Original Article

Comparison between Modelflow® and echocardiography in the determination of cardiac output during and following pregnancy at rest and during exercise

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ABSTRACT

During pregnancy, assessment of cardiac output ($\dot{Q}$), a fundamental measure of cardiovascular function, provides important insight into maternal adaptation. However, methods for dynamic $\dot{Q}$ measurement require validation. The purpose of this study was to estimate the agreement of $\dot{Q}$ measured by echocardiography and Modelflow® at rest and during submaximal exercise in non-pregnant (*n* = 18), pregnant (*n* = 15, 22-26 weeks gestation) and postpartum women (*n* = 12, 12-16 weeks post-delivery). Simultaneous measurements of $\dot{Q}$ derived from echocardiography [criterion] and Modelflow® were obtained at rest and during low-moderate intensity (25% and 50% peak power output) cycling exercise and compared using Bland-Altman analysis and limits of agreement. Agreement between echocardiography and Modelflow® was poor in non-pregnant, pregnant and postpartum women at rest (mean difference ± SD: -1.1 ± 3.4; -1.2 ± 2.9; -1.9 ± 3.2 L.min^{-1}), and this remained evident during exercise. The Modelflow® method is not recommended for $\dot{Q}$ determination in research involving young, healthy non-pregnant and pregnant women at rest or during dynamic challenge. Previously published $\dot{Q}$ data from studies utilising this method should be interpreted with caution.

Keywords: Prenatal; Submaximal exercise; Finger photoplethysmography; Validity.

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INTRODUCTION

During pregnancy, resting maternal cardiac output ($\dot{Q}$), a fundamental measure of cardiovascular function, provides important insight into maternal adaptation. When pregnancy progresses in a healthy manner, $\dot{Q}$ increases above non-pregnant values by approximately 30% (Meah et al., 2016). However, suboptimal changes have been observed in women with gestational hypertensive complications, indicating that the accurate measurement of $\dot{Q}$ assists in distinguishing between normal and complicated pregnancies (Melchiorre et al., 2011). The assessment of dynamic cardiovascular function during exercise has been used to identify cardiovascular disease risk in the general population (Balady et al., 2004; D'Amore & Mora, 2006; Gibbons et al., 2002; Shin et al., 2015), and there is growing interest in the use of such testing in pregnant women to predict the development of gestational complications (Bijl et al., 2019; Meah et al., 2018). In order to assess acute dynamic responses, methods that are valid for measurement of $\dot{Q}$ in this population are needed.

Assessment of $\dot{Q}$ using the gold-standard method of thermodilution with pulmonary artery catheterization (PAC) is not desirable in otherwise healthy pregnant women (Waksmonski, 2014). Non-invasive methods are therefore essential for cardiovascular assessments during pregnancy. Echocardiography is currently the preferred method due to its lack of radiation exposure, availability, mobility and relatively high temporal resolution (Bijl et al., 2019; Mor-Avi et al., 2011) as well as excellent agreement with PAC (Cornette et al., 2017). However, echocardiography requires considerable skill to acquire reliable results; measurements are not continuous; and calculation of $\dot{Q}$ requires offline analysis. Furthermore, acquisition of echocardiographic images during exercise can also be challenging; consequently, other non-invasive methods may be more suited for dynamic assessments of cardiac function.

The Modelflow® method allows real time, operator independent beat-by-beat blood pressure and $\dot{Q}$ monitoring using finger photoplethysmography and subsequent arterial pressure wave contour analysis. This method is particularly useful in tracking hemodynamic change during physiological perturbations, such as exercise; requires little technical skill, is reliable (Waldron et al., 2018) and provides immediate feedback with easy analysis (Rang et al., 2007). It may, therefore, provide an attractive alternative to more complex $\dot{Q}$ measurement techniques during exercise. Previous work in non-pregnant individuals has shown good agreement in Modelflow® $\dot{Q}$ measurement compared with acetylene uptake during submaximal exercise (Critoph et al., 2013). However, the accuracy of resting $\dot{Q}$ measurement using this method has been questioned in pregnant populations (Bijl et al., 2019; Elvan-Taspinar et al., 2003) and therefore may also be poor during exercise.

The aim of this study was to estimate the degree of agreement between $\dot{Q}$ derived from echocardiography and the Modelflow® methods in non-pregnant, pregnant and postpartum women at rest and during submaximal aerobic exercise. This may have substantial impacts upon the interpretation of $\dot{Q}$ data from previously published studies using the Modelflow® method, as well as influence study design for future research. We hypothesized that there would be poor agreement between the two methods both at rest and during dynamic measurement in all groups.

MATERIALS AND METHODS

Ethical approval and participant recruitment

The study took place in the Cardiff School of Sport and Health Sciences, Cardiff Metropolitan University between January 2015 and April 2017. The data presented in this manuscript is a secondary analysis of a larger cross-sectional study that investigated cardiovascular responses to physiological challenges during and after pregnancy (Meah et al., 2019). As such, the power calculation for the sample size (n = 10 per group) was calculated to achieve the primary aim of the study. All procedures received local institutional research ethics board approval and conformed to the Declaration of Helsinki, apart from registration in a database. Informed consent was obtained from all individual participants included in the study.

Women were recruited from the local community through advertisements and social media. Non-pregnant women were eligible to participate if they were pre-menopausal and had not experienced a previous pregnancy. Pregnant (nulliparous) and postpartum (primiparous) women were eligible for inclusion if they had a singleton, uncomplicated pregnancy. Exclusion criteria included current smokers, pre-existing cardiovascular or metabolic disease, any contraindication to exercise in pregnancy (CSEP, 2015), and use of medication at time of inclusion.

Forty-five Caucasian women were included in the analyses (non-pregnant women, *n* = 18, pregnant women between 22-26 weeks gestation, *n* = 15, postpartum women 12-16 weeks post-delivery, *n* = 12). The baseline characteristics of the population are presented in Table 1 and have been published previously (Meah et al., 2019). Based upon self-report, volunteers were healthy non-smokers, free from cardiovascular and/or metabolic diseases and were not taking any medication at the time of inclusion. The average time point of assessment for pregnant women was ($\bar{x}$ ± SD): 25.4 ± 0.6 weeks gestation, and for postpartum women 15.1 ± 1.3 weeks post-delivery. The distribution of infant sex and method of delivery (vaginal, elective and emergency Caesarean section) were similar between pregnant and postpartum groups. Non-pregnant women were nulliparous and had not tried to conceive.

Table 1. Participant demographics.

	Non-pregnant	**Pregnant** (22-26 weeks)	**Postpartum** (12-16 weeks)	***p*-value**	**Partial eta squared**
n	18	15	12		
Age (years)	29 ± 4 *	32 ± 3	33 ± 2	**< .001**	.307
Height (cm)	166 ± 7	167 ± 4	165 ± 4	.87	.017
Body mass (kg)	64 ± 13	73 ± 8	67 ± 11	.10	.138
BMI (kg.m^{-2})	23 ± 4	26 ± 4	25 ± 4	.11	.135
Heart rate (bpm)	58 ± 9	71 ± 7 *	57 ± 9	**< .001**	.841
SBP (mmHg)	112 ± 7	109 ± 8	105 ± 6	**.047** †	.175
DBP (mmHg)	67 ± 6	63 ± 5	61 ± 4	.06	.162
MAP (mmHg)	82 ± 6	78 ± 5	76 ± 4	**.037** †	.185
Gestational age at delivery (weeks) ‡	-	40.5 ± 2.1	39.7 ± 1.5	.30	.045
Birthweight (kg) ‡	-	3.5 ± 0.5	3.2 ± 0.5	.13	.092

