Original Article

Clinical validation of bioreactance for the measurement of cardiac output in pregnancy

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Summary

Maternal cardiac dysfunction is associated with pre-eclampsia, fetal growth restriction and haemodynamic instability during obstetric anaesthesia. There is growing interest in the use of non-invasive cardiac output monitoring to guide antihypertensive and fluid therapies in obstetrics. The aim of this study was to validate thoracic bioreactance using the NICOM® instrument against transthoracic echocardiography in pregnant women, and to assess the effects of maternal characteristics on the absolute difference of stroke volume, cardiac output and heart rate. We performed a prospective study involving women with singleton pregnancies in each trimester. We recruited 56 women who were between 11 and 14 weeks gestation, 57 between 20 and 23 weeks, and 53 between 35 and 37 weeks. Cardiac output was assessed repeatedly and simultaneously over 5 min in the left lateral position with NICOM and echocardiography. The performance of NICOM was assessed by calculating bias, 95% limits of agreement and mean percentage difference relative to echocardiography. Multivariate regression analysis evaluated the effect of maternal characteristics on the absolute difference between echocardiography and NICOM. The mean percentage difference of cardiac output measurements between the two methods was ±17%, with mean bias of −0.13 l.min^{-1} and limits of agreement of −1.1 to 0.84; stroke volume measurements had a mean percentage difference of ±15%, with a mean bias of −0.8 ml (−10.9 to 12.6); and heart rate measurements had a mean percentage difference of ±6%, with a mean bias of −2.4 beats.min^{-1} (−6.9 to 2.0). Similar results were found when the analyses were confined to each individual trimester. The absolute difference between NICOM and echocardiography was not affected by maternal age, weight, height, race, systolic or diastolic blood pressure. In conclusion, NICOM demonstrated good agreement with echocardiography, and can be used in pregnancy for the measurement of cardiac function.

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Accepted: 30 April 2020
Keywords: bioreactance; cardiac function; cardiac output; Doppler echocardiography; haemodynamics; pre-eclampsia; stroke volume

Introduction

During normal pregnancy, maternal cardiovascular adaptation is characterised by an initial decrease in systemic vascular resistance (SVR) and increase in cardiac output until the middle of the second trimester. Thereafter, SVR increases and cardiac output declines towards the end of pregnancy [1]. In contrast, maternal cardiac maladaptation, characteristic of pre-eclampsia and fetal growth restriction, is associated with a reduction in stroke volume and cardiac output, and an increase in SVR [2–6].

These distinct haemodynamic patterns may be useful for screening and treatment of pre-eclampsia and fetal growth restriction. As early as the first trimester of pregnancy, lower stroke volume and cardiac output, suggestive of intravascular volume depletion and higher SVR, have potential as markers for screening for fetal growth restriction [7]. In women with gestational hypertension, blood pressure control can be optimised by accounting for maternal race plus the assessment of cardiac output response to the chosen antihypertensive drug [8]. In addition, echocardiography studies have shown that women with early pre-eclampsia have left ventricular diastolic dysfunction [9–11], which increases the risk of pulmonary oedema in cases of unmonitored volume expansion. Predicting fluid responsiveness is crucial in the management of severe pre-eclampsia, especially in the context of volume depletion and left ventricular dysfunction, to balance the risks of renal failure and pulmonary oedema [12]. Furthermore, there is a need for non-invasive continuous cardiac output assessment to guide management of oxytocin and vasopressor therapy during operative delivery in patients with cardiac disease or severe pre-eclampsia [13–15].

Thermodilution is the gold standard for measurement of cardiac output. However, its invasive nature and potential serious complications have rendered it obsolete in routine clinical practice [16]. Two-dimensional transthoracic echocardiography (TTE) is non-invasive but requires training and significant expertise that may not be available out-of-hours. Thoracic bioreactance is a new method of cardiac output measurement that measures the simultaneous relative phase shifts of an oscillating current applied across the thoracic cavity, producing a signal that is strongly correlated with aortic flow [16]. This signal is unaffected by the distance between the two electrodes and the amount of thoracic fluid [17], both of which might affect the reliability of the results in pregnancy.

