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Citation: Jones, Thomas, Houghton, David, Cassidy, Sophie, MacGowan, Guy, Trenell, Michael and Jakovljevic, Djordje (2015) Bioreactance is a reliable method for estimating cardiac output at rest and during exercise. *British Journal of Anaesthesia*, 115 (3). pp. 386-391. ISSN 0007-0912

Published by: Oxford University Press

URL: <https://doi.org/10.1093/bja/aeu560> <<https://doi.org/10.1093/bja/aeu560>>

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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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2+3 will be included on Guy A. MacGowan

**4-roy and kieren**

**Add in chris day and djordjes new one**

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

4: Thankyou for highlighting the affiliations. A few changes need to be made. which include:

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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<sub>2</sub> consumption (W<sub>max</sub>) on two separate occasions (trials 1 and 2). Participants cycled for five 3 min stages at 20, 40, 60, 80 and 90% W<sub>max</sub>. 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.

**Key words:** Bioreactance, Cardiac Monitoring, Cardiac Output, Graded Exercise

# 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<sup>1</sup>. 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<sup>2</sup>. Cardiac output monitoring during surgery is  
7 associated with reduced length of hospital stay and postoperative complications<sup>3-5</sup>.  
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<sup>6-10</sup>.

11

12 Thermodilution and direct Fick<sup>11-13</sup> 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<sup>14 15</sup>. The  
16 risk:benefit ratio of these assessment methods has also been brought into question<sup>14</sup>. 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<sub>2</sub> and inert gas rebreathing, transthoracic Doppler, thoracic  
24 bioimpedance cardiography, and electrical velocimetry (modified bioimpedance)<sup>2 16-18</sup>.

1 Unfortunately whilst these methods are safe they are associated with certain limitations  
2 precluding their accuracy and reliability<sup>13 19</sup>.

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<sup>20 21</sup>. 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<sup>20</sup>. 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<sup>20 22</sup>.

14

15 The ability of bioreactance to monitor rapid changes in blood flow has recently been  
16 confirmed by Marik, et al.<sup>23</sup>. 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<sup>19 20 22-25</sup>. 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<sup>26 27</sup>.

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

13

## 14 **Methods**

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

20

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

22

23 participated in the study. All participants were non-smokers and free from any cardiac and  
24 respiratory disorders. All participants attended the exercise laboratory on 2 separate days, day  
25 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  $\dot{V}O_{2\max}$  (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<sup>-1</sup>. 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<sup>-1</sup> 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  $(220-\text{age})^{28}$ . 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  $\dot{V}O_{2\max}$ .

21

22 Exercise protocol was performed twice on study day 2 with  $\geq 3$  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

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

5  
6 The bioreactance system comprises of a radio frequency generator that creates a high  
7 frequency current that is introduced across the thoracic cavity. The NICOM<sup>®</sup> has been  
8 described previously<sup>19 20 25</sup>. It analyses the relative phase shift of electronic current across the  
9 thorax. In brief the four dual surface electrodes are used to establish electrical contact with  
10 the body. The skin was prepared by shaving where required and using adhesive paper to  
11 ensure an optimal signal from the electrodes. Two electrodes were placed over the trapezius  
12 muscle on either side of the upper torso and two on the lower posterior torso lateral to the  
13 margin of the latissimus dorsi musculature. The right and left sensors of the device generate  
14 independent signals which are subsequently integrated to generate the final signal analysed.  
15 The blood that is present in the thoracic cavity absorbs electrons, which results in a delay in  
16 the signal, which is proportional to the volume of blood flow. This is called a phase shift and  
17 is recorded and the figure is translated to the flow of the blood. The signal that is detected by  
18 the electrodes is then processed separately and averaged after digital processing at 30 or 60 s  
19 intervals. The signal processing unit of the NICOM<sup>®</sup> determines the relative phase shift ( $\Delta\phi$ )  
20 between the input signals relative to the output signal. The  $\Delta\phi$  is in response to any changes  
21 in blood flow that pass through the aorta. The CO is then derived by  $CO = (C \times VET \times \Delta\phi$   
22  $dt_{max}) \times HR$ , where C is the constant of proportionality and VET is ventricular ejection  
23 fraction time<sup>19</sup>. The value of C has been previously validated to account for patient age,  
24 gender, height and weight<sup>22</sup>. CO can then be calculated from stroke volume and HR.

25

## 1 **Statistical methods**

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

15

## 16 **Results**

17 Physical characteristics of study participants are: age 26.3 (4.2) years, height 171.5 (8) cm,  
18 body mass 67.4 (7.9) kg, and peak oxygen consumption 41.5 (8.7) ml kg min<sup>-1</sup>. Data  
19 pertaining to the systemic bias between trials for all assessed cardiac and respiratory variables  
20 are presented in Table 1. There was a non-significant (< 5%) difference between trials 1 and  
21 2 for all variables ( $p > 0.05$ ).

22

23

*Table 1 about here*

24

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 W<sub>max</sub>  
9 the differences in cardiac output between trials 1 and 2 were 4 and 1%, respectively. At  
10 moderate (i.e. 60% of W<sub>max</sub>) and high (80 and 90% of W<sub>max</sub>) 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 W<sub>max</sub>) to 7% (at 20%  
17 of W<sub>max</sub>, 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.