*Key: Data presented as within sample mean ± within sample standard deviation; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial blood pressure. * = significantly different to all other groups. † = indicates overall effect was significant, but non-significant differences between groups were identified in post-hoc comparisons. ‡ = indicates differences between groups were identified using independent t-tests that were corrected for multiple comparisons using the Bonferroni correction. Some of the presented data has previously been published elsewhere (Meah et al., 2019).*

Study design

Participants attended the laboratory on two different occasions. On the first study visit, participants completed physical activity readiness screening questionnaires, specifically, non-pregnant and postpartum women completed the American College of Sports Medicine screening questionnaire (Balady et al., 1998) and pregnant women completed the PARMed-X for Pregnancy (CSEP, 2015). When eligibility was confirmed, participants underwent anthropometric assessment and an incremental submaximal aerobic exercise test up to 70% heart rate [HR] reserve on an upright cycle ergometer (Corival, Lode, Groningen, Netherlands). HR reserve was calculated prior to the start of the test using the Karvonen method (Karvonen et al., 1957), in which resting HR was measured during 5 minutes of quiet rest and maximal HR was estimated 208 - 0.7(age) (Tanaka et al., 2001). The achieved power output at 70% HR reserve was extrapolated to HR maximum and peak power estimated. This value was then adjusted for reduced cycling performance associated with the supine and left lateral position (multiplied by 0.7) (Egana et al., 2013).

In the second visit, blood pressure was measured manually on the left arm after five minutes of seated rest using the auscultatory method. Two measurements of systolic and diastolic blood pressure (SBP and DBP) were taken and averaged. Mean arterial pressure was calculated as [(⅓ × SBP) + (⅔ × DBP)]. Participants then underwent simultaneous echocardiography and finger photoplethysmography for assessment of $\dot{Q}$ at rest, and during light to moderate intensity (25% and 50% peak power output [PPO]) aerobic exercise completed on a supine cycle ergometer (Angio 2003, Lode, Groningen, Netherlands). The supine ergometer was tilted 30-45 degrees to the left to avoid potential compression of the inferior vena cava in pregnant women. Women cycled at each intensity for five to seven minutes. All measurements were performed in the same room, under standardised conditions and by the same researcher and were only collected after steady state exercise was reached (stabilization of HR and blood pressure).

Modelflow®

Continuous measurement of $\dot{Q}$ was completed using a non-invasive beat-by-beat finger photoplethysmography system (FinometerPRO, FMS, Finapres Measurement Systems, Arnhem, Netherlands). Although this particular system is no longer in production, the ModelFlow® method for $\dot{Q}$ estimation is still used in newer finger photoplethysmography equipment from the same manufacturer (e.g. the Finometer MIDI). A finger cuff was placed around the participant's right middle finger. A height correction unit was placed at both hand and heart level in order to correct for hydrostatic pressure differences. A brachial cuff was placed on the upper arm, and return-to-flow calibration performed according to the manufacturer's instructions at the beginning of each test. Furthermore, 'PhysioCal,' a process that fine-tunes finger cuff pressure and quality of the plethysmogram, was used throughout the exercise test to ensure the maintenance of good quality signals. Physical characteristics (age, height and body mass) of each participant were uploaded to the software. In this method, $\dot{Q}$ is estimated through analysis of the pressure wave contour using aortic characteristic impedance, compliance and estimated cardiac afterload, as described previously (Dyson et al., 2010). Data were recorded continuously (PowerLab, ADInstruments, Chalgrove, UK) and saved for later offline analysis. Average values were calculated from 20 continuous cardiac cycles selected from a clean trace after 15 minutes of rest, and within the final two minutes of low and moderate intensity aerobic exercise (LabChart v7, ADInstruments, Chalgrove, UK). This time period coincided with echocardiographic image acquisition.

Echocardiography

Echocardiographic measurements of $\dot{Q}$ were acquired using a commercially available ultrasound (Vivid E9, GE Medical Systems, Horten, Norway) and 1.5-4.6 MHz phased array transducer (M5S, GE Medical

Systems, Horten, Norway) by one trained sonographer (VLM). A three-lead electrocardiograph (ECG) was attached to the participant to determine heart rate (HR). All images were collected at end-expiration over five cardiac cycles at the time periods described previously. Two-dimensional images were acquired within a range of 70-90 frames per second. Images were saved for later offline analysis (EchoPAC version 110.1.1, GE Medical, Horton, Norway) and all parameters were reported as an average of measurements completed on three different cardiac cycles. Apical 4- and 2-chamber views were acquired in accordance with current guidelines to allow for the calculation of cardiac volumes using the Simpson's biplane method (Lang et al., 2015). The area change, from end-diastole to end-systole, was used to estimate left ventricular volumes from both the apical 4-chamber and apical 2-chamber views. This method was chosen to as it takes into account the shape of the left ventricle along its entire length (which is altered as a result of pregnancy-induced remodelling) and also allowed estimation of end-diastolic volume (EDV) and end-systolic volume (ESV). Stroke volume was calculated as EDV-ESV. Consequently, $\dot{Q}$ was derived the product of SV and HR averaged from the corresponding ECG trace on analysed cardiac cycles.

Statistical analysis

The data analysis approach taken in the present study was that of a criterion-related framework, and, because echocardiography is the most accepted technique for $\dot{Q}$ assessment in healthy pregnant women (Bijl et al., 2019), measurements gathered from echocardiography were deemed to be the criterion measurements (Bland, 2000). Data for $\dot{Q}$ were calculated for all women at rest and for each group (non-pregnant, pregnant and postpartum) during each physiological state (rest, low intensity and moderate-intensity aerobic exercise). Data were analysed using Minitab v18 and IBM SPSS v24.

Intra-observer reliability of $\dot{Q}$ measurements using echocardiography and repeated measurements using the Modelflow® method at rest and during exercise were assessed in a subset of participants using coefficients of variation (CV). For this protocol, an initial set of resting measurements were collected within a 20-minute period, after which a second set of measurements were collected. Participants then cycled at 25% PPO. During this exercise bout, an initial set of echocardiographic images was acquired as described above following achievement of steady state. A second set of images was collected immediately after the completion of the first set, whilst the volunteer remained cycling. This exercise bout did not last longer than 7 minutes in total for any participant and there were no statistical differences between the first and second measures at rest or during exercise. These values were used to derive CV as the ratio of the standard deviation of a subject's two $\dot{Q}$ scores (SD_X) expressed to a 95% probability, and the mean of those two scores ($\bar{x}_X$),: CV = [(1.96 × SD_X)/ $\bar{x}_X$].(Bland, 2015) The CV were then compared using independent samples *t*-tests to identify if there were differences in the reliability of each method.

Agreement between echocardiography (E) measurements of $\dot{Q}$ and those gathered from the Modelflow® (M) was first identified and then quantified using the 95% limits of agreement method (LoA) originally described by Bland and Altman (1986). Identification of agreement included plotting a scatterplot (*Bland and Altman plot*) of the mean values gathered from the two measurement methods [(E + M)/2] for each subject on the *X*-axis, corresponding to the differences (residual errors) between each subject's values (E - M) on the *Y*-axis. Quantification of agreement between measurement methods included: i) confirming residual errors as normally distributed in the populations from which the three samples were drawn (Anderson-Darling test), ii) estimating systematic bias with respect to the mean difference between the two measurement methods ($\bar{x}_{diff}$), iii) estimating random variation between the two measurement methods expressed as ($\pm$ 1.96 $\times$ SD_{diff}), iv) when residual errors were normally distributed, agreement between measurement methods was expressed as exact 95%LoA, i.e. $\bar{x}_{diff} \pm (1.96 \times SD_{diff})$ and when residual errors were not normally distributed, agreement

between measurement methods was expressed as inexact 95%LoA, i.e. $\bar{x}_{diff} \pm (2.0 \times SD_{diff})$, and, in both cases results were described as upper- and lower-limits superimposed on the Bland and Altman plots (Atkinson & Nevill, 1998), v) homoscedastic error quantified by establishing whether a non-significant ($p > .05$), positive linear relationship existed between the *absolute* residual errors and mean values for each subject by computing a Pearson's product-moment correlation and observational confirmation from a scatterplot, and, vi) estimating confidence intervals (95%*CI*) for the 95%LoA as: 95%*CI* = 95% limit $\pm$ (1.96 $\times$ SE), where the standard error (SE) = $\sqrt{(3 \times SD_{diff}^2/n)}$ (Bland & Altman, 2003). We deemed an acceptable $\bar{x}_{diff}$ to be $\pm$1.0 L.min^{-1} as this reflects an error of approximately 15% from established norms for the population (Meah et al., 2016) and greater deviations could be clinically meaningful.

