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Haemodynamic Monitoring Devices: Best Practice & Research Clinical Anaesthesiology

**Bioimpedance and Bioreactance Methods for Monitoring Cardiac Output**

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## **Abstract**

Noninvasive continuous cardiac output monitoring may have wide clinical applications in anesthesiology, emergency care and cardiology. It can improve outcomes, establish diagnosis, guide therapy and help risk stratification. The present article describes the theory behind the two noninvasive continuous monitoring methods for cardiac output assessment such as bioimpedance and bioreactance. The review discusses the advantages and disadvantages of these methods and highlights the recent method comparison studies. The use of bioimpedance and bioreactance to estimate cardiac output under haemodynamic challenges is also discussed. In particular, the article focuses on performance of the two methods in the assessment of fluid responsiveness using passive leg raising test and cardiac output response to exercise stress testing.

**Key words:** Cardiac output; Noninvasive; Bioimpedance; Bioreactance; Volume responsiveness; Exercise.

## **Introduction**

Cardiac output is a fundamental physiological measure used for diagnosis and guiding therapy in many clinical conditions. Monitoring of cardiac output has wide clinical application in anesthesiology, emergency care and cardiology.(1) Measurement of cardiac output is essential in critically ill, injured and unstable patients as it provides an indication of systemic oxygen delivery and global tissue perfusion.(2) Cardiac output monitoring during surgery is associated with reduced length of hospital stay and postoperative complications.(3-5) Measurement of cardiac output under pharmacological and physiological stimulations defines overall function and performance of the heart and is an excellent predictor of prognosis in heart failure.(6-8)

The first method for estimation of cardiac output was described in 1870 by Adolf Fick.(9) This method was the reference standard by which all other methods of determining cardiac output were evaluated until the introduction of the pulmonary artery catheter (PAC) in the 1970s.(10) Cardiac output measurement with a PAC using the bolus thermodilution method has become the gold standard and reference method used to compare novel technologies.(11, 12) These methods are however invasive, expensive, require specialist expertise, and are associated with inherent risks and complications such as catheter-related infections, arrhythmias and bleeding.(13) These limitations preclude the use of invasive cardiac output monitoring in large number of patients limiting the application of this useful diagnostic and prognostic marker.

The development of minimally invasive and non-invasive, sensitive, operator-independent and cost-effective techniques for cardiac output monitoring has been the focus of attention for several decades.(2) Minimally invasive methods frequently used and described are transoesophageal Doppler, transpulmonary thermodilution, pulse counter and pulse power analysis, and non-invasive techniques such as CO<sub>2</sub> and inert gas rebreathing, transthoracic

Doppler, thoracic bioimpedance cardiography, electrical velocimetry (modified bioimpedance) and bioreactance.(2, 12, 14, 15) The aim of the present review is three fold: 1) to describe the theory behind bioimpedance, electrical velocimetry, and bioreactance as methods for noninvasive continuous cardiac output monitoring; 2) to discuss the advantages and disadvantages of these methods and review the recent method comparison studies; and 3) to introduce the reader to modern uses of these devices (e.g. fluid responsiveness / passive leg raising, physiological stress).

### **Bioimpedance method for measuring cardiac output**

Thoracic bioimpedance cardiography for measuring stroke volume, cardiac output and other cardiovascular variables was first described by Kubicek and associates in 1960s.(16) Its initial testing and application was performed in aerospace programs when central haemodynamic measurements and cardiac function were evaluated in astronauts.(17) The basis for its use was later pioneered by Lababidi and colleagues in 1970,(18) with significant software refinements and technical improvements over the following decades based on animal and human research. In the 1980s, Sramek et al(19) developed a less cumbersome impedance cardiography device with a new stroke volume equation that substituted the cylindrical model of the chest used by Kubicek et al(16) with that of a truncated cone. In 1986, Bernstein(20) modified the equation of Sramek et al(19) by introducing into the formulae the actual in addition to ideal weight, which accounting for deviations from ideal body weight. The purpose was to determine more accurately the volume of the thorax.(4) The technique finally became popularized in 1990s when its use in clinical settings was evaluated by several multicentre studies reporting improvement in determination of left

ventricular ejection time, change in impedance with systole, and other markers of systole and diastole providing greater accuracy of non-invasive hemodynamic data.(21, 22)

The underlying theory behind the bioimpedance cardiography is that thorax is considered as a cylinder perfused with fluid (blood) which has a specific resistivity. The technique is based on the measurements of impedance (or resistance) to transmission of a small electrical current throughout the body (wholebody bioimpedance) or chest area (thoracic bioimpedance).

