View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by St George's Online Research Archive

ULTRASOUND in Obstetrics & Gynecology isuog

Non-Invasive Cardiac Output monitoring in Pregnancy: Comparison to echocardiographic assessment

Journal:	*Ultrasound in Obstetrics and Gynecology*
Manuscript ID	UOG-2015-0765.R1
Wiley - Manuscript type:	Original Article
Date Submitted by the Author:	03-Feb-2016
Complete List of Authors:	Vinayagam, Dimuth; St George's Healthcare NHS Trust, Women's Directorate Patey, Olga; SGUL, Fetal Medicine Unit Thilaganathan, Basky; St Georges Hospital, Fetal Medicine Unit Khalil, Asma; St George's Hospital London, Obstetrics & Gynaecology
Manuscript Categories:	Obstetrics
Keywords:	Non-invasive cardiac output monitoring, transthoracic echocardiography, USCOM®, NICOM®, hemodynamics

SCHOLARONE™ Manuscripts

For Review

NON-INVASIVE CARDIAC OUTPUT MONITORING IN PREGNANCY: COMPARISON TO ECHOCARDIOGRAPHIC ASSESSMENT

D. Vinayagam, O. Patey, B. Thilaganathan, A. Khalil

Fetal Medicine Unit, St George's Hospital, St George's University of London, UK.

Cranmer Terrace, London SW17 0RE

Short title: Non-invasive cardiac output monitoring vs echocardiography in pregnancy

Corresponding author:

Dr Asma Khalil

Fetal Medicine Unit

St George's University of London

London SW17 0RE

Telephone: (Work) +442032998256

Mobile: +447917400164.

Fax: +442077339534

E-mail: akhalil@sgul.ac.uk; asmakhalil79@googlemail.com

Keywords

Non-invasive cardiac output monitoring, echocardiography, USCOM®, NICOM®, hemodynamics

For Peer Review

Abstract

Objectives: There is a paucity of data regarding the reliability of using non-invasive monitors in pregnancy. The aim of this study was to compare hemodynamic measurements obtained by non-invasive methods, against those obtained by 2-dimensional transthoracic echocardiography.

Methods: We recruited a total of 114 healthy pregnant and postpartum women who had cardiac output (CO) estimations obtained by two non-invasive devices as well as 2-D transthoracic echocardiography (TTE). The non-invasive devices employed in this cross comparison study were USCOM® (continuous wave Doppler analysis of trans-aortic blood flow) and NICOM® (thoracic bioreactance). Accuracy and precision statistics were presented as bias, precision, 95% limits of agreement (LOA) and mean percentage difference (MPD).

Results: USCOM® had a bias ranging from 0.4-0.9L/min. The mean percentage difference of USCOM® was 28% in the third trimester cohort. NICOM® had a bias ranging from -0.9 L/min to 0.6L/min with a mean percentage difference of 32% in the third trimester group. We observed no agreement between the non-invasive devices and TTE in the first and second trimesters - we found an MPD of 38% for USCOM in both the first and second trimesters, and an MPD of 70% and 61% for NICOM in the first and second trimesters, respectively. We found excellent repeatability (ICC = 0.969, 95% CI 0.953-0.980) and reproducibility (ICC= 0.896, 95% CI 0.812-0.944) for USCOM®, and comparable repeatability for NICOM® (ICC = 0.953, 95% CI 0.927-0.969).

Conclusion: We have demonstrated good agreement between USCOM® and NICOM® when compared against 2-d transthoracic echocardiography, specifically in the third trimester of pregnancy. Our findings suggest that both devices have good intraobserver repeatability/ interobserver reproducibility and can be utilised by healthcare professionals of different levels of experience. Future studies should take into account the significant differences in the precise maternal hemodynamic values obtained by these devices, and consider developing device-specific reference ranges in pregnancy and the postpartum period.