Bioreactance has been validated in non-pregnant populations against thermodilution [18]. Previous validation studies comparing bioreactance and TTE techniques in pregnancy have either included only a small number of women, or measurements using the two methods were not simultaneous, and have provided conflicting results [19–21]. Our aim was to validate cardiac output assessment using bioreactance against TTE with an appropriately powered study and simultaneous paired recordings.

Methods

The study was approved by the NHS Research Ethics Committee. Pregnant women with healthy, singleton pregnancies were identified consecutively at routine antenatal and scanning visits between July and August 2019. They were recruited in matched-number groups across three trimesters at 11–14 weeks, 20–23 weeks and 35–37 weeks gestation. Maternal and fetal well-being was confirmed by history taking, blood pressure measurement and fetal scans. Women with a known history of congenital or acquired cardiac abnormality were not recruited. All participants provided written informed consent. All studies were performed in the same room under standardised conditions with a monitored room temperature of 23–26°C, with the woman in the left lateral decubitus position.

For thoracic bioreactance measurements, we used the NICOM® monitor (Cheetah Medical Ltd, Maidenhead, UK). The four dual-surface electrodes were applied across the woman's back, with two upper electrodes under the spine of the scapulae posterior to the mid-clavicular line and two lower electrodes at the level of T10. Three-lead ECG electrodes were applied at the front of the chest under the right and left clavicles and the lower edge of the left rib cage. A TTE scan was performed to confirm normal cardiac structure. The woman was allowed to rest for 10 min, and the NICOM monitor was calibrated. The TTE examination was carried out simultaneously with NICOM measurements over an average period of 5 min. NICOM measurements were taken at 30-s intervals for 10 cycles, and the mean of the 10 cycles was analysed.

The TTE was performed by two qualified clinicians (MGA and AC) using a Canon Aplio i900 device (Canon Medical System Europe, London, UK) equipped with a single crystal phased-array linear transducer (cardiac i6SX1) of frequency range 1.8–6 MHz. All measurements were performed according to recommendations of the American Society of Echocardiography [22]. We first measured the diameter of the left ventricular outflow tract (LVOT) from the inner to inner edge of the aortic valve at the level of the annulus, during expiration in the parasternal long-axis view. This was followed by measurement of the left ventricular outflow tract–velocity time integral (LVOT-VTI), with the pulsed-wave Doppler sample at the centre of the LVOT in the apical five-chamber view. Over a period of 5 min, the parasternal long-axis measurements, followed by apical five-chamber view measurements, were performed three times. Cine loops were obtained at end-expiration in raw DICOM format and stored in an archiving system for later analysis (PACS, Software V3.0SP0005; Canon Medical System). Offline analysis was conducted at the end of the study by a single investigator (MGA) who was blinded to the NICOM values.

The left ventricular outflow tract cross-sectional area (LVOT-CSA) was derived as follows: LVOT-CSA = $\pi \times$

(aortic root radius)^2. Stroke volume was derived as: stroke volume = LVOT-CSA × LVOT-VTI. Heart rate was obtained by measuring the R-R interval using the electrocardiogram and multiplying this interval by 60. Cardiac output was calculated using the formula: cardiac output = stroke volume × heart rate.

We calculated that a sample size of 100 women would achieve a relative precision of 0.17 for the 95%CI limits of agreement. The expected Bland–Altman limits of agreement were ±0.34 × SD of the difference between TTE and NICOM. These limits of agreement are the minimum recommended [23]. We planned to recruit 170 women to adjust for potential NICOM signal failure, inability to obtain TTE views, or missing data.

The Kolmogorov–Smirnov test was used to test the normality of the distribution of maternal characteristics and haemodynamics, and the absolute difference in stroke volume, heart rate and cardiac output between TTE and NICOM. Multivariate regression analysis was used to evaluate the effect of maternal characteristics (maternal age, weight, height, smoking, parity, race, systolic and diastolic blood pressure) on the absolute difference between TTE and NICOM of cardiac output, stroke volume and heart rate. IBM SPSS Statistics 23 was used for the statistical analysis (IBM Corp, Armonk, NY, USA).