Bioimpedance is therefore the electrical resistance to a high-frequency low-amplitude current (e.g. 1.4-1.8 mA at 30-75 kHz,) transmitted from electrodes placed on the upper and lower thorax.(23) Conduits of low impedance (lowest resistance, equals high conductance) are blood and plasma (150 and 63 ohm/cm). Resistance of electrical current is higher (lower conductance) for cardiac muscle, lungs - reflecting air, and fat (750, 1275, and 2500 ohm/cm).(23) When alternating low-level electrical current is applied to the whole body or thoracic area, the primary distribution is to the blood and extracellular fluid. Changes in the body's resistance to electrical current flow over time (in milliseconds) are associated with dynamic changes in the blood and plasma.(24) As the aortic valve opens and blood is ejected rapidly into the aorta and the arterial branches, impedance to electrical current flow is decreased. During diastole, impedance to electrical flow returns to baseline. Therefore, the changes in impedance that are noted by a thoracic bioimpedance cardiography device reflect an increase in aortic pressure during systole, whereas changes in whole-body impedance reflect a proportional increase in the measurable conductance of the whole body during systole.(23, 24)

Thoracic bioimpedance systems use electrodes applied at the base of the neck (thoracic inlet) and the costal margins (thoracic outlet), while the whole body systems use electrodes attached to limb extremities.(24) Standard thoracic bioimpedance cardiography systems apply a high-frequency electric current of known amplitude and frequency across the thorax and

measure changes in voltage (amplitude of the returning signal compared with the injected signal). The ratio between voltage and current amplitudes is a measure of transthoracic direct current resistance which is known as impedance [ $Z_o$ ], and this varies to the proportion of the amount of fluid to thorax. The instantaneous rate of the change of  $Z_o$  related to instantaneous blood flow in the aorta. Therefore, the stroke volume is proportional to the product of maximal rate of the change in  $Z_o$  ( $dZ_o/dt_{max}$ ) and ventricular ejection time (VET).(2, 23)

#### *Validation studies of bioimpedance cardiography*

Several investigations found that bioimpedance compared favourably with thermodilution method in different settings including cardiac catheterization, surgical and emergency patients.(22, 25, 26) Van De Water and associates(27) evaluated thoracic bioimpedance against thermodilution method in 53 post cardiac surgery patients. They concluded that bioimpedance is less variable and more reproducible than is thermodilution.(27) Koobi et al(28) suggested bioimpedance is a useful non-invasive method for assessment of extracellular volume changes induced by coronary artery bypass grafting operations. Spiess and colleagues(29) used bioimpedance intraoperatively for patients undergoing coronary artery bypass graft surgery and found that the technique initially compared well with thermodilution, but, immediately postoperatively, the limits of agreement were wide. Of note, good correlation between two methods was also seen during opening of the chest. Similarly, Spinale et al.(30) reported good correlation between bioimpedance and thermodilution in patients following CABG but poor correlation in patients who developed severe tachycardia and frequent arrhythmias. Most recently, Lorne and associates (31) evaluated impedance cardiography in 32 subjects undergoing surgery with general anaesthesia. Their results demonstrated a high coefficient of correlation with oesophageal Doppler in addition to good

trending ability and acceptable limits of agreement. The authors conclude that impedance cardiography is a reliable method for non-invasive monitoring of cardiac output.(31)

In contrast with previous investigations, a meta-analysis which included 154 studies reported a poor agreement between cardiac output measurements obtained by thoracic cardiac impedance and a reference method.(32) The authors suggested that the overall coefficient of correlation value of 0.67 indicates that impedance cardiography might be useful for trend analysis of different groups of patients. However, for diagnostic interpretation, the coefficient of correlation of 0.53 might not meet the required accuracy and therefore great care should be taken when thoracic impedance cardiography is applied to the cardiac patient.(32)

Additionally, Critchley and Critchley (11) reviewed 23 studies comparing impedance cardiography with thermodilution. In an unweighted pooling of the data from these studies, they found a mean percentage error of 37%. They went on to suggest a narrower limit of 30% as acceptable, which they derived from the theoretical scatter expected in agreement between two methods whose agreement is each  $\pm 20\%$  in relation to the true value. In this case, agreement between the two methods was 28.3%, which they rounded up to 30% for simplicity. Their argument assumed that the precision of thermodilution as the reference method was no worse than  $\pm 20\%$  in relation to the real cardiac output. This they justified with reference to a review by Stetz et al.(33) which examined the accuracy and reproducibility of measurement of cardiac output by thermodilution, and a study by Mackenzie et al.(34) which compared three different devices for thermodilution measurement.