Other metrics included: i) the mean of subjects' individual CVs derived as described previously but expressed as a percentage: $\bar{x}$ CV% = [Σ(((1.96 $\times$ SD_X)/ $\bar{x}_X$) $\times$ 100)/n], ii) intraclass correlation coefficients (ICC (3,1))(Shrout & Fleiss, 1979) and 95%*CI*s, iii) technical error of measurement (TEM) expressed as: 95%TEM = $\pm$ [1.96 $\times$ $\sqrt{(\Sigma(x_E - x_M)^2/2n)}$], and as a percentage of the criterion (E) mean: 95%TEM% = [(95%TEM/ $\bar{x}_E$) $\times$ 100], and, v) mean percentage errors between $\dot{Q}$ measurements expressed relative to the criterion measure derived as: PE% = $\pm$ [Σ(($\bar{x}$ E – M $\bar{x}$ /E) $\times$ 100)/n] – in the determination of $\dot{Q}$, percentage error is considered acceptable if this value falls below 30% (Critchley & Critchley, 1999). Percentage error was also expressed as a ratio of the *absolute error* (i.e. $\pm$ 0.5 of the smallest unit of measurement (0.1 L.min^{-1}) = $\pm$ 0.5 $\times$ 0.1 = 0.05 L.min^{-1}) and the mean for the criterion measure: $\bar{x}$ PE% = [(0.05 $\div$ $\bar{x}_E$) $\times$ 100].

It should be noted that these analyses were also completed for SV and HR. In all cases, measurement of HR between the two methods showed very good agreement, but there was poor agreement in the measurement of SV (data not shown), following the same trends as $\dot{Q}$.

RESULTS

In some women, it was not possible to acquire optimal echocardiographic images during exercise (2 non-pregnant and 4 postpartum women). Therefore, analysis of data during exercise was completed with a reduced sample of the population (exact numbers are highlighted in tables).

Reliability

Table 2. Intra-observer reliability of cardiac output ($\dot{Q}$) measurement using the Modelflow® method and echocardiography at rest and during submaximal aerobic exercise. Data are presented as $\bar{x}$ ± SD.

	Rest		**During cycling exercise at 25% PPO**	
	Measure 1	*Measure 2*	*Measure 1*	*Measure 2*
Modelflow®				
Sample size	44		42	
$\dot{Q}$ (L.min^{-1})	5.0 ± 1.7	4.9 ± 1.5	7.4 ± 2.9	7.7 ± 2.6
CV (%)	11.3		11.9	
Echocardiography				
Sample size	*21*		*10*	
$\dot{Q}$ (L.min^{-1})	3.9 ± 1.0	3.8 ± 0.9	6.9 ± 1.7	6.9 ± 1.5
CV (%)	3.2		3.9	

Key: $\bar{x}$ ± SD = within sample mean ± within sample standard deviation, CV = coefficient of variation, expressed as a percentage; $\dot{Q}$ = cardiac output, PPO = peak power output. Repeated measures (Measure 1 and Measure 2) were acquired within 2 minutes of each other. Modelflow® estimates were taken from within the same period of echocardiographic image acquisition. Repeated measures were completed in a subset of the cohort hence reduced sample sizes for echocardiography.

Table 3. Cardiac Output (L.min^{-1}) obtained with two methods at rest in all women, and the three study groups.

Group	Instrument	$\bar{x}$ ± SD	95% LoA: $\bar{x}_{diff}$ ± (1.96 × SD_{diff}) lower LoA *vs* upper LoA (lower 95% *CI*) (upper 95% *CI*)	Intraclass correlation: ICC[3,1] (95% *CI*)	Coefficient of variation: $\bar{x}$ CV%	Technical error of measurement: ±95% TEM 95% TEM%	Percentage error: ±PE% $\bar{x}$ PE%
All women (*n* = 45)	Echocardiography	3.8 ± 0.9	-1.3 ± 3.1 -4.4 *vs* 1.8 (-5.2 to -3.6) (1.0 to 2.6)	0.400 (0.124 to 0.619)	53.2%	± 2.9 76.3%	± 1.3% 46.6%
	Modelflow®	5.1 ± 1.8					
Non-pregnant (*n* = 18)	Echocardiography	3.2 ± 0.5	-1.1 ± 3.4* -4.5 *vs* 2.3 -5.9 to -3.1 0.9 to 3.7	0.178 (-0.302 to 0.586)	63.3%	± 2.7 84.4%	± 1.6% 51.4%
	Modelflow®	4.3 ± 1.8					
Pregnant (*n* = 15)	Echocardiography	4.8 ± 0.8	-1.2 ± 2.9 -4.1 *vs* 1.7 -5.3 to -2.9 0.5 to 2.9	0.191 (-0.338 to 0.629)	20.3%	± 2.5 52.1%	± 1.0% 34.3%
	Modelflow®	6.0 ± 1.5					
Postpartum (*n* = 12)	Echocardiography	3.4 ± 0.6	-1.9 ± 3.2* -5.1 *vs* 1.3 -6.7 to -3.5 0.3 to 2.9	0.363 (-0.237 to 0.763)	28.1%	± 3.3 97.1%	± 1.5% 54.7%
	Modelflow®	5.3 ± 1.9					

*Key: $\bar{x}$ ± SD = within sample mean ± within sample standard deviation; 95% LoA = 95% limits of agreement; $\bar{x}_{diff}$ and SD_{diff} = within sample mean and standard deviation for differences between Echocardiography and Modelflow® scores (Echocardiography- Modelflow®); n = sample size; 95%CI = 95% confidence interval; * = error was heteroscedastic, consequently approximate 95% limits of agreement are presented, i.e. $\bar{x}_{diff}$ ± (2.0 × SD_{diff}).*

Table 4. Cardiac Output (L.min^{-1}) obtained with two methods during cycling exercise at 25% peak power output in the three study groups.

Group	Instrument	$\bar{x}$ ± SD	95% LoA: $\bar{x}_{diff}$ ± (1.96 × SD_{diff}) lower LoA *vs* upper LoA (lower 95% *CI*) (upper 95% *CI*)	Intraclass correlation: ICC[3,1] (95% *CI*)	Coefficient of variation: $\bar{x}$ CV%	Technical error of measurement: ±95% TEM 95% TEM%	Percentage error: ±PE% $\bar{x}$ PE%
Non-pregnant (*n* = 18)	Echocardiography	6.2 ± 1.0	-0.3 ± 6.3 -6.6 *vs* 6.0 -9.1 to -4.1 3.5 to 8.5	0.007 (-0.450 to 0.461)	31.1%	± 4.3 69.3%	± 0.8% 40.1%
	Modelflow®	6.5 ± 3.1					
Pregnant (*n* = 15)	Echocardiography	7.3 ± 1.1	-0.9 ± 5.8* -6.7 *vs* 4.9 -9.2 to -4.2 2.4 to 7.4	0.276 (-0.256 to 0.680)	19.6%	± 2.7 37.0%	± 0.7% 27.7%
	Modelflow®	8.2 ± 3.2					
Postpartum (*n* = 12)	Echocardiography	5.7 ± 0.8	-2.4 ± 3.2* -5.6 *vs* 0.8 -7.2 to -4.0 -0.8 to 2.4	0.478 (-0.135 to 0.826)	23.0%	± 3.9 68.4%	± 0.9% 40.9%
	Modelflow®	8.1 ± 2.1					

*Key: $\bar{x}$ ± SD = within sample mean ± within sample standard deviation; 95% LoA = 95% limits of agreement; $\bar{x}_{diff}$ and SD_{diff} = within sample mean and standard deviation for differences between Echocardiography and Modelflow® scores (Echocardiography- Modelflow®); n = sample size; 95%CI = 95% confidence interval, * = error was heteroscedastic, consequently approximate 95% limits of agreement are presented, i.e. $\bar{x}_{diff}$ ± (2.0 × SD_{diff}).*

Table 5: Cardiac Output (L.min^{-1}) obtained with two methods during cycling exercise at 50% peak power output in the three study groups.