Results

The study population included 166 women, with 56 in the first, 57 in the second and 53 in the third trimester. Maternal characteristics are presented in Table 1. There were three women who smoked (one in each trimester), two women with chronic hypertension (one in the first and one in the second trimester) and one woman in the second trimester who had diabetes.

The mean percentage difference of cardiac output measurements between the two methods was ±17%, with mean bias of −0.13 l.min^{-1} and limits of agreement of −1.1 to 0.84; stroke volume measurements had a mean percentage difference of ±15%, with a mean bias of −0.8 ml (−10.9 to 12.6); and heart rate measurements had a mean percentage difference of ±6%, with a mean bias of −2.4 beats.min^{-1} (−6.9 to 2.0; Fig. 1). The mean percentage difference, bias and limits of agreement of cardiac output, stroke volume and heart rate in each individual trimester demonstrate equally good agreement between TTE and NICOM (Table 2).

In multivariate regression analysis, maternal characteristics and systolic and diastolic pressure had no effect on the absolute difference between TTE and NICOM (see also Supporting Information, Table S1).

Table 1 Maternal characteristics of the study cohort. Values are mean (SD), median (IQR [range]) or number (proportion).

	First trimester n = 56	**Second trimester n = 57**	**Third trimester n = 53**
Age; years	33.3 (4.4)	33.8 (4.9)	34.7 (5.0)
Weight; kg	69.5 (60.1-77.0 [44.0-115.0])	70.0 (63.4-78.5[54.0-113.0])	77.0 (70.3-89.0 [55.0-106.4])
Height; cm	168 (163-172 [152-180])	166 (161-172 [148-182])	165 (162-170 [152-188])
Gestational age; weeks	12.8 (0.6)	21.4 (0.5)	35.7 (0.3)
Systolic pressure; mmHg	111.0 (106.6-115.9 [93.5-167.3])	112.5 (107.3-116.5 [100.0-130.3])	110.5 (104.1-121.4 [98.0-133.3])
Mean pressure; mmHg	79.3 (76.7-82.8 [66.7-130.9])	79.8 (77.0-84.3 [72.1-95.4])	83.2 (76.3-88.6 [72.2-97.4])
Diastolic pressure; mmHg	63 (60.8-67.9 [53.3-90.0])	63.3 (60.8-68.5 [57.5-79.5])	67.8 (62.4-72.6 [56.5-81.8])
Smoking	1 (2%)	1 (2%))	1 (2%)
Race			
White	44 (79%)	39 (68%)	123 (74%)
Black	7 (13%)	10 (18%)	24 (15%)
South Asian	2 (4%)	5 (9%)	8 (5%)
East Asian	0	0	5 (3%)
Mixed	3 (5%)	3 (5%)	0
Nulliparous	32 (57%)	28 (49%)	26 (49%)
Previous pre-eclampsia or fetal growth restriction	3 (5%)	6 (11%)	8 (15%)
No previous pre-eclampsia or fetal growth restriction	21 (38%)	23 (40%)	19 (36%)
Chronic hypertension	1 (2%)	1 (2%)	0
Diabetes	0	1 (2%)	0

