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Title:

Bioreactance is a reliable method for estimating cardiac output at rest and during exercise

Running head:

Reliability of bioreactance during graded exercise

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1: The addition of "All authors read and approved the final manuscript" at the end of the 'Authors' contributions' section is fine, the authors are happy with this addition.

2: Reference [1] should be changed to

3: Reference [13] volume is 37 and page numbers should be changed to 3092-7

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International Diabetes Federation. *IDF Diabetes Atlas, 6th edn.* Brussels, Belgium: International Diabetes Federation, 2013.

Abstract:

Background: Bioreactance is a novel non-invasive method for cardiac output measurement that involves the analysis of blood flow-dependent changes in the phase shifts of electrical currents applied across the chest. The present study evaluated the test-retest reliability of bioreactance for assessing hemodynamic variables at rest and during exercise.

Methods: 22 healthy participants (26 (4) years) performed an incremental cycle ergometer exercise protocol relative to their individual power output at maximal O_2 consumption (Wmax) on two separate occasions (trials 1 and 2). Participants cycled for five 3 min stages at 20, 40, 60, 80 and 90% Wmax. Haemodynamic and cardiorespiratory variables were assessed at rest and continuously during the exercise protocol.

Results: Cardiac output was not significantly different between trials at rest ($p = 0.948$) nor at any stage of the exercise protocol (all $p > 0.30$). There was a strong relationship between cardiac output estimates between the trials (ICC = 0.95, $p < 0.001$) and oxygen consumption (ICC = 0.99, $p < 0.001$). Stroke volume was also not significantly different between trials at rest ($p = 0.989$) or during exercise (all $p > 0.15$), and strong relationships between trials were found (ICC = 0.83, $p < 0.001$).

Conclusions: The bioreactance method demonstrates good test-retest reliability for estimating cardiac output at rest and during different stages of graded exercise testing including maximal exertion.

1   Introduction

2   Monitoring of cardiac output (CO) has wide clinical application in anesthesiology,

3   emergency care and cardiology. It can improve outcomes, establish diagnosis, guide therapy

4   and help risk stratification in different clinical groups[1]. Measurement of cardiac output is

5   essential in critically ill, injured and unstable patients as it provides an indication of systemic

6   oxygen delivery and global tissue perfusion[2]. Cardiac output monitoring during surgery is

7   associated with reduced length of hospital stay and postoperative complications[3-5].

8   Measurement of cardiac output under pharmacological and physiological stimulations defines

9   overall function and performance of the heart, predicts prognosis and survival in heart failure

10   can help explain the mechanisms of exercise intolerance, and improves risk stratification[6-10].

11

12   Thermodilution and direct Fick[11-13] remain the "gold standard" and reference methods for

13   assessing CO. Whilst "gold standard" these methods have inherent limitations as they are

14   invasive, costly, require specialist skills and associated with noteworthy risks and

15   complications such as catheter-related infections, arrhythmias and bleeding[14] [15]. The

16   risk:benefit ratio of these assessment methods has also been brought into question[14]. These

17   limitations preclude the use of invasive cardiac output monitoring in large number of patients

18   limiting the application of this useful diagnostic and prognostic marker.

19

20   Over the previous decades several minimally invasive and non-invasive methods for

21   assessing cardiac output have been developed including; trans-esophageal Doppler,

22   transpulmonary thermodilution, pulse contour and pulse power analysis, and non-invasive

23   techniques such as CO_2 and inert gas rebreathing, transthoracic Doppler, thoracic

24   bioimpedance cardiography, and electrical velocimetry (modified bioimpedance)[2] [16-18].

1   Unfortunately whilst these methods are safe they are associated with certain limitations

2   precluding their accuracy and reliability[13 19].