For Peer Review

Introduction

Pregnancy is associated with significant changes in maternal hemodynamics, which increases as gestation advances. In pathological conditions these changes can be even more profound and are of increased clinical significance both during and following pregnancy (1-4). In routine clinical practice, reliance is placed on maternal heart rate and brachial blood pressure as surrogate markers to provide information on cardiac indices such as maternal stroke volume (SV) and cardiac output (CO). Despite being relatively crude, these proxy markers are routinely used to guide clinical management, cardiovascular resuscitation and restore hemodynamic homeostasis. In previous decades, changes in maternal hemodynamics were investigated using dye dilution techniques (5) and pulmonary artery catheterization (PAC) (6). CO measurement with a PAC using the bolus thermodilution method has become the gold standard and the reference method to compare novel, non-invasive technologies against (7, 8). Such invasive techniques would be undesirable in current obstetric practice due to significant risk of complications such as infection, vascular injury and cardiac arrhythmias. Furthermore, validation of non-invasive methods in the obstetric population against such invasive techniques would also not be practically or ethically feasible. Transthoracic echocardiography (TTE) is a widely accepted methodology for CO estimation in pregnancy due to its non-invasive nature and absence of ionising radiation; its use in expectant mothers is considered entirely safe and acceptable. TTE has been validated in pregnancy against thermodilution and dye dilution techniques, and has been reported to be an accurate method for CO estimation (9, 10). However, access to TTE in labor requires both costly equipment and clinical expertise, thereby limiting availability.

More recently, a plethora of non-invasive cardiac monitors have become readily available for clinical use, providing an opportunity to accurately assess maternal hemodynamic status in the peripartum period. Two such commercially available devices are the ultrasound cardiac output monitor (USCOM®, USCOM Ltd, Australia) and NICOM® (Non-Invasive Cardiac Output Monitor, Cheetah Medical, USA) which use continuous-wave Doppler and thoracic bioreactance analyses, respectively, to estimate hemodynamic indices in simple-to-use platforms. USCOM® is an operator-dependant device which is potentially subject to inter- and intra-observer variation. Proficient use of this device is associated with an individual learning curve, and a requirement to attend a training session and carry out approximately 30 test cases before being able to obtain data for clinical or research purposes. As obtaining a haemodynamic profile using USCOM® requires access to the suprasternal notch (and some extension of the subjects neck), it is not practically feasible to provide continuous haemodynamic evaluation (eg intraoperatively) or intrapartum. NICOM® is entirely operator-independent and therefore not subject to inter-observer variation. NICOM® electrodes can be placed on the thorax and continuous haemodynamic variables can be obtained twice a minute, and can therefore be utilised during an operative procedure (eg caesarean section) with minimal disruption to the patient or the medical team caring for the patient. A drawback of NICOM® is the ongoing cost of consumables (skin surface electrodes).

The aim of this study was to compare hemodynamic measurements obtained by these different non-invasive methods against those obtained by 2-dimensional TTE.

Methods

Pregnant women aged 16 and over with healthy, singleton pregnancies were recruited from various (booking, scanning and routine antenatal) clinics at our tertiary center. Women from three, discrete gestational age groups were recruited in each trimester. In the postnatal

group, all study participants were recruited within 72 hours of delivery. Women receiving antihypertensive medication, with a known history of congenital / acquired heart disease or an incidental finding of a structural abnormality on echocardiogram were excluded. Women who had a pulse rate over 100bpm or a mean arterial pressure greater than 125mmHg were excluded. Written consent was obtained from all study participants and local research ethics committee approval (12/LO/0810) was sought prior to data collection. The study obstetrician examined all women and both maternal and fetal wellbeing were confirmed prior to obtaining any measurements.

All non-invasive and echocardiographic studies were performed in the same room, under standardised conditions by the same operators for the entire cohort. A single operator, following a 5-minute period of inactivity, obtained non-invasive measurements simultaneously. Both assessors were blinded to each other's recordings. Patients less than 24 weeks (ie those in the first and second trimester groups) were in a semi-recumbent position, and those in the third trimester were assessed in a left lateral position in order to avoid aortacaval compression by the gravid uterus.