More recently, Peyton and Chong (35) performed a meta-analysis and reviewed published data since 2000 on four different minimally invasive methods, one being transthoracic impedance cardiography, adapted for use during surgery and critical care. They examined the agreement in adult patients between bolus thermodilution and each method. A meta-analysis

was done using studies in which the first measurement point for each patient could be identified, to obtain a pooled mean bias, precision, and percentage error weighted according to the number of measurements in each study. They identified 13 studies in total using bioimpedance with 435 measurements and reported mean weighted bias, precision, and percentage error of -0.10 l/min, 1.14 l/min, 42.9%. The authors concluded that none of the four methods including bioimpedance has achieved agreement with bolus thermodilution which meets the expected 30% limits.(35)

#### *Limitations of bioimpedance cardiography and new attempts to improve the method*

Earlier studies reported unacceptable levels of agreement between bioimpedance and thermodilution.(32, 36, 37) Strong negative correlation was also reported between the accuracy of bioimpedance and increased fluid accumulation within the thorax with report of systematic underestimation of cardiac output by bioimpedance.(38) It was believed that devices of new generation, using novel computer technology and improved algorithms will improve accuracy of cardiac output determination by bioimpedance.(2, 29) However, poor correlation and agreement between bioimpedance and the reference method was reported in the setting of cardiac catheterization laboratory, heart failure, intensive care unit and in patients with increase lung water.(37-39)

The major limitations in bioimpedance cardiography have been identified and include difficulties providing accurate cardiac output estimation in the following situations: changes in tissue fluid volume, respiration-induced changes in the volume of pulmonary and venous blood that “noise” must be filtered out from desired changes in volumetric blood flow of the aorta, changes in electrode contact and positioning, arrhythmias as ventricular ejection time is determined using the interval between QRS complexes, acute changes in tissue water, for

example, pulmonary or chest wall oedema or pleural effusion, noise from electrocautery, mechanical ventilation and surgical manipulation, changes in myocardial contractility, for example from anaesthetic drugs or ischemia, body motion, patients body size, and other physical factors that impact on electric conductivity between the electrodes and the skin (e.g. temperature and humidity).(2, 40, 41)

### *Electrical velocimetry*

In an attempt to overcome the limitations associated with bioimpedance, investigators searched for way to improve existing bioimpedance technique. Recently, electrical velocimetry was introduced as a new bioimpedance method with the new algorithm for processing the impedance signal.(42) The electrical velocimetry, also known as cardiometry, uses the second derivate ( $d^2Z/dt^2$ ) rather than the slope ( $dZ/dt[\max]$ ) of the impedance wave to measure aortic blood flow. Two main differences between bioimpedance and electrical velocimetry are defined. Firstly, the volume of the electricity participating tissue (VEPT) was a homogenously blood filled cylinder or truncated cone in bioimpedance. In the electrical velocimetry, using the new algorithm, only the intrathoracic blood volume compartment is the VEPT. Second difference is based on the conceptualization of what the Newtonian hemodynamic equivalent  $dZ/dt_{\max}$  represents the electrical domain.(43) In the older method,  $dZ/dr_{\max}$  represents the ohmic equivalent of the peak flow in the ascending aorta, whereas in the electrical velocimetry equation  $dZ/dt_{\max}$  represents the ohmic equivalent of the peak aortic blood acceleration.(44)The method has been validated on several occasions in both adults and children. Data from adults suggest it may be better than classical bioimpedance with limits of agreement at approximately the  $\pm 30\%$  acceptance mark. (12) In children, it seems less accurate and there are no published data on trending abilities of electrical

velocimetry method.(12) The one study reported that in adult patients electrical velocimetry overestimated cardiac output to thermodilution with 17% at rest and 34% during exercise.(45)

In summary, the accuracy and reliability of the majority of thoracic bioimpedance devices have been evaluated with inconclusive and conflicting results, which may lead to inappropriate clinical decision and interventions.

### **Bioreactance method for measuring cardiac output**

Due to the limitations associated with bioimpedance devices, newer methods of processing the impedance signal have been developed. It was suggested that in addition to changing resistance to blood flow ( $Z_o$ ), changes in intrathoracic volume also produce changes in electrical capacitive and inductive properties that results in phase shifts of the received signal relative to the applied signal.(46) Techniques for detecting relative phase shifts are inherently more robust and less susceptible to noise (e.g. the comparison between AM and FM radio). The new method, named bioreactance, accurately measures phase shift of an oscillating current in voltage that occur when current traverses the thoracic cavity, as opposed to traditional bioimpedance method, which only relies on measured changes in signal amplitude.(46) According to bioreactance the human thorax can be considered as an electric circuit with resistor (R) and a capacitor (C). Taken together R and C generate the thoracic impedance ( $Z_o$ ).(2) The values R and C determine the 2 components of impedance: amplitude (a) – the magnitude of the impedance measured in ohms; and phase ( $\phi$ ) – the direction of the impedance measured in degrees. The pulsatile ejection of blood from the heart modifies the value of amplitude and the phase of R and the value of C, leading to instantaneous changes in the amplitude and the phase of  $Z_o$ . Phase shifts can occur only

because of pulsatile flow.(2, 46) The overwhelming majority of thoracic pulsatility stems from the aorta. Therefore, the bioactance signal is strongly correlated with aortic flow. Furthermore, because the underlying level of thoracic fluid is relatively static, neither the underlying level of thoracic fluids nor their changes induce any phase shifts and do not contribute to the bioactance signal. The bioactance monitor contains a highly sensitive phase detector that continuously captures thoracic phase shift, which together results in the bioactance signal.(2, 46)