3

4   Bioreactance, a novel method for continuous non-invasive cardiac output monitoring, has

5   received increased attention in clinical and research practice in the recent years. The

6   bioreactance method estimates CO by analysing the frequency of relative phase shift of

7   electronic current across the thorax[20 21]. In contrast to impedance cardiography which is based

8   on the analysis of transthoracic voltage amplitude changes in response to high frequency

9   current, the bioreactance analyses the frequency spectra variations of the delivered oscillating

10   current[20]. This approach is supposed to result in the improved precision of the bioreactance

11   system as demonstrated by a 100 fold larger signal-to-noise ratio than that of bioimpedance

12   and thus make it less susceptible to interference from adipose tissue, electrode placement and

13   excessive movement[20 22].

14

15   The ability of bioreactance to monitor rapid changes in blood flow has recently been

16   confirmed by Marik, et al.[23]. The authors compared carotid Doppler against bioreactance in

17   patients with unstable cardiac conditions during passive leg raising. A strong correlation was

18   reported in blood flow between the two methods in critically ill patients, with an accelerated

19   response to these volume changes reported by bioreactance. Bioreactance cardiac output

20   monitoring has been used in intensive care unit, during and following cardiac surgery,

21   patients with chronic obstructive pulmonary disease and healthy individuals[19 20 22-25]. Other

22   studies demonstrated that bioreactance measurements of cardiac output at rest and during

23   exertion can identify cardiovascular function abnormalities, indexing disease severity, help

24   prognosis and risk stratification, and track responses to treatment in clinical practice[26 27].

When assessing cardiac output at rest or during physiological challenge, it is essential that method demonstrates acceptable level of reliability i.e. test-retest reliability which refers to the reproducibility of values of a variable when measured the same subjects twice. This is important because even small changes in cardiac output and stroke volume may have significant clinical implications when evaluating the effect of pharmacological and non-pharmacological interventions and risk stratification. Based on available literature, it appears that test-retest reliability of bioreactance, as a novel and potent method for non-invasive continuous cardiac output monitoring has not been evaluated. Based on higher signal-to-noise ratio and improved performance[19][20] we hypothesize that bioreactance method demonstrates acceptable test-retest reliability for evaluating cardiac output at rest and during physiological stimulation such as graded exercise testing. Additionally, we evaluated association between cardiac output and oxygen consumption at peak exercise.

Methods

All experimental procedures were approved by the Faculty's Research Ethics Committee in accordance with the Declaration of Helsinki. In all cases, after being informed of the benefits and potential risks of the investigation all participants completed a standardised health-screening questionnaire, undertook a resting electrocardiogram and gave their written informed consent.

Twenty two healthy individuals (10 males and 12 females) mean age

participated in the study. All participants were non-smokers and free from any cardiac and respiratory disorders. All participants attended the exercise laboratory on 2 separate days, day 1 involved an initial assessment of maximal aerobic capacity ($\dot{V}O_{2max}$) and day 2 required 2

1   visits consisting of an incremental exercise cycle ergometer protocol at individual pre-

2   determined workloads based on participants power output at $\dot{V}O_{2max}$ (Wmax). Participants

3   were required to abstain from eating for a minimum of 2 hours prior to the commencement of

4   each test and from vigorous exercise 24 hours prior to the test. Participants were also

5   instructed not to consume alcohol and caffeine containing foods and beverages on test days.

6

7   Participants completed a maximal progressive exercise test on an electro-magnetically braked

8   recumbent cycle ergometer (Corival, Lode, Groningen, Netherlands). All participants began

9   cycling against a resistance of 40 W, this increased continually throughout the test at a ramp

10   rate of 15 W min^{-1}. Cessation of the assessment occurred when participants reached volitional

11   exhaustion or were unable to maintain a cadence of 60-70 revolutions per minute. It was

12   considered that a maximal effort was achieved if participants met any of two of the following

13   criteria: i) a change in $\dot{V}O_2 < 2$ ml kg min^{-1} across two stages of the incremental test; ii) a

14   respiratory exchange ratio of 1.15 or greater, or iii) $\geq 90\%$ age predicted maximum heart rate

15   (220-age)[28]. Expired gases were measured via online metabolic gas exchange system (Cortex

16   metalyser 3B, Leipzig, Germany) and heart rate was measured via short range telemetry

17   (Polar RS400, Finland). Peak oxygen consumption was defined as the average oxygen uptake

18   during the last minute of exercise, expressed as millilitres per kilogram of body weight per

19   minute and litres per minute. The Wmax was defined as the power output expressed in W at

20   the point at which participants reached their individual $\dot{V}O_{2max}$.