USCOM®

The ultrasound cardiac output monitor (USCOM®, USCOM Ltd, Australia) employs continuous wave Doppler, with a non-imaging probe in the suprasternal notch to obtain velocity time integrals (VTI) of transaortic or transpulmonary blood flow at the left or right ventricular outflow tract respectively. Using an anthropometric algorithm, which correlates the outflow tract diameter with the patient's given height, USCOM® uses the VTIs to compute SV, CO and a complete hemodynamic profile. USCOM® tracings were obtained in flowtracer mode (automated tracing of each Doppler profile), and a single operator analyzed all images, and excluded poor quality Doppler profiles. Each acquisition used for analysis had a minimum of 2 consecutive Doppler profiles (figure 1). The operator received formal training in the use of USCOM and performed over 50 measurements prior to recruiting patients to this study.

Intraobserver repeatability of USCOM® was assessed by each patient having two separate, consecutive Doppler acquisitions obtained within 5 minutes of one another. Interobserver reproducibility of USCOM® was assessed by two operators. Doppler acquisitions were obtained within 10 minutes of each other. Both operators were blinded to one another's recordings. All repeatability and reproducibility studies were performed in pregnant study participants (not in the postnatal cohort). The second operator is a research midwife who received informal training by the study investigator (DV), formal training by an USCOM® representative and carried out the recommended 30 cases prior to collecting data used for reproducibility analysis.

NICOM®

The Non-Invasive Cardiac Output Monitor, NICOM® (Cheetah Medical, USA) uses thoracic bioreactance technology which is based on analysis of thoracic voltage amplitude changes in response to a high-frequency injected current. The NICOM® device analyses the variations in frequency spectra (relative phase shifts) after delivering a transthoracic alternating current and uses several assumptions (about thoracic shape and fluid volumes) and algorithms, to compute SV, CO and an array of hemodynamic parameters. NICOM® surface electrodes were placed on participants (posterior aspect of the thorax) prior to them lying supine / left lateral position, and readings were obtained simultaneously to USCOM® readings. Following calibration, two separate complete sets of data were collected for each patient. The first set of data was used for comparison analysis; the second was used for repeatability analysis.

For Peer Review

TTE

Two-dimensional transthoracic echocardiography views were obtained by a single, qualified (adult and paediatric/fetal) cardiac sonographer using a GE Vivid E9 (GE Healthcare, Little Chalfont, UK) with a single crystal phased array M5Sc transducer. Participants were scanned in the left lateral position and multiple recordings of three views were obtained (parasternal long axis, apical four-chamber, and apical five-chamber views). Three-lead electrocardiogram was used in order to enable image gating. Analysis was performed using dedicated analysis software (EchoPAC, GE Healthcare, Little Chalfont, UK). All measurements were performed according to recommendations from the American Society of Echocardiography (11).

After cardiac structural normality was confirmed, two methods of cardiac output estimation were employed in this study. The results presented are from comparison to the first method described. Comparison statistics with the latter method are provided in the supplementary material.

1. Left ventricular outflow tract cross sectional area – velocity time integral (LVOT CSA – VTI) method determines the SV as a product of the LVOT cross-sectional area and LVOT velocity time integral obtained by pulsed wave (PW) Doppler. The diameter of LVOT was measured in the parasternal long axis view, at the level of the aortic valve (AV) annulus in early systole (figure 2). The measurement was obtained from the inner edge to the inner edge of the aortic cusp insertion. Due to the inherent error of the tomographic plane to underestimate the annulus diameter, we obtained 3-5 recordings of the AV dimensions, and then an average value was used in subsequent calculations. Assuming a circular shape of the LVOT, the area of the LVOT was calculated using the formula CSA = $0.785 \times D^2$.

Measurements of the LVOT VTI were obtained from the apical five-chamber view. A pulsed wave Doppler sample was positioned at the center of LVOT, 3-5mm proximal to the aortic valve (figure 3). If the AV opening click was present in the Doppler recording, the sample volume was withdrawn slightly into the outflow tract. The sample volume length was 2-5mm in order to narrow the spectral broadening of the PW signal. Care was taken to ensure that the ultrasound beam was parallel to the blood flow in the LVOT. Multiple PW Doppler recordings were obtained in order to avoid underestimation of the LVOT velocities. The LVOT VTI envelope was traced along the leading velocity (outer edge of the densest envelope) with at least 3-4 beats measured and averaged. The SV was calculated as a product of VTI multiplied by CSA of the LVOT (Figure 3). Heart rate (HR) was obtained by measuring the R-R interval using the ECG and then by multiplying the R-R interval by 60. CO for both methods was calculated using the formula: CO = SV x HR.