The bioactance device is comprised of a high-frequency (75kHz) sine wave generator and four dual-electrode “stickers” that are used to establish electrical contact with the body.

Within each sticker, one electrode is used by the high-frequency current generator to inject the high-frequency sine wave into the body, while the other electrode is used by the voltage input amplifier. Two stickers are placed on the right side, and two stickers are placed on the left side of the thorax. The stickers on the same side of the body are paired, so that the currents are passed between the outer electrodes of the pair and voltages are recorded from between the inner electrodes. A non-invasive cardiac output measurement signal is thus determined separately from each side of the body, and the final cardiac output measurement signal is obtained by averaging these two signals.(46)

The system’s signal processing unit detects the relative phase shift ( $\Delta\phi$ ) of the input signal (determined by the receiving electrodes) relative to injected signal. The peak rate of change of  $\phi$  ( $d\phi/dt_{\max}$ ) is proportional to the peak aortic flow. The stroke volume (SV) is calculated from the following formula:  $SV = C \times VET \times d\phi/dt_{\max}$ , where C is a constant of proportionality, VET is ventricular ejection time determined by bioactance and electrocardiographic signals. Specifically, the peak of the QRS complex of the ECG is used as the timing mark of the start of each beat. VET is then calculated as the time interval between the start of ejection, defined by the first zero crossing of  $d\phi/dt$  signal, and the end of

ejection, defined by the second zero crossing of  $d\phi/dt$  signal.(46) Unlike bioimpedance, bioreactance-based cardiac output measurements do not use static impedance ( $Z_0$ ) and do not depend on the distance between the electrodes for the calculations of SV, both factors that reduce the reliability of the results.(46) The phase shift between the injected current and output signal received from the thorax is due to changes in blood volume in the aorta.

### *Validation studies of bioreactance*

Several validation studies of bioreactance method have been conducted over the previous years. In initial evaluation, Keren and associates (46) reported strong correlation between bioreactance cardiac output and reference method ( $r=0.84-0.90$ ) in preclinical and clinical setting. Squara et al (47) compared the bioreactance method with thermodilution in 110 patients after cardiac surgery. The mean difference between the two methods was 0.16 l/min and limits of agreement were  $\pm 1.04$  l/min with relative error of 9%. The precision of the bioreactance method was better than that of thermodilution as demonstrated with the ability to track changes in cardiac output accurately. In a multicentre evaluation study, involving 5 centres and 111 patients from cardiac catheterization laboratory, cardiac care units and intensive care units, Raval and colleagues (48) reported a bias of -0.09 l/min and limits of agreement of  $\pm 2.4$  l/min between bioreactance and thermodilution with coefficient of correlation being  $>0.70$  between the two methods. The authors concluded that bioreactance method has acceptable accuracy and challenging clinical environments. The bioreactance was also validated against thermodilution and Fick methods at baseline and after adenosine vasodilator challenge in patients with pulmonary hypertension undergoing right heart catheterization.(49) Results revealed that that bioreactance was more precise than thermodilution ( $3.6\pm 1.7\%$  vs.  $9.9\pm 5.7\%$ ,  $p<0.001$ ). Bland Altman analysis revealed a mean

bias and limits of agreement of  $-0.37 \pm 2.6$  l/min and  $0.21 \pm 2.3$  l/min, respectively. The adenosine challenge resulted in a similar mean increase in CO with each method. Other studies also demonstrated that cardiac output determined by bioreactance is comparable to that of minimally invasive methods including arterial pulse wave analysis and pulse wave counter based methods. (50, 51)