Group	Instrument	$\bar{x}$ ± SD	95% LoA: $\bar{x}_{diff}$ ± (1.96 × SD_{diff}) lower LoA *vs* upper LoA (lower 95% *CI*) (upper 95% *CI*)	Intraclass correlation: ICC[3,1] (95% *CI*)	Coefficient of variation: $\bar{x}$ CV%	Technical error of measurement: ±95% TEM 95% TEM%	Percentage error: ±PE% $\bar{x}$ PE%
Non-pregnant (*n* = 18)	Echocardiography	7.8 ± 0.8	-1.0 ± 9.0 -10 *vs* 8.0 -13.9 to -6.1 4.1 to 11.9	0.030 (-0.458 to 0.505)	37.8%	± 6.4 82.0%	± 0.6% 53.1%
	Modelflow®	8.9 ± 4.7					
Pregnant (*n* = 15)	Echocardiography	8.9 ± 1.7	-2.2 ± 9.8 -12.0 *vs* 7.6 -16.3 to -7.7 3.3 to 11.9	0.114 (-0.406 to 0.579)	29.6%	± 7.3 82.0%	± 0.6% 52.6%
	Modelflow®	11.1 ± 5.0					
Postpartum (*n* = 12)	Echocardiography	7.5 ± 1.2	-3.7 ± 5.0* -8.7 *vs* 1.3 -11.7 to -5.7 -1.7 to 4.3	0.352 (-0.411 to 0.825)	26.4%	± 6.1 81.3%	± 0.7% 50.2%
	Modelflow®	11.2 ± 2.9					

*Key: $\bar{x}$ ± SD = within sample mean ± within sample standard deviation; 95% LoA = 95% limits of agreement; $\bar{x}_{diff}$ and SD_{diff} = within sample mean and standard deviation for differences between Echocardiography and Modelflow® scores (Echocardiography- Modelflow®); n = sample size; 95%CI = 95% confidence interval; * = error was heteroscedastic, consequently approximate 95% limits of agreement are presented, i.e. $\bar{x}_{diff}$ ± (2.0 × SD_{diff}).*

Intra-observer CV for measurement of $\dot{Q}$ using echocardiography was 3.2% at rest (Meah et al., 2019) and 3.9% during exercise, as presented in Table 2. The CV was markedly greater at rest and during exercise for $\dot{Q}$ estimated by the Modelflow® method.

Cardiac output at rest

There was poor agreement between resting $\dot{Q}$ derived from echocardiography and $\dot{Q}$ derived using the Modelflow® method when all groups were combined in one analysis, as well as in separate analyses for each group (non-pregnant, pregnant and postpartum women, Table 3; Figures 1 to 4. In all groups, the $\bar{x}_{diff}$ was greater than 1.0 L.min^{-1} and the percentage error was greater than the *a priori* agreement target of 30%. Heteroscedastic error, in which the size of the error term differs across values of $\dot{Q}$, was identified in the datasets of non-pregnant and postpartum women, as such, approximate LoA were calculated and presented.

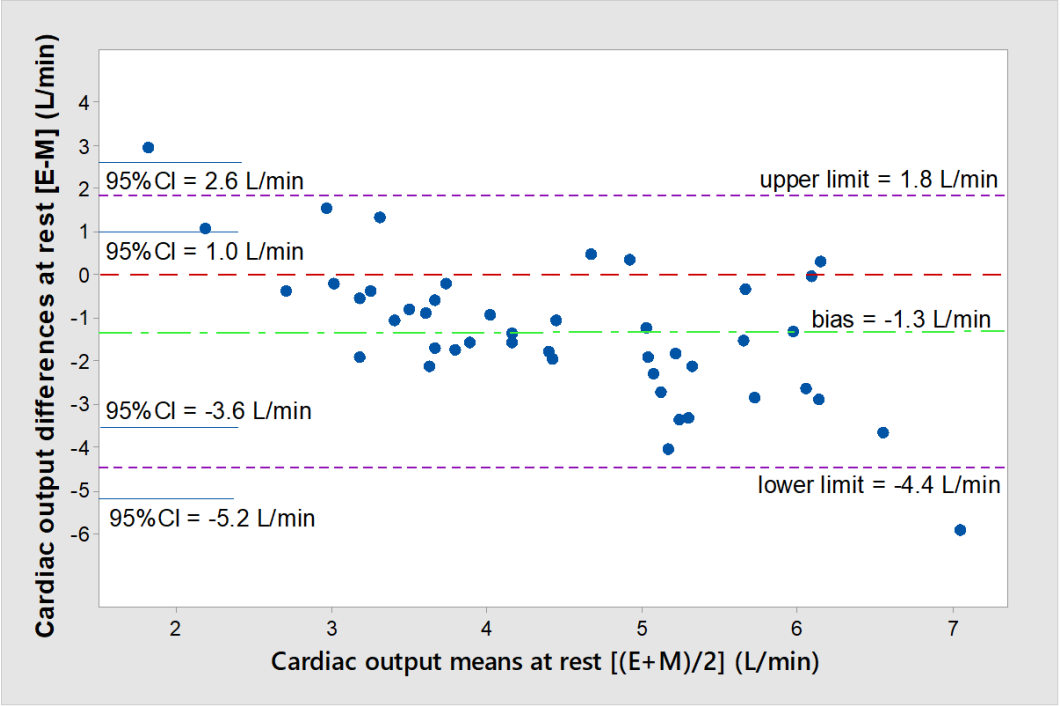

Figure 1. Bland and Altman plot summarising limits of agreement for cardiac output estimated using echocardiography (E) and the Modelflow (M) in all women (n = 45) at rest (95%CI = the 95% confidence interval for both upper and lower limits of agreement).