2. Single-plane Simpson rule - Left ventricular end diastolic volume (LVEDV) and end systolic volume (LVESV) were automatically calculated by tracing the endocardial border in diastole and systole in the apical four-chamber view respectively (figures 1 and 2, supplementary material). Volumes were automatically calculated by mathematically dividing the ventricle along its long axis into a series of discs of equal height. The ventricular volume is then represented by the sum of the volume of each of the discs. The ventricular SV was calculated as SV = LVEDV - LVESV.

Statistical analysis

All statistical analysis was carried out using IBM SPSS Statistics version 21. The Shapiro-Wilk test for normality was performed on all data sets to assess distribution. The correlation coefficients, in order to assess the linear relationship between the two methods, are expressed as either Pearson's (normally distributed data) or Spearman's (non-normally distributed data). The accuracy and precision statistics provided include bias (mean difference between two methods), precision (standard deviation of differences), 95% limits of agreement (bias +/- 1.96 SD) and mean percentage difference (MPD) (LOA / mean between two methodologies). Bland-Altman plots are provided in the supplementary material (figures 3-18).

Intraobserver repeatability and interobserver reproducibility are expressed as an intra-class correlation coefficient (ICC) with 95% confidence intervals (95% CI). A two-way mixed effects model was used when calculating the intra-class correlation coefficients.

A mean percentage difference of 30% between two methodologies for cardiac output estimation has been proposed to be a level of clinical acceptability (7).

Results

A total of 114 participants were recruited to the study between January and October 2015 (Figure 4). Following exclusions, a total of 98 datasets across the four groups were analyzed. We excluded 5 cases of echocardiographic assessment due to poor views – predominantly in women in the third trimester and with raised body mass index (BMI). We also deemed 2 USCOM® Doppler acquisitions as unsuitable for analysis – this was because both acquisitions (upon quality control, prior to analysis) were not felt to represent the VTI obtained at the aortic valve. We did not have any failure to obtain haemodynamic variables using NICOM® in the study cohort. All patients had measurements obtained by both non-invasive monitors and echocardiography. Table 1 shows the basic demographic data of the entire study cohort.

Heart Rate

Heart rate correlation between the non-invasive monitors and echocardiography was strong (USCOM® r=0.866, p<0.01; NICOM® r=0.846, p<0.01). The HR correlation between the two monitors was also strong (r=0.920, p<0.01). Comparison between USCOM® and echocardiography showed a bias of 0.3bpm, precision of 7bpm with 95% limits of agreements of -13 to +14bpm and a MPD of 17%. Comparison between NICOM® and echocardiography revealed similar agreement with a bias of 0.5bpm, precision of 7 bpm and 95% limits of agreements of -14 to +15 bpm and a MPD of 17%. When compared to each other, the HR analysis of both non-invasive devices demonstrated a bias of -0.9bpm, precision of 4bpm with 95% limits of agreements of -9 to +7 bpm and a MPD of 10%.

Stroke Volume

Comparison between USCOM® and echocardiography showed a moderate correlation (r=0.330, p<0.05). Further analysis demonstrated a bias of 11.4mls, precision of 16.4mls, 95% limits of agreement from -20 to +43mls and a MPD of 45%. Comparison between NICOM® and echocardiography showed a weak correlation (r=0.272, p<0.05). Further analysis revealed a bias of -1.9mls, precision of 19.9mls, 95% limits of agreement from -40.8 to 36.9mls and a MPD of 60%.

For Peer Review

Cardiac Output

The correlation coefficients and precision analyses for USCOM® and for NICOM® in each trimester and in the postpartum group are presented in tables 2 and 3, respectively.
Figures 5 and 6 demonstrate the positive and negative bias of each non-invasive methodology when compared to TTE CO estimates. USCOM® exhibits a largely positive bias, which is evident in the majority of patients at lower TTE CO estimates. However NICOM® did not demonstrate such skewed bias, and indeed the proportion of readings with positive and negative bias appears similar, irrespective