On the other note, two recent studies questioned the accuracy of the bioreactance method. Kober and colleagues (52) tested hypothesis that bioreactance can accurately and precisely assessed cardiac index and its trending ability when compared with transpulmonary thermodilution during cytoreductive surgery in ovarian carcinoma in 15 patients. Results demonstrated concordance correlation coefficient for repeated measures correlating bioreactance and thermodilution was 0.32, bias was 0.26 l/min with limits of agreement of 1.39 and 1.92 l/min with percentage error of 50.7%. The authors suggested that bioreactance showed acceptable accuracy and trending ability but poor precision and concluded that cardiac index measurement can not be solely based on bioreactance in patients undergoing cytoreductive surgery in ovarian carcinoma. Kupersztynch-Hagege et al (53) evaluated the ability of a bioreactance method to estimate cardiac index and to track relative changes induced by volume expansion in 48 critically ill patients. Between bioreactance and thermodilution methods, the authors reported the bias of 0.9 l/min and limits of agreement of 2.2 and 4.1 l/min, with percentage error of 82% and non-significant correlation between the two methods. The authors concluded that bioreactance can not accurately estimate the cardiac output in critically ill patients. However, several methodological limitations of this study have been identified and presented in an editorial by Denman and colleagues (54) suggesting that there is a lack of adequate data presented to support the authors' conclusions.

### *Limitations of bioreactance*

Like several other noninvasive methods, bioreactance cardiac output measurement is based on the assumption that the area under the flow pulse is proportional to the product of peak flow and ventricular ejection time. However, there may be situations, especially during periods of low flow, in which this assumption may not be valid and readings may have decreased accuracy. (46)

### *Direct comparison studies between bioimpedance and bioreactance*

Bioimpedance and bioreactance are noninvasive and continuous cardiac output monitoring methods with potential great clinical implications. Both are based on analysis of impedance signal but bioreactance has been suggested as a new promising method developed as a refinement of bioimpedance. (2, 40) Limited number of studies made direct comparison between bioimpedance and bioreactance methods for estimating cardiac output. Within a large multicentre evaluation of bioreactance, Raval and colleagues (48) performed a sub-study comparing bioreactance with continuous cardiac output thermodilution and bioimpedance. In a subset of 7 a typical, awake, cardiac care unit patients cardiac output was continuously recorded over an approximately 200 minutes. While thermodilution and bioreactance generally tracked each other (with changes appearing first in bioreactance), bioimpedance systematically underestimated cardiac output for long periods of time and also showed higher degree of variability than bioreactance and thermodilution methods. Cardiac output averaged  $5.4 \pm 2.1$  l/min by thermodilution,  $5.5 \pm 1.4$  l/min by bioreactance and  $2.7 \pm 0.8$  l/min by bioimpedance. In a comparison study design, Jakovljevic and colleagues (55) reported bioimpedance and bioreactance cardiac output estimates at rest and during different

exercise intensity in healthy adults. Results suggested non-significant difference between the two methods at rest but at peak exercise bioimpedance underestimated cardiac output by 3.2 and 2.6 l/min compared to bioreactance and theoretically calculated cardiac output based on measured oxygen consumption. Due to wide limits of agreement between bioimpedance and bioreactance (-2.98 to 5.98 l/min) the authors concluded that the two methods can not be used interchangeable further suggesting that bioreactance cardiac outputs are similar to those estimated from measured oxygen consumption.

Based on these direct comparison studies it appears that bioreactance method provides cardiac output estimates that closely reflect those obtained by thermodilution whereas bioimpedance systematically underestimates cardiac output. Similarly bioimpedance appears to underestimate cardiac output for a given physiological demand and under exercise stress testing when compared with bioreactance.

### ***Modern use of bioimpedance and bioreactance***

Evaluating cardiac output under pharmacological and physiological stimulation has been used to improve outcomes, establish diagnosis, guide therapy and help risk stratification in different clinical settings. Non-invasive cardiac output monitoring can play a crucial role in the assessment of volume responsiveness in intensive care unit, that is patients respond to fluid administration by increased cardiac output. (56) In clinical cardiology, haemodynamic response to exercise can help explain of the mechanisms of exercise intolerance in different degrees of heart failure as well as to improve risk stratification and predict survival.(57, 58) This section describes the use of bioreactance and bioimpedance to evaluate volume responsiveness and hemodynamic response to exercise.

### *Assessment of volume responsiveness using bioactance and bioimpedance methods*

In patients with signs of inadequate tissue perfusion, fluid administration generally is regarded as the first step in resuscitation and critical care medicine.(2) Too little fluid may result in tissue hypoperfusion and worsen organ dysfunction whereas overprescription of fluid can reduce oxygen delivery and compromises patient outcome.(59) Several studies suggest that early aggressive resuscitation of critically ill patients may limit or reverse tissue hypoxia and progression to organ failure and improve outcome whereas overzealous fluid resuscitation has been associated with increased complications, length of intensive care unit and hospital stay and mortality.(60-64)

The primary target of a fluid challenge is to increase stroke volume and to assess volume responsiveness. If the fluid challenge does not increase stroke volume, volume loading has no useful benefit and may be harmful to the patient.(2, 59) Clinical studies have consistently demonstrated that only 50% of hemodynamically unstable patients are volume responsive.(65) Therefore it is suggested that the first step in the resuscitation of hemodynamically unstable patient is to determine whether the patient is a volume responder.(2)