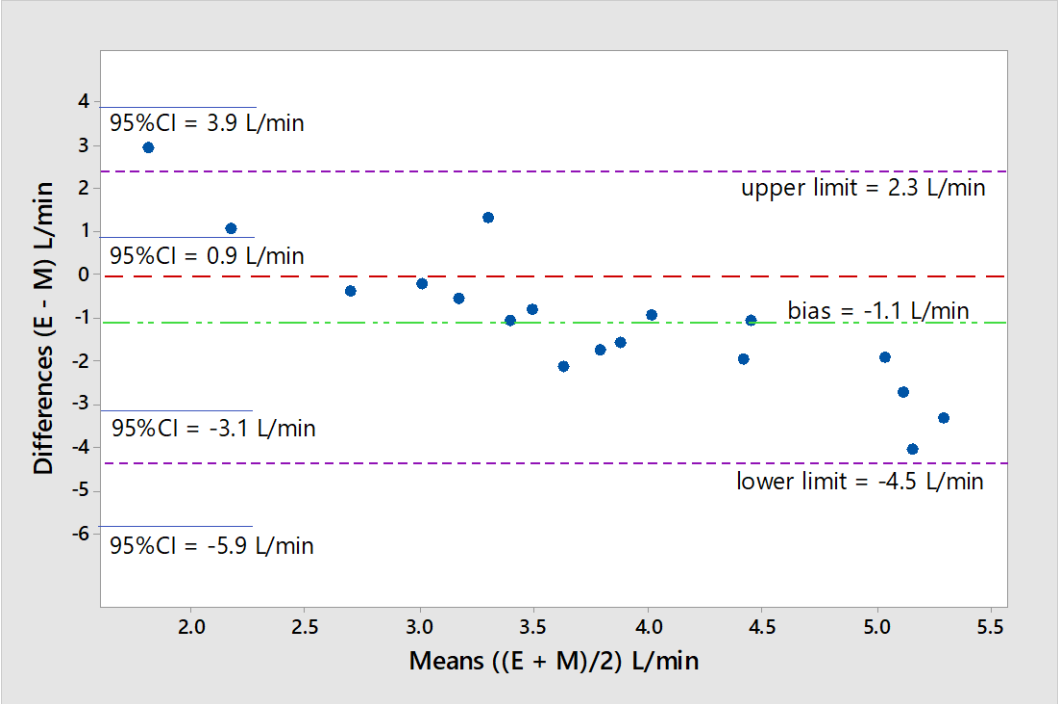

Figure 2. Bland and Altman plot summarising limits of agreement for cardiac output estimated using echocardiography (E) and the Modelflow (M) in non-pregnant women at rest (95%*CI* = the 95% confidence interval for both upper and lower limits of agreement).

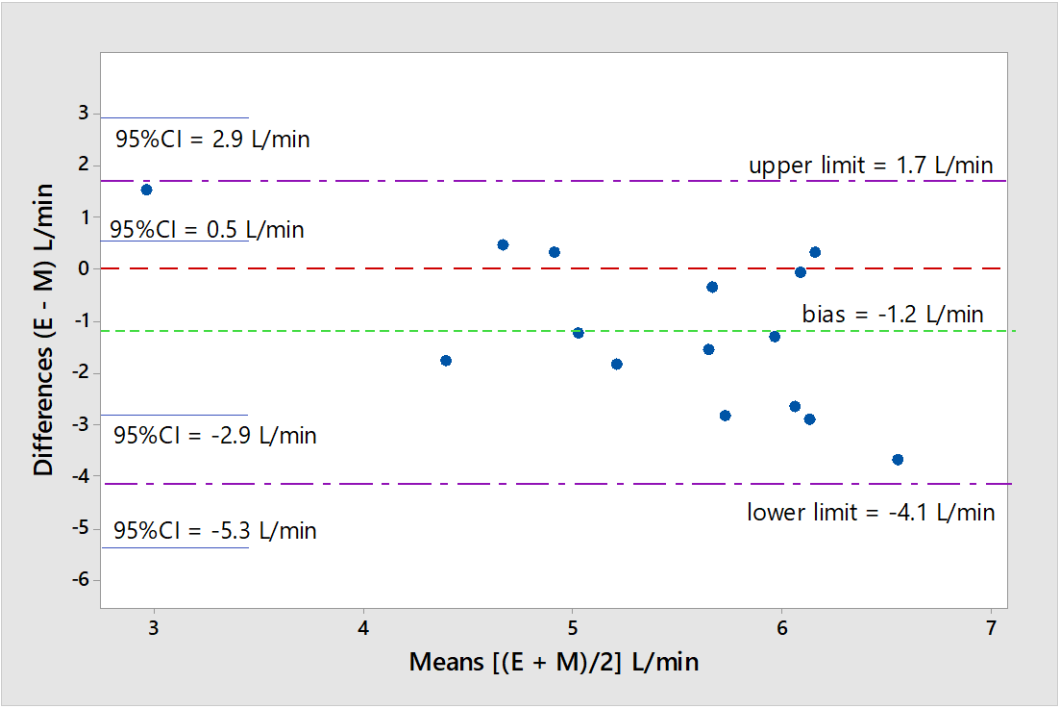

Figure 3. Bland and Altman plot summarising limits of agreement for cardiac output estimated using echocardiography (E) and the Modelflow (M) in pregnant women at rest (95%*CI* = the 95% confidence interval for both upper and lower limits of agreement).

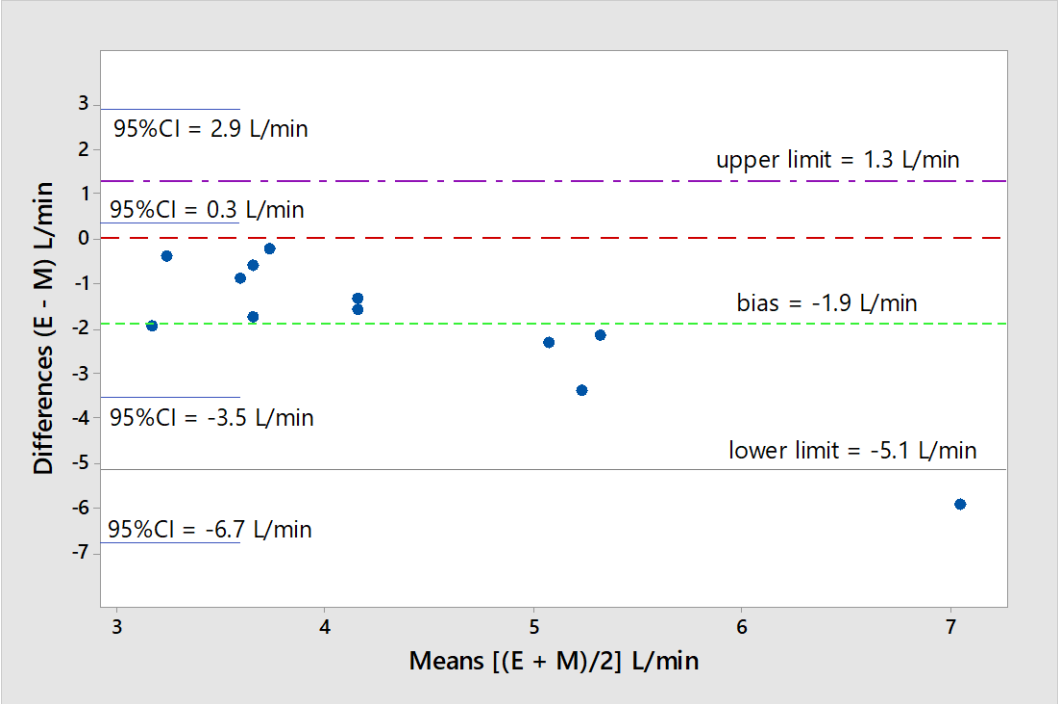

Figure 4. Bland and Altman plot summarising limits of agreement for cardiac output estimated using echocardiography (E) and the Modelflow (M) in postpartum women at rest (95%*CI* = the 95% confidence interval for both upper and lower limits of agreement).