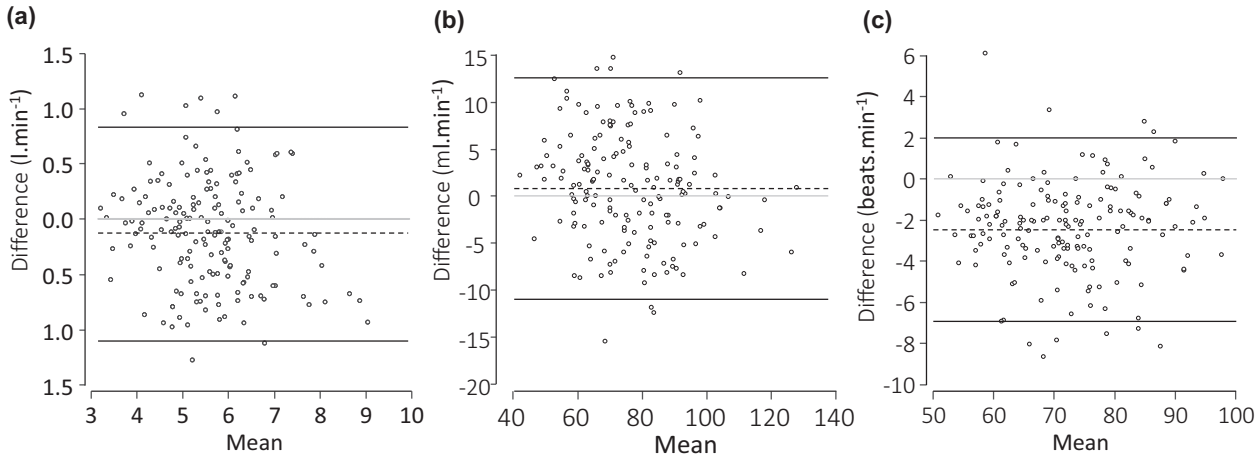

Figure 1 Bland–Altman plot of difference between TTE and NICOM measurements of (a) cardiac output (b) stroke volume and (c) heart rate. Dotted line – bias; solid lines – upper and lower limits of agreement.

Table 2 Accuracy and precision statistics for NICOM vs. TTE.

	First trimester n = 56	**Second trimester n = 57**	**Third trimester n = 53**
Cardiac output; l.min^{-1}	5.54 (4.67–6.12)	5.30 (4.58–6.05)	5.52 (4.91–6.57)
Bias; l.min^{-1}	−0.20	−0.05	−0.15
Precision; l.min^{-1}	0.45	0.48	0.55
95% limits of agreement; l.min^{-1}	−1.08; +0.69	−0.97; +0.88	−1.23; +0.94
Mean percentage difference; %	−7.10	−1.72	−5.12
Stroke volume; ml	77.7 (67.5–86.4)	76.1 (64.8–86.9)	74.2 (63.1–86.5)
Bias; ml	0.19	1.14	0.59
Precision; ml	5.55	6.19	6.42
95% limits of agreement; ml	−10.69; 11.07	−11.01; 13.29	−12.01; 13.19
Mean percentage difference; %	14.24	16.01	16.73
Heart rate; beats.min^{-1}	69.2 (60.7–73.5)	68.7 (61.3–78.3)	73.7 (68.77–84.2)
Bias; beats.min^{-1}	−2.40	−2.25	−2.73
Precision; beats.min^{-1}	2.25	2.03	2.58
95% limits of agreement; beats.min^{-1}	−6.81; 2.01	−6.21; 1.73	−7.79; 2.34
Mean percentage difference; %	−6.72	−6.18	−6.99

Discussion

Bioreactance using NICOM demonstrated good agreement with TTE and meets the recommended level of clinical acceptability throughout gestation. This agreement between both non-invasive cardiac output assessment methods was not affected by maternal characteristics.

Invasive methods such as thermodilution or the Fick technique are the gold standard for measurement of cardiac output. However, even these have an acceptable inherent error of ±10–20% because of cyclical changes in cardiac output resulting from breathing and the lack of measurement precision [24, 25]. In one study using thermodilution, an inherent error of 22% was reduced to 13% by averaging triplicate measurements [26]. When assessing the agreement of two methods for the measurement of cardiac output, at least triplicate measurements should be taken by each method. We averaged three TTE readings and ten NICOM readings for the comparison of the two methods.

Agreement between two different techniques of measurement can be expressed as accuracy (how close the measurement is to the reference value) and precision (how close the values of repeated measurements are to each other) of both methods, which can be represented graphically in a Bland–Altman plot. A limitation of accuracy and precision is that they do not provide an insight into the

absolute value of the measurement relative to the size of agreement. For example, a 1 $l.min^{-1}$ difference in cardiac output has a different clinical impact for an absolute value of 5 $l.min^{-1}$ vs. 10 $l.min^{-1}$. In order to overcome this shortcoming, the use of the percentage error of the limits of agreement for each set of data has been proposed [27]. In a meta-analysis of 25 studies using bias and precision statistics to compare cardiac output measurement techniques, Critchley et al. proposed that a cut-off of 30% should be used as the acceptable percentage error of the limits of agreement when assessing the agreement between two techniques of cardiac output measurement [27, 28]. Therefore, in our study we used the accuracy and precision and percentage error of the limits of agreement between TTE and NICOM.