It has been demonstrated that passive leg raising (PLR) test can predict fluid responsiveness as its physiological effects are associated with an increase in venous return and cardiac preload.(66) The PLR is therefore an alternative to predict the hemodynamic response to fluid administration since it can be used as a “self-volume challenge” at the bedside which is easy to perform and completely reversible.(67) Lifting the legs passively from the horizontal plane in a lying subject induces a gravitational transfer of blood from the lower part of the body toward the central circulatory compartment and especially toward the cardiac cavities.(68) Technically, PLR is best performed by both elevating the lower limbs to 45°, while at the

same time lowering the patient into the supine position from a 45° semi-recumbent position. This technique has recently gained interest as a test for monitoring functional hemodynamic and assessing fluid responsiveness since it is a simple way to transiently increase cardiac preload from the shift of venous blood from the legs.(69) The physiological response to PLR test is similar to that induced by a 200-300 ml fluid bolus.(68) The PLR increases the aortic flow time—a marker of left cardiac preload—to the same proportion in both responders and nonresponders, suggesting that this test actually performs as a volume challenge.(69) The changes in the descending aortic blood observed during a PLR test were closely correlated with those induced by the subsequent volume expansion.(67) Moreover, a PLR-induced increase in aortic blood flow by more than 10% predicted a fluid-induced increase in aortic blood flow by more than 15% (i. e., fluid responsiveness) with very good sensitivity and specificity.(66) The PLR is validated independently for its accuracy in assessing fluid responsiveness by observing changes in stroke volume.(68) If the increase in SV is 10% or greater from baseline then the patient is fluid responsive, but if it is less than 10% they are not fluid responsive.(70) Therefore, the PLR manoeuvre coupled with non-invasive and continuous assessment of stroke volume and cardiac output will appear to be ideal method for determining volume responsiveness.(59) Indeed, both bioactance and bioimpedance methods have been evaluated for the assessment of volume responsiveness.

*Bioreactance evaluation in the assessment of volume responsiveness.* Marik and colleagues (59) evaluated the accuracy of bioreactance response to PLR test in 34 hemodynamically unstable patients and used brachial arterial Doppler ultrasound flow as the reference technique. The PLR manoeuvre had a sensitivity of 94% and a specificity of 100% for predicting volume responsiveness. Results further revealed that bioreactance stroke volume variation was 18% in responders and 15% in nonresponders. There was a strong correlation

between the percent change in bioactance stroke volume index by PLR and the concomitant change in carotid blood flow ( $r=0.59$ ,  $p=.0003$ ). The authors concluded that a PLR test coupled with the bioactance noninvasive cardiac output monitoring is simple and accurate method of assessing volume responsiveness in critically ill patients. In a separate investigation, Benomar and associates (71) studied the feasibility of predicting fluid responsiveness by PLR using a bioactance method. In a two centre study design, they recruited 75 intensive care unit adult patients immediately after cardiac surgery. Bioactance cardiac output was measured at baseline, during a PLR, and then during a 500 ml fluid infusion. The least minimal significant change was 9%. Cardiac output was  $4.17\pm 1.04$  l/min at baseline,  $4.38\pm 1.14$  L l/min during PLR,  $4.16\pm 1.08$  l/min upon return to baseline, and  $4.85\pm 1.41$  l/min after fluid infusion. The change in cardiac output following fluid bolus was highly correlated with the change in cardiac output following PLR ( $r = 0.77$ ). It was concluded that it is clinically valid to use the bioactance method to predict fluid responsiveness from changes in cardiac output during PLR. Additionally, Lee and colleagues (72) evaluated bioactance to monitor changes in stroke volume after administration of fluid bolus in pediatric setting in 26 mechanically ventilated children. Results demonstrated that bioactance stroke volume variation predicted fluid responsiveness during mechanical ventilation after ventricular septal defect repair in children. Kupersztych-Hagege and colleagues,(53) however, reported that bioactance cannot accurately estimate cardiac output and fluid responsiveness through PLR test in critically ill patients. However, this study design, data analysis and interpretation have been criticized and conclusions opposed by the other authors (54, 73) who highlighted several significant deficiencies which include marked deviation from appropriate use of bioactance method, erroneous interpretation of referencing citing bioactance, and lack of adequate data presented to support conclusions.

Based on available literature it seems that bioimpedance can be used as a clinical tool to evaluate volume responsiveness in different clinical settings.