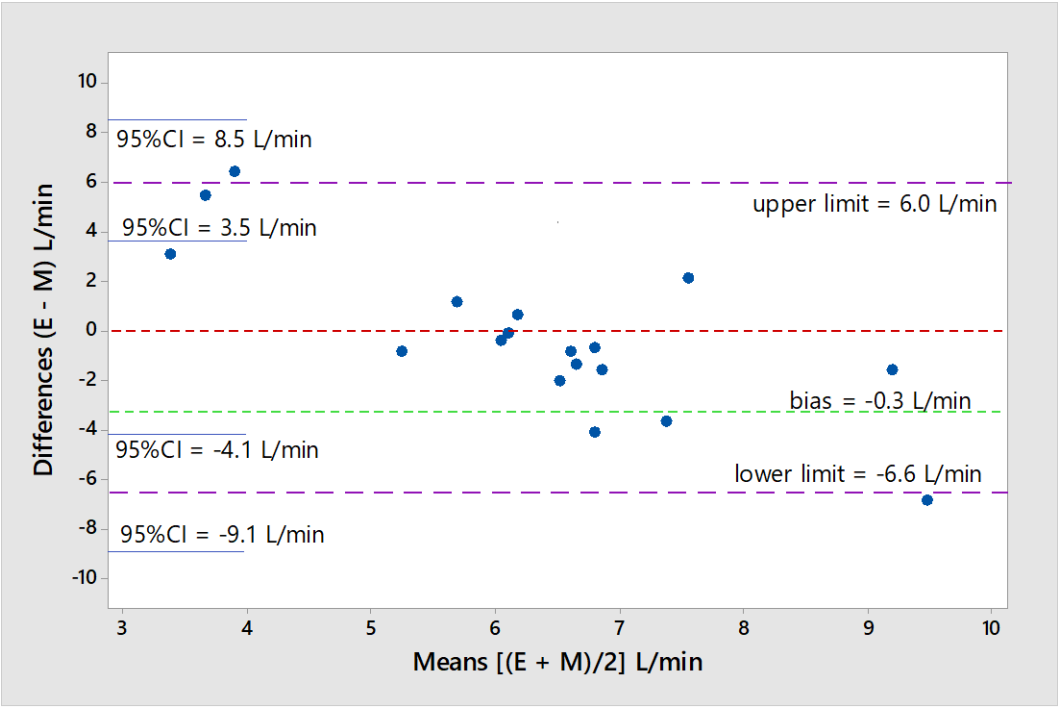

Figure 5. Bland and Altman plot summarising limits of agreement for cardiac output estimated using echocardiography (E) and the Modelflow (M) in non-pregnant women at 25% of maximal aerobic exercise (95%*CI* = the 95% confidence interval for both upper and lower limits of agreement).

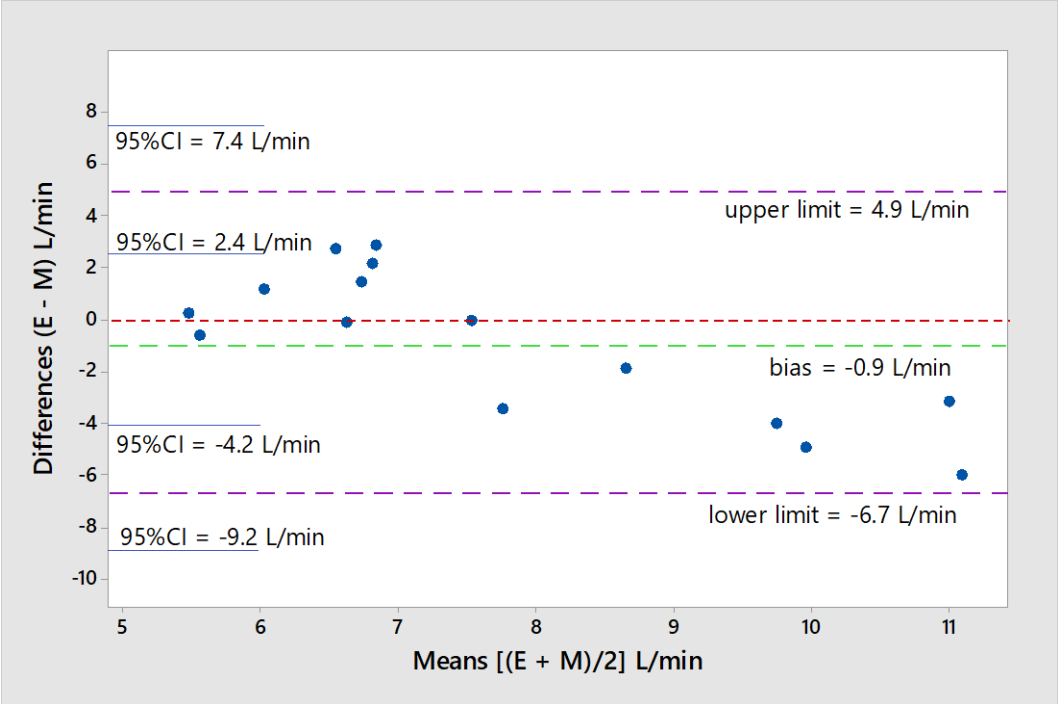

Figure 6. Bland and Altman plot summarising limits of agreement for cardiac output estimated using echocardiography (E) and the Modelflow (M) in pregnant women at 25% of maximal aerobic exercise (95%*CI* = the 95% confidence interval for both upper and lower limits of agreement).

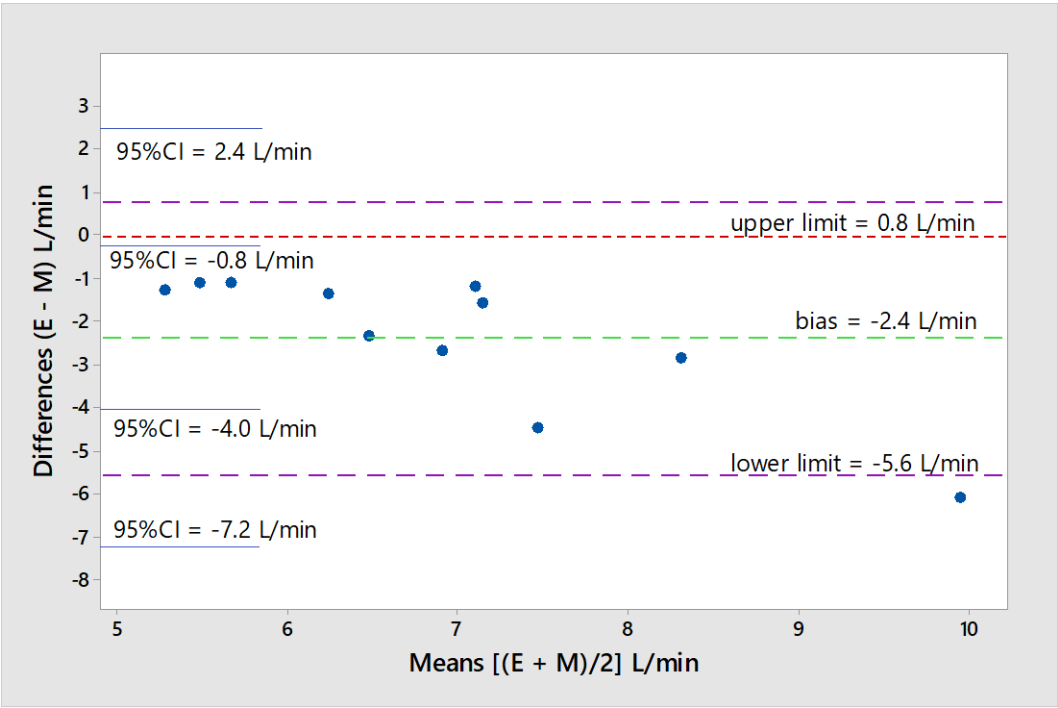

Figure 7. Bland and Altman plot summarising limits of agreement for cardiac output estimated using echocardiography (E) and the Modelflow (M) in postpartum women at 25% of maximal aerobic exercise (95%*CI* = the 95% confidence interval for both upper and lower limits of agreement).