21

22   Exercise protocol was performed twice on study day 2 with ≥ 3 h interval between trials 1

23   and 2. Participants were required to complete five 3 min stages (equating to 15 min of cycling)

24   at intensities relative to 20, 40, 60, 80 and 90% Wmax. Cardiac and hemodynamic responses

25   including cardiac output, cardiac index, stroke volume and stroke volume index, and heart

rate were recorded at rest and throughout the incremental exercise protocol using a non-invasive bioreactance system (NICOM®, Cheetah Medical, Delaware, USA). Simultaneously, respiratory and gas exchange measurements were recorded (Cortex metalyser 3B, Leipzig, Germany).

The bioreactance system comprises of a radio frequency generator that creates a high frequency current that is introduced across the thoracic cavity. The NICOM® has been described previously[19 20 25]. It analyses the relative phase shift of electronic current across the thorax. In brief the four dual surface electrodes are used to establish electrical contact with the body. The skin was prepared by shaving where required and using adhesive paper to ensure an optimal signal from the electrodes. Two electrodes were placed 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. The right and left sensors of the devise generate independent signals which are subsequently integrated to generate the final signal analysed. The blood that is present in the thoracic cavity absorbs electrons, which results in a delay in the signal, which is proportional to the volume of blood flow. This is called a phase shift and is recorded and the figure is translated to the flow of the blood. The signal that is detected by the electrodes is then processed separately and averaged after digital processing at 30 or 60 s intervals. The signal processing unit of the NICOM® determines the relative phase shift ($\Delta\varphi$) between the input signals relative to the output signal. The $\Delta\varphi$ is in response to any changes in blood flow that pass through the aorta. The CO is then derived by CO = (C x VET x $\Delta\varphi$ dt_{max}) x HR, where C is the constant of proportionality and VET is ventricular ejection fraction time[19]. The value of C has been previously validated to account for patient age, gender, height and weight[22]. CO can then be calculated from stroke volume and HR.

Statistical methods

Statistical analyses were performed using PASW statistical analysis software (Version 19, IBM, USA). Data are presented as mean (standard deviation). The alpha level of 0.05 was set prior to data analysis and normality of distribution was assessed using a Kolmogorov-Smirnov test. Relative reliability was determined using intra-class correlation coefficients (ICC), calculated using the two-way random method previously described by Weir[29]. Absolute reliability was determined using standard error of measurement (SEM) with 95% confidence intervals (95%CI), which were calculated independently of intra-class correlation coefficients. Systemic bias in the repeatability between trials was assessed using paired sample *t*-tests. The relationship between cardiac output and oxygen consumption was assessed with Pearson's coefficient of correlation. Data analyses were performed on both combined resting and exercise data and data from each individual stage of the incremental exercise protocol for CO, cardiac index (CI), stoke volume (SV), stroke volume index (SVI), heart rate (HR) minute ventilation (VE) and oxygen consumption ($\dot{V}O_2$).

Results

Physical characteristics of study participants are: age 26.3 (4.2) years, height 171.5 (8) cm, body mass 67.4 (7.9) kg, and peak oxygen consumption 41.5 (8.7) ml kg min^{-1}. Data pertaining to the systemic bias between trials for all assessed cardiac and respiratory variables are presented in Table 1. There was a non-significant (< 5%) difference between trials 1 and 2 for all variables ($p > 0.05$).

Table 1 about here

1   Reliability statistics for cardiac and respiratory responses to the incremental exercise protocol

2   are presented in Tables 2 and 3. These data demonstrate strong relative (Table 2) and test-

3   retest absolute (Table 3) reliability.