Most recently, the use of bioimpedance in goal directed fluid therapy management has been demonstrated. In a prospective study Waldron and colleagues (74) evaluated performance of the bioimpedance against esophageal doppler monitor to guide the goal-directed fluid therapy in one hundred surgery adult patients. Results revealed non-significant difference and good agreement between the two methods. Authors concluded that bioimpedance can be a viable method to guide goal directed fluid therapy.

*Bioimpedance evaluation in the assessment of volume responsiveness.* In contrast with bioimpedance, it appears that limited number of clinical studies have tested the accuracy of bioimpedance to predict volume responsiveness using PLR.(67) Fellahi and colleagues (75) tested the hypothesis that bioimpedance could be an alternative to pulse contour analysis for cardiac index measurement and prediction in fluid responsiveness in 25 intensive care unit adult patients following cardiac surgery. The data were collected at baseline, during passive leg raising, and after fluid challenge. Bias and limits of agreement were 0.59 l/min and -0.73-1.62 l/min, with percentage error of 45%. A significant relationship was found between bioimpedance and pulse contour analysis percent changes after fluid challenge. Areas under the receiver operating characteristic curves for changes in cardiac index to predict fluid responsiveness were 0.72 for pulse counter analysis and 0.81 for bioimpedance. The authors concluded that the two methods can not be used interchangeable but seem consistent to monitor cardiac index continuously and could help to predict fluid responsiveness by using passive leg raising. Further clinical validation of bioimpedance to predict fluid responsiveness it warranted.

*Assessment of haemodynamic response to physiological stress testing using bioreactance and bioimpedance methods*

The cardiopulmonary exercise stress testing has been widely used in clinical cardiology and particularly in the management of patients with chronic heart failure. Data obtained from cardiopulmonary exercise testing are used to classify severity of disease, evaluate the effect of therapy, estimate prognosis, identify mechanisms of exercise intolerance, and develop therapeutic interventions.(76) Monitoring cardiac output during stress testing can define degree of cardiac dysfunction and has been shown to improve risk stratification, predict survival and explain the mechanisms of exercise intolerance in different stages of heart failure.(6-8, 57, 58) As the gold standard invasive methods, such as thermodilution and direct Fick, are associated with inherent risks and require specialist expertise, both bioreactance and bioimpedance methods may have a significant clinical implication in cardiac output evaluation under exercise stress testing.

*Bioreactance exercise cardiac output.* Several studies evaluated bioreactance performance under physiological stress testing. The first evaluation of bioreactance under stress testing was performed Myers and associates (77) in 23 patients with heart failure. Results demonstrated strong relationship between bioreactance cardiac output and peak oxygen consumption. In conclusion, the authors suggested that bioreactance cardiac output can clinical evaluation of patients with heart failure. Maurer and colleagues (78) determined the feasibility of using bioreactance during exercise testing in a multicentre study using 210 symptomatic patients with chronic heart failure while measuring gas exchange measures for peak oxygen consumption. Results demonstrated a significant correlation between bioreactance cardiac output and New York Heart Association functional class, peak oxygen consumption and other indices of cardiac and functional performance. In a substudy, the

authors also demonstrated good agreement between bioreactance and inert gas rebreathing method with mean bias of 0.4 l/min (limits of agreement 1.5-2.3 l/min), and strong coefficient of correlation ( $r=0.8$ ) between the two methods. It was concluded that bioreactance can be a useful method for indexing disease severity, prognostication, and for tracking responses to treatment in clinical practice and in clinical trials. Rosenblum et al. (79) evaluated the hypothesis that bioreactance exercise cardiac output and cardiac power output will add significantly to peak oxygen consumption as means of risk-stratifying patients with heart failure. They tested 127 patients with reduced ejection fraction using symptom-limited exercise testing and in addition to gas exchange variables, measured cardiac output using bioreactance. Patients were followed-up on average 404 days to assess endpoints including death, heart transplant, or left ventricular assist device implantation. Results indicated that among patients with heart failure, peak cardiac power measured with bioreactance and peak oxygen consumption has similar association with adverse outcomes and peak power added independent prognostic information to peak oxygen consumption in those with advanced disease.

These studies demonstrate capability of bioreactance to evaluate cardiac output under cardiopulmonary exercise testing and emphasizes its the importance risk stratification and prognosis in heart failure. It should however be noted that no study evaluated accuracy of bioreactance against thermodilution under cardiopulmonary exercise testing. Therefore, future studies are warranted to validate bioreactance under physiological stress testing.