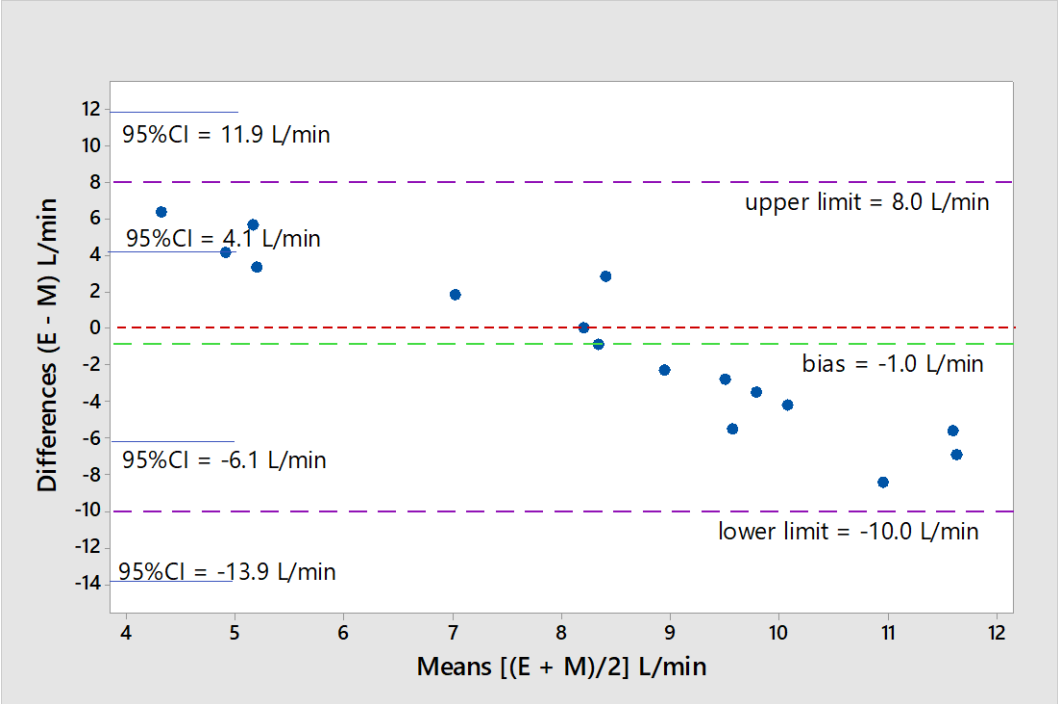

Figure 8. Bland and Altman plot summarising limits of agreement for cardiac output estimated using echocardiography (E) and the Modelflow (M) in non-pregnant women at 50% of maximal aerobic exercise (95%*CI* = the 95% confidence interval for both upper and lower limits of agreement).

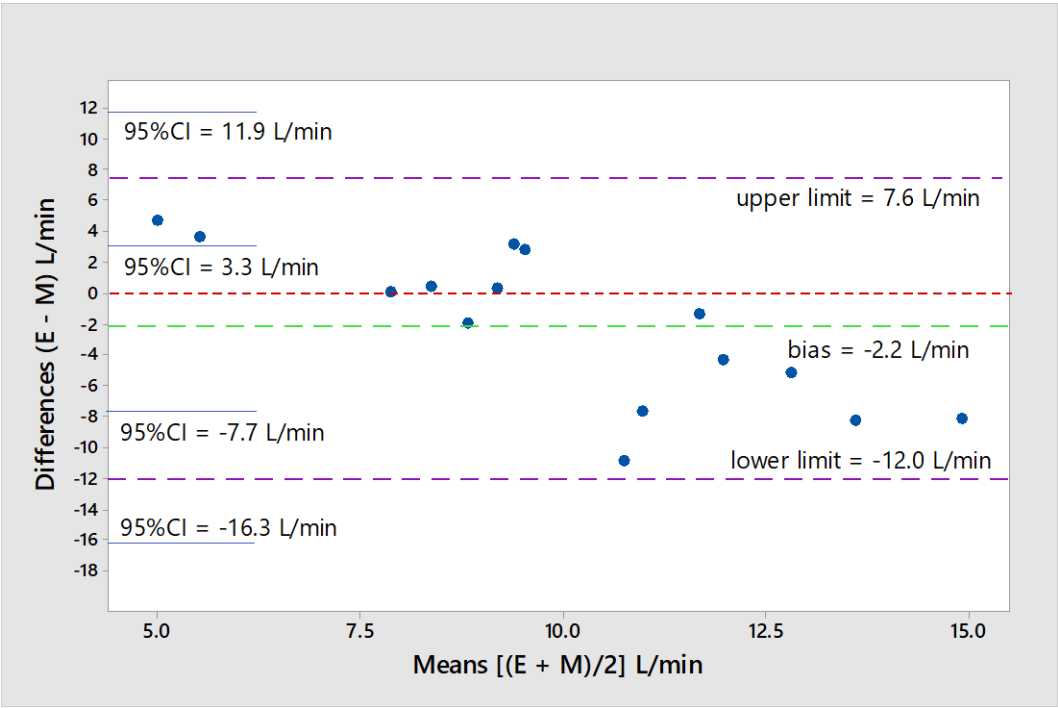

Figure 9. Bland and Altman plot summarising limits of agreement for cardiac output estimated using echocardiography (E) and the Modelflow (M) in pregnant women at 50% of maximal aerobic exercise (95%*CI* = the 95% confidence interval for both upper and lower limits of agreement).

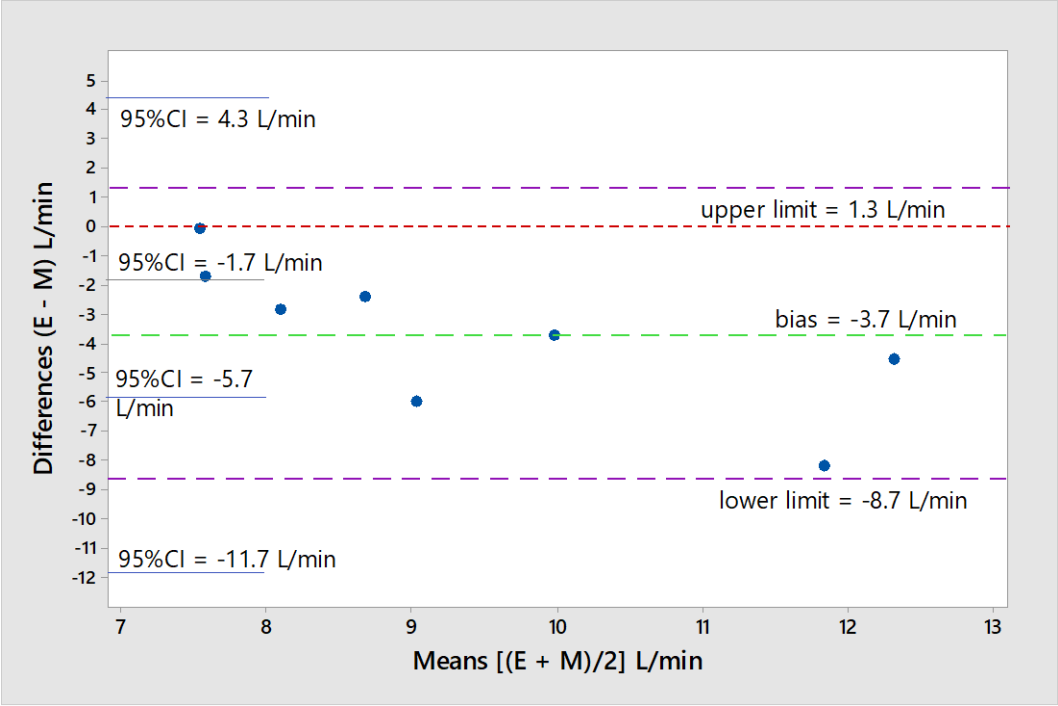

Figure 10. Bland and Altman plot summarising limits of agreement for cardiac output estimated using echocardiography (E) and the Modelflow (M) in postpartum women at 50% of maximal aerobic exercise (95%*CI* = the 95% confidence interval for both upper and lower limits of agreement).