We used TTE as the gold standard for the estimation of cardiac output in pregnancy as previous studies have demonstrated good agreement between this and thermodilution [29]. Cornette et al. demonstrated a bias of 0.43 $l.min^{-1}$ and a percentage error of 18.4% when comparing the cardiac output of 34 critically ill pregnant women with right-heart catheterisation with that obtained from Doppler echocardiography [29]. A study of 16 women also verified that thermodilution- and Doppler-derived estimations for maternal stroke volume and cardiac output were significantly correlated [30]. Although the ideal strategy to validate NICOM would be to compare it with thermodilution, in healthy pregnant women, this is not feasible.

We performed all the measurements in the left lateral position to avoid inferior vena cava compression by the gravid uterus, and haemodynamic variation introduced during movement between positions. The reduction in preload due to vena cava compression is evident from as early as 20 weeks gestation, with an increase of 27% in stroke volume and left atrial diameter changing from the supine to the left lateral position [31].

Three previous studies compared TTE and NICOM in pregnancy, with conflicting results. Our results agree with those of Doherty et al. who examined 35 healthy pregnant women at a median of 29 weeks gestation; they took simultaneous paired TTE and NICOM measurements of cardiac output in the left lateral position and reported a clinically acceptable mean percentage difference of ±26% between the two techniques. This study was limited by small sample size, narrow gestational age window and restriction to nulliparous women. On the contrary, studies that did not perform the TTE and NICOM measurement simultaneously, and in the same maternal position for each modality, reported poor agreement between the two methods. McLaughlin et al. assessed 20 women at around 24 weeks gestation and demonstrated that NICOM overestimated stroke volume and cardiac output compared with Doppler echocardiography, with a bias of 22 (95% limits of agreement −1.6 to 45) ml and 1.8 (95% limits of agreement −0.2 to 3.8) $l.min^{-1}$, respectively [21]. In this study, NICOM was performed in a semi-recumbent position, and TTE was performed 15 min later in the left lateral position. Vinayagam et al. indicated that NICOM agreement with TTE improved during pregnancy, based on the observed mean percentage difference of 70%, 61% and 32% in the first, second and third trimesters, respectively [19]. However, in this study patients < 24 weeks gestation were examined semi-recumbent while those ≥ 24 weeks were left lateral; furthermore TTE and NICOM were not performed simultaneously. Lastly, only a single set of NICOM measurements was obtained for analysis. These factors raise the possibility of a greater inherent error due to data being collected over a larger physiological range in the cardiac and respiratory cycle.

The strengths of our study are the large sample size and the stringent study protocol, with multiple measurements performed simultaneously in the left lateral position for all patients. TTE measurements were recorded consistently during expiration, and paired LVOT and VTI were measured and averaged three times to limit any error in stroke volume calculation due to the geometric alteration of LVOT associated with each cardiac systole [32]. In addition, this is the first study that assesses the effect of maternal physical characteristics on the absolute difference of cardiac output assessment between both modalities. Finally, although NICOM had been successfully validated in locations rich in electrical noise such as cardiac catheterisation laboratories and operating theatres, it is unclear whether simultaneous operation of ECG and bioreactance in a hyperdynamic circulation such as that in pregnancy could affect heart rate measurements. To overcome this uncertainty, heart rate was calculated manually based on the R-R interval, and checked over at least three cardiac cycles to ensure consistency.

In summary, bioreactance using NICOM demonstrated good agreement with TTE throughout pregnancy, therefore affirming its clinical utility for the measurement of maternal stroke volume and cardiac output in pregnant women irrespective of age, weight, height, race, systolic and diastolic blood pressure.

Acknowledgements

We thank Dr. A. Douiri, Lecturer in Medical Statistics, King's College London for advice on the power calculation. The

study was supported by a grant from the Fetal Medicine Foundation (Charity No: 1037116). NHS Research Ethics Committee (REC reference: 12/LO/1593). No other external funding or competing interests declared.

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Supporting Information

Additional supporting information may be found online via the journal website.

Table S1. Multivariate regression analysis on the effect of maternal characteristics and blood pressure on the absolute difference between TTE and NICOM.