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*Figure 2 about here*

As detailed in Table 1 heart rate, peak oxygen consumption, and mean ventilation were similar between trials. Relative and absolute reliability statistics presented in Tables 2 and 3 demonstrate good reliability. In addition, no significant differences between the trials were found in heart rate, peak oxygen consumption, and mean ventilation at rest or at any of the exercise intensities ( $p > 0.05$ ).

Data demonstrate a strong relationship between cardiac output and oxygen consumption at peak exercise for both trials (Trial 1;  $r = 0.64, p = 0.001$ , Trial 2;  $r = 0.66, p < 0.001$ ).

## **Discussion**

The primary finding of this study is that bioreactance demonstrates acceptable test-retest reliability for estimating cardiac output and stroke volume at rest and during physiological stress induced by exercise testing. Additionally, the exercise protocol employed in the present study elicited similar cardiorespiratory responses between trials and a strong relationship was identified between cardiac output and peak oxygen consumption for both trials. This illustrates the ability of the exercise protocol to elicit reliable hemodynamic and cardiorespiratory responses on separate occasions in the absence of changes in health and clinical status of an individual.

The assessment of cardiac output in a reliable manner is an essential tool to accurately assess any improvements or decrements in cardiac function of numerous patient groups. As previously stated this is of particular importance in cardiac patients as small changes in

1 cardiopulmonary data due to disease or intervention may have significant clinical  
2 implications<sup>30</sup>. 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 bioactance 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<sup>11 12</sup>.

9  
10 The CO values reported in the present study are consistent with recent research employing  
11 bioactance in a comparable population and at similar exercise intensities<sup>19</sup>. The authors  
12 Jakovljevic, et al.<sup>19</sup> reported resting CO values of 6.5 L min<sup>-1</sup> 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<sup>19</sup> was  
15 consistently correlated with CO estimates derived from measured oxygen consumption<sup>31</sup>. 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.<sup>25</sup> also reported similar CO as  
18 assessed via bioactance at similar exercise intensities as the present study and previous  
19 study<sup>19</sup>. In addition resting and near maximal cardiac index reported in the present study is  
20 similar to that previously reported<sup>25</sup>. The data presented in this article further substantiates  
21 the previous work<sup>19 25</sup> and demonstrates that bioactance 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<sup>26 27</sup>.  
25 Overall, data presented in the present study indicate that bioactance can provide reliable

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

4

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

14

## 15 **Conclusions**

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

1 **Author contributions:**

2 Study conceived and designed by DGJ, TWJ and DH.

3 Data collection performed by DGJ, TWJ, DH and SC.

4 Data extraction and analyses performed by TWJ.

5 Interpretation of data and preparation of manuscript performed by DGJ, TWJ, DH, SC, GAM  
6 and MIT.

7

8

9 **Acknowledgements:**

10

11

12 **Conflict of Interest disclosures:**

13 This study is *not* industry sponsored; TWJ, DH, MIT, SC, GAM and DGJ report no conflict  
14 of interests.

15

16

17 **Funding:**

18 This work was supported by the UK National Institute for Health Research Biomedical  
19 Research Centre for Ageing and Age-related Diseases award to Newcastle upon Tyne  
20 Hospitals NHS Foundation Trust. MIT is supported by the UK National Institute for Health  
21 Research Senior Research Fellowship. DGJ is supported by the Research Councils UK  
22 Centre for Ageing and Vitality. The funding sources did not have a direct role in the design,  
23 collection, analysis or interpretation of data, nor in the manuscript preparation, which is  
24 solely the remit of the author(s).

25

26

27 **Guarantor statement:**

28 Thomas W. Jones and Djordje G. Jakovljevic take responsibility for the content of the  
29 manuscript, including the data and analysis.

30

31

32 **Notation of prior abstract publication/presentation:**

33 N/A

34

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1 **Tables**

2 **Table 1.** The mean values and standard deviations for cardiac and respiratory variables  
3 obtained at rest and during the incremental exercise protocol.  
4

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

5 Note: *p* value determined from test-retest data using paired sample t-test for measurement  
6 outcomes. Data analyses performed on resting and exercise data combined (n = 22, data  
7 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 <sup>-1</sup> )	0.95*
Heart rate (beats min <sup>-1</sup> )	0.99*
Stroke volume (ml beat <sup>-1</sup> )	0.88*
Minute ventilation (L min <sup>-1</sup> )	0.99*
Oxygen consumption (L min <sup>-1</sup> )	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 <sup>-1</sup> )	11.1	±0.7	±3.0	1.2
Heart rate (beats min <sup>-1</sup> )	6.7	±6.4	±26.3	10.3
Stroke volume (ml beat <sup>-1</sup> )	9.8	±3.5	±14.6	5.7
Minute ventilation (L min <sup>-1</sup> )	12.0	±5.4	±21.3	8.4
Oxygen consumption (L min <sup>-1</sup> )	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.  $W_{max}$  = 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.  $W_{max}$  = power output in Watts (W) at  $\dot{V}O_{2max}$  (n = 22).