Cardiac output during exercise

Similar to the comparisons at rest, in non-pregnant and postpartum women, there was poor agreement between $\dot{Q}$ derived from echocardiography and $\dot{Q}$ derived using the Modelflow® method at both low- and moderate-intensity exercise (Tables 4 and Figures 5, and 7 to 10). However, in pregnant women performing low-intensity exercise, both $\bar{x}_{diff}$ and percentage error were acceptable as per the *a priori* targets, while heteroscedastic error was identified (Figure 6). In contrast, during moderate-intensity exercise, there was poor agreement between the two methods in the measurement of $\dot{Q}$ in pregnant women (Figure 9).

DISCUSSION

The aim of this study was to estimate the agreement between $\dot{Q}$ derived from echocardiography and the Modelflow® method in non-pregnant, pregnant and postpartum women at rest and during submaximal aerobic exercise. In support of our hypothesis, there was poor agreement in $\dot{Q}$ between these methods in female populations at rest and during a dynamic exercise challenge. The Modelflow® method is therefore not recommended for use in research involving young, healthy non-pregnant and pregnant women, and previously published $\dot{Q}$ data from studies utilising this method should be interpreted with caution.

During pregnancy, maternal $\dot{Q}$ provides important insight into maternal cardiac function. Understanding hemodynamic status during pregnancy is increasingly utilized in clinical decision making in obstetrics and as such, non-invasive, accessible and operator independent methods are in high demand for this population. Whilst various non-invasive methods for $\dot{Q}$ determination exist, it is essential to confirm their validity and reliability in measurement of this fundamental parameter (Bijl et al., 2019). In addition, dynamic testing in

pregnant women for the prediction of later complications is gaining in interest, and as such, methods that allow continuous and real-time measurements of $\dot{Q}$ are a necessity for these assessments. The data from this study indicate that the Modelflow® method, despite its ease of use, does not provide agreeable measures of $\dot{Q}$ as measured by echocardiography in healthy non-pregnant and pregnant women.

The Modelflow® method uses photoelectric plethysmography in combination with a volume-clamp technique through an inflatable finger cuff to estimate $\dot{Q}$. Analysis of the pressure wave contour allows the determination of SV based upon aortic characteristic impedance, compliance and estimated cardiac afterload (Dyson et al., 2010). Due to its ease of use, and the potential for operator independent, real-time measurements of blood pressure and $\dot{Q}$, this method may be particularly useful in the monitoring of dynamic hemodynamics. Previous studies including non-pregnant individuals showed good agreement between Modelflow® and acetylene uptake estimations of $\dot{Q}$ during submaximal exercise (Critoph et al., 2013) as well as good repeatability of measurement (Waldron et al., 2018). In contrast, our data, collected in a small cohort of healthy non-pregnant and pregnant women, demonstrated insufficient agreement in $\dot{Q}$ from echocardiography and the Modelflow® method during exercise.

The accuracy of $\dot{Q}$ estimation using Modelflow® may be affected by changing states of vascular resistance (Elvan-Taspinar et al., 2003), such as that experienced during exercise, as well as potential movement artefact from dynamic movement on the peripheral signal (Waldron et al., 2018). However, we also identified a lack of agreement between the two methods at rest, in which women were stationary and in a stable hemodynamic state. Therefore, these factors alone cannot explain the poor agreement between methods. It is possible that the inaccurate estimation of $\dot{Q}$ may be related to the Modelflow® device algorithm that requires the input of anthropometric characteristics to estimate individual aortic pressure-area relationships. This suggestion has been made regarding error in measurement during exercise in males (Waldron et al., 2018) but also under resting conditions during pregnancy due to changes in aortic properties (Ulusoy et al., 2006). As such, these algorithms may require adjustment (Rang et al., 2007) and further specification by the company for use in pregnant women and/or during exercise. Furthermore, the use of transfer functions to estimate aortic waveforms from a peripheral signal may be invalid during pregnancy and further complicated by the known existence of different blood pressure phenotypes with varying central-to-peripheral waveform changes (Picone et al., 2018). Despite the potential for invalid assumptions during pregnancy, the agreement for $\dot{Q}$ estimation between Modelflow® and echocardiography was also poor in non-pregnant and postpartum women and may be a result of differences in peripheral circulation in females (Kavroulaki et al., 2010).

In previous investigations, determination of $\dot{Q}$ using non-invasive methods in pregnant women have highlighted: i) that there are inevitable differences between techniques, ii) that different methods should not be used interchangeably, and, iii) that it may be more appropriate to develop gestation-specific ranges for each technique (Masini et al., 2019). In the case of the Modelflow® method, $\dot{Q}$ was non-physiological in some cases (e.g. 0.3 L.min^{-1} at rest and 19 L.min^{-1} during light intensity exercise [25% PPO]), and heteroscedastic error was identified. In this study, $\dot{Q}$ was determined by the simultaneous application of echocardiography and Modelflow®, thereby reducing the opportunity for error from biological differences that might be observed in consecutive measurements such as changes in posture or environment. It is important to note that the measurements of $\dot{Q}$ from echocardiography were taken over three cardiac cycles and acquired at end expiration, whilst $\dot{Q}$ derived using the Modelflow® method was averaged over 20 cardiac cycles, collected during free breathing. Since mild fluctuations in stroke volume can occur between inspiration and expiration (Claessen et al., 2014), these methodological differences may account for some of the discrepancy between both methods. However, the mean difference between the methods in all groups (1.4 L.min^{-1}) was far greater

than the expected fluctuations in $\dot{Q}$ across respiration in a stable state (Stevens et al., 1985). As such, we recommend that other validated, non-invasive methods should be used instead of the Modelflow ® method to determine $\dot{Q}$ in healthy women.

Methodological validation studies should use the most accurate and reliable reference technique (Cecconi et al., 2009), however, we were unable to use PAC, the gold standard method of $\dot{Q}$ measurement, in this population of healthy women. We used the recommended criterion method for $\dot{Q}$ measurement in pregnancy, echocardiography (Bijl et al., 2019), which has recently been shown to have a percentage error of 19.1% when compared to PAC in women with complicated gestation.(Cornette et al., 2017) As such, we consider our comparisons between echocardiography and the Modelflow® method to be appropriate. Two-dimensional echocardiography is not without its limitations however; indeed, the quality and interpretation of echocardiographic measurement may be limited by a number of factors, including sonographer image acquisition and analysis, however data for this study were collected by a single, experienced cardiac sonographer in accordance with guidelines.

CONCLUSIONS

In healthy non-pregnant, pregnant and postpartum women, there was poor agreement between $\dot{Q}$ derived using echocardiography and $\dot{Q}$ derived through the Modelflow® method. Despite its ease of use, the Modelflow® estimation of $\dot{Q}$ in women prior to, during and after pregnancy is inaccurate both at rest and during submaximal exercise. Future research should avoid the Modelflow® estimation of $\dot{Q}$ and previously published $\dot{Q}$ data from research using this method should be interpreted with caution.

AUTHOR CONTRIBUTIONS

VL Meah: Conception / design of the work, Acquisition, analysis, and interpretation of data, Manuscript preparation, Approval of final submission, Accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. K Backx: Conception / design of the work, Critical revision of manuscript, Approval of final submission, Accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. RE Shave: Protocol/project development, Critical revision of manuscript, Approval of final submission, Accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. EJ Stöhr: Protocol/project development, Critical revision of manuscript, Approval of final submission, Accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. SM Cooper: Data analysis, Statistics, Manuscript writing, Approval of final submission, Accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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DISCLOSURE STATEMENT

All authors have no conflict of interest.

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