*Bioimpedance exercise cardiac output.* An earlier investigation was performed by Thomas (80) who evaluated performance of bioimpedance in healthy volunteers and critically ill patients. Results revealed that bioimpedance systematically underestimated exercise-induced increase in stroke volume and cardiac output. In a consequent study Thomas and Crowther

(81) evaluated bioimpedance in 102 consecutive male patients with suspected coronary disease prior to cardiac catheterization. In conclusion authors suggested that impedance measurements are not a clinically valuable diagnostic tool and that majority of patients with abnormal responses could be identified more simply by their poor exercise tolerance or abnormal blood pressure response. In contrast, Belardinelly and colleagues (82) examined the accuracy and the reproducibility of impedance cardiography in measuring cardiac output and stroke volume at rest and during incremental exercise versus thermodilution and direct Fick in 25 patients with ischemic cardiomyopathy. Results revealed no significant differences in stroke volume and cardiac output between the three methods at any matched work rate. The authors concluded that impedance cardiography is accurate and reproducible method of measurement of cardiac output and stroke volume over a wide range of workloads. Good agreement between bioimpedance and direct Fick methods has also been previously demonstrated during maximal exercise testing and its reproducibility confirmed in 20 healthy subjects.(83) Charloux and associates (84) evaluated reliability and accuracy of impedance cardiography in 40 patients referred to cardiac catheterization under steady state dynamic leg exercise. The mean difference in cardiac output between the impedance cardiography and direct Fick method and 0.3 l/min during exercise and limits of agreement  $-2.3-2.9$  l/min during exercise. The difference between the two methods exceeded 20% in 9.3% of the cases during exercise. The authors concluded that impedance cardiography provides a clinically acceptable and non-invasive evaluation of cardiac output under exercise condition. Similar findings on accuracy and reproducibility of impedance cardiography under exercise testing were reported by other investigations in health and disease.(85, 86) A review paper by Yancy and colleagues (87) highlighted the use of impedance cardiography in assessment and diagnosis, prognosis and treatment of heart failure, however its use during exercise testing was not discussed. Kemps and associated (88) evaluated impedance cardiography against

direct Fick method under resting and exercise conditions in heart failure and concluded that impedance cardiography overestimates cardiac output at rest and during exercise but may still be useful method to determine haemodynamic changes in response to exercise.

In summary, performance of bioimpedance method under exercise testing has been evaluated by a large number of investigators over the previous decades. This should not be surprising considering that first bioimpedance method was described in 1960s. Available evidence suggests conflicting results on accuracy and reproducibility of bioimpedance when compared with a reference method for evaluation of stroke volume and cardiac output. Future investigations are warranted to refine bioimpedance method and improve its accuracy for evaluating cardiac output under resting and exercise conditions.

## **Summary**

Bioimpedance and bioreactance methods have been developed for noninvasive continuous monitoring of cardiac output in clinical settings. While bioimpedance was developed several decades ago, bioreactance is a novel, advanced modification of thoracic bioimpedance method for monitoring cardiac output. Bioimpedance uses electric current stimulation for identification of impedance variations induced by cyclic changes in blood flow caused by the heart beating. Cardiac output is continuously estimated using electrodes and analyzing the occurring signal variation with different mathematical models. Despite many adjustments of the mathematical algorithms, clinical validation studies of bioimpedance continue to show conflicting results. In contrast to bioimpedance which is based on the analysis of transthoracic voltage amplitude changes in response to high frequency current, the bioreactance technique analyzes the frequency spectra variations of the delivered oscillating current. This approach is supposed to result in a higher signal-to-noise ratio and thus in an improved performance of the method. In fact, initial validation studies reveal promising

results. Both bioimpedance and bioreactance have been evaluated to assess fluid responsiveness and cardiac output during stress testing. Direct comparison studies revealed that bioimpedance underestimated cardiac output compared to bioreactance. Large multicentre validation studies are warranted to establish the validity and reliability of bioimpedance and bioreactance methods in challenging clinical settings.

### ***Practice Points***

- Bioimpedance and bioreactance are noninvasive methods for continuous cardiac output monitoring, with bioreactance being a novel, refined method for processing the impedance signal.
- In contrast to bioimpedance which is based on the analysis of transthoracic voltage amplitude changes in response to high frequency current, the bioreactance technique analyzes the frequency spectra variations of the delivered oscillating current. Therefore, bioreactance is inherently more robust and has higher signal-to-noise ratio.
- Bioimpedance might be useful for trend analysis but great care should be taken for diagnostic interpretation as the method is associated with several limitations that may affect its accuracy.
- Initial validation studies reveal promising results in regards to bioreactance performance in different clinical settings.

### ***Research Agenda***

- Further refinement of bioimpedance method is necessitated as available validity and reliability studies reveal conflicting results.
- Accuracy of bioimpedance to assess fluid responsiveness requires further investigations.
- Even several studies reported accuracy of bioreactance method to estimate cardiac output, future large multicentre studies are warranted to demonstrate its validity and

reproducibility in challenging clinical settings including volume responsiveness assessment and central haemodynamic response to physiological and pharmacological stimulations.

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