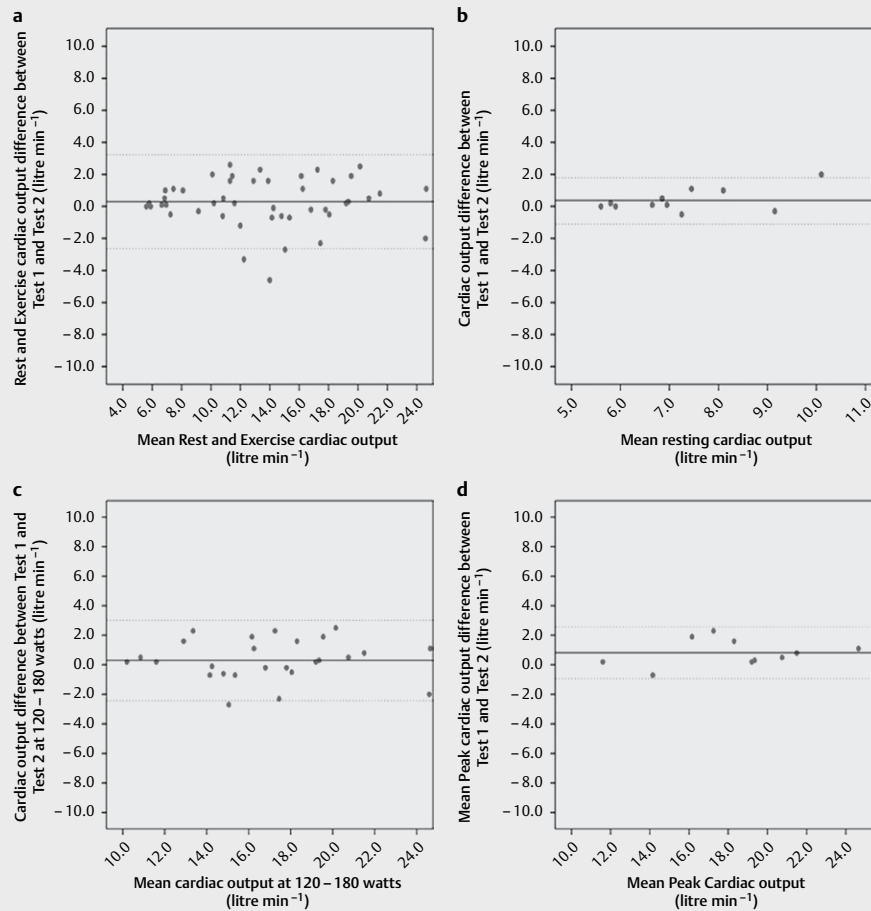


► **Fig. 2** Relationship between cardiac output estimates obtained at Test 1 and Test 2 when taken together (rest and exercise data).

man analysis has been used extensively to show agreement between comparative cardiac output measurements, it has been criticized, as it does not provide a useful standard parameter such as percentage error for which the quality of repeated measurement could be based upon [8]. Therefore to verify results from coefficients of variation and Bland-Altman analyses, as well as to ascertain cardiac output trending capability, polar plots were constructed. Results showed a mean

polar angle of 3 degrees, radial limits of agreement of 19° and a concordance rate of 87%. These results are significant as Critchley and colleagues [8] note that for good trending to occur, mean polar angle or angular bias must be less than ± 5°, radial limits of agreement should be within ± 30° and a concordance rate of 95%. Therefore, it is reasonable to suggest that inert gas rebreathing shows acceptable cardiac output trending. The concordance rate in the present study was lower than expected perhaps due to 30 data points used in the analysis after central data exclusion.

The current study is not without limitation. First, relatively small sample size of healthy volunteers can potentially reduce generalization of the study findings. However, by collecting data at rest and during different levels of exercise intensity, we provided sufficient data points for the study to adequately assess reproducibility between repeated measures. Second, the feature of the rebreathing method is that it requires a subject to ‘learn how to perform rebreathing maneuver,’ i. e., a learning effect. Detailed explanation and familiarization with the rebreathing procedures was carried out with each study participant, resulting in a valid rebreathing maneuver being performed. Third, there might have been sampling bias, as the study comprised a 3-min rest period followed by a progressive exercise test of 4 steady-state stages each lasting 3 min, meaning that intensity and time were correlated in the experiment.



► **Fig. 3** Bland-Altman plots to demonstrate limits of agreement between Test 1 and Test 2 at rest and exercise (combined data, **a**); at rest **b**; high intensities (120–180watts, **c**); and at peak exercise **d**. The solid line represents the mean difference and the dashed lines represent lower and upper limits of agreement between Test 1 and Test 2.

Conclusion

The findings of the present study suggest that the inert gas re-breathing method demonstrates acceptable test-retest reproducibility in measuring cardiac output at rest and at submaximal to peak levels of metabolic demand during cardiopulmonary exercise stress testing. The present study encourages integration of non-invasive cardiac output monitoring in cardiopulmonary exercise stress testing procedures as cardiac and metabolic data generated during higher intensity and peak exercise could help improve understanding of exercise intolerance. Future prospective studies are warranted to define clinical (i. e., diagnostic and prognostic) and cost-effectiveness of non-invasive gas rebreathing cardiac output assessment.

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Conflict of Interest

The authors declare no conflict of interest.

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