4

5   *Table 2 about here*

6

7   Cardiac output was similar between the trials 1 and 2 at rest (0.7 (10.3) %) and all stages of

8   the incremental exercise protocol (Figure 1). At low exercise intensity i.e. 20-40% of Wmax

9   the differences in cardiac output between trials 1 and 2 were 4 and 1%, respectively. At

10 moderate (i.e. 60% of Wmax) and high (80 and 90% of Wmax) exercise intensity the

11 difference was only between 1 and 2% (Figure 1).

12

13 *Table 3 about here*

14

15 Non-significant differences between the trial 1 and 2 were reported for stroke volume at all

16 stages of the protocol, with mean difference ranging from 1% (at 80% of Wmax) to 7% (at 20%

17 of Wmax, Figure 2). When resting and exercise data points are considered together (n=132),

18 the mean difference between trial 1 and 2 was only 2%.

19

20 *Figure 1 about here*

21

22 Participants mean cardiac index and stroke volume index were not significantly different

23 between the trials when data analyses included combined resting and exercise data (Table 1).

24 Furthermore, neither mean cardiac index nor stroke volume index was significantly different

25 between trials at rest or at any exercise stage.

1

2   *Figure 2 about here*

3

4   As detailed in Table 1 heart rate, peak oxygen consumption, and mean ventilation were

5   similar between trials. Relative and absolute reliability statistics presented in Tables 2 and 3

6   demonstrate good reliability. In addition, no significant differences between the trials were

7   found in heart rate, peak oxygen consumption, and mean ventilation at rest or at any of the

8   exercise intensities ($p > 0.05$).

9

10   Data demonstrate a strong relationship between cardiac output and oxygen consumption at

11   peak exercise for both trials (Trial 1; $r = 0.64$, $p = 0.001$, Trial 2; $r = 0.66$, $p < 0.001$).

12

13   **Discussion**

14   The primary finding of this study is that bioreactance demonstrates acceptable test-retest

15   reliability for estimating cardiac output and stroke volume at rest and during physiological

16   stress induced by exercise testing. Additionally, the exercise protocol employed in the present

17   study elicited similar cardiorespiratory responses between trials and a strong relationship was

18   identified between cardiac output and peak oxygen consumption for both trials. This

19   illustrates the ability of the exercise protocol to elicit reliable hemodynamic and

20   cardiorespiratory responses on separate occasions in the absence of changes in health and

21   clinical status of an individual.

22

23   The assessment of cardiac output in a reliable manner is an essential tool to accurately assess

24   any improvements or decrements in cardiac function of numerous patient groups. As

25   previously stated this is of particular importance in cardiac patients as small changes in

8

1 cardiopulmonary data due to disease or intervention may have significant clinical

2 implications[30]. It may therefore be suggested that inaccurate and unreliable measures may

3 contribute to misinterpretation of data and potentially misdiagnosis. The excellent reliability

4 of bioreactance in measuring haemodynamics (at rest and continuously during exercise)

5 reported in the present study illustrates its potential clinical application. Furthermore, its

6 ability to assess cardiac output noninvasively, inexpensively and without specialist training of

7 the assessor permits its application in an increased number of patient groups when compared

8 to more invasive and "gold standard" catheter based measurement techniques[11 12].

9

10 The CO values reported in the present study are consistent with recent research employing

11 bioreactance in a comparable population and at similar exercise intensities[19]. The authors

12 Jakovljevic, et al.[19] reported resting CO values of 6.5 L min^{-1} which are similar to those

13 reported in the present study. Similar values were also reported at comparable submaximal

14 and near maximal exercise intensities. Furthermore the CO data previously reported[19] was

15 consistently correlated with CO estimates derived from measured oxygen consumption[31]. We

16 have also demonstrated a strong relationship between cardiac output and oxygen

17 consumption at peak exercise in the present study. Elliott, et al.[25] also reported similar CO as

18 assessed via bioreactance at similar exercise intensities as the present study and previous

19 study[19]. In addition resting and near maximal cardiac index reported in the present study is

20 similar to that previously reported[25]. The data presented in this article further substantiates

21 the previous work[19 25] and demonstrates that bioreactance is accurate and reliable for

22 assessing haemodynamic variables at various exercise intensities. Furthermore, cardiac

23 output data from the present study that are associated particularly with stages of low to

24 moderate intensities are consistent with those identified in different stages of heart failure[26 27].

25 Overall, data presented in the present study indicate that bioreactance can provide reliable

measures of cardiac output independent of any other physiological measures (e.g. oxygen consumption) and potential elevated electrical noise, body motion, perspiration and body temperature associated with graded exercise.

The present study is not without limitations. Firstly, the study participants were young, healthy adults whereas older people and those with chronic conditions were not included. It may be speculated therefore that the present findings cannot be generalized to a wider, clinical applications. However, the study protocol allowed analysis of bioreactance cardiac output test-retest reliability not only at peak exercise but also at low to moderate levels of exercise intensities that are often observed in individuals with chronic conditions and in older people. Secondly, no gold standard for cardiac output measurement (i.e. thermodilution or direct Fick) was included. The additional risks posed to the study participants with these procedures precluded them from being undertaken.

Conclusions

In conclusion, bioreactance method demonstrates good test-retest reliability for estimating cardiac output and stroke volume at rest and during different stages of graded exercise testing including maximal exertion. Future large studies are warranted to assess the reliability of bioreactance at both rest and exercise in different clinical groups where monitoring of cardiac output has been shown to improve risk stratification and clinical outcomes.

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Tables

Table 1. The mean values and standard deviations for cardiac and respiratory variables obtained at rest and during the incremental exercise protocol.

Variable	Trial 1	Trial 2	t-test (p-value)
Cardiac output (L min^{-1})	13.7 (4.4)	13.4 (4.1)	0.518
Heart rate (beats min^{-1})	123.7 (37.8)	124.3 (36.7)	0.905
Stroke volume (ml beat^{-1})	112.9 (22.5)	109.5 (18.7)	0.179
Minute ventilation (L min^{-1})	46.2 (30.0)	47.6 (30.3)	0.732
Oxygen consumption (L min^{-1})	1.6 (0.9)	1.6 (0.9)	0.882

Note: p value determined from test-retest data using paired sample t-test for measurement outcomes. Data analyses performed on resting and exercise data combined (n = 22, data points =132).

1　**Table 2.** Relative reliability statistics for cardiac and respiratory variables at rest and during
2　the incremental exercise protocol.
3

Variable	ICC
Cardiac output (L min^{-1})	0.95*
Heart rate (beats min^{-1})	0.99*
Stroke volume (ml beat^{-1})	0.88*
Minute ventilation (L min^{-1})	0.99*
Oxygen consumption (L min^{-1})	0.99*

4　*Significant correlation between trials 1 and 2 ($p < 0.001$). Data analyses performed on
5　resting and exercise data combined (n = 22, data points =132).
6

1 **Table 3.** Absolute reliability statistics for cardiac and respiratory variables at rest and during
2 the incremental exercise protocol.
3

Variable	Change in mean (%)	95%CI	Sx	SRD
Cardiac output (L min^{-1})	11.1	±0.7	±3.0	1.2
Heart rate (beats min^{-1})	6.7	±6.4	±26.3	10.3
Stroke volume (ml beat^{-1})	9.8	±3.5	±14.6	5.7
Minute ventilation (L min^{-1})	12.0	±5.4	±21.3	8.4
Oxygen consumption (L min^{-1})	12.1	±0.2	±0.7	0.3

4 Note: Sx = standard error of the mean, SD = standard deviation, SRD = smallest real
5 difference. Data analyses performed on resting and exercise data combined (n = 22, data
6 points =132).
7

1 **Figure legends**

2 **Figure 1.** Mean cardiac output at rest and at individual stages of the incremental exercise

3 protocol on trials 1 and 2. Wmax = power output in Watts (W) at $\dot{V}O_{2max}$ (n = 22).

4

5 **Figure 2.** Mean stroke volume at rest and at individual stages of the incremental exercise

6 protocol on trials 1 and 2. Wmax = power output in Watts (W) at $\dot{V}O_{2max}$ (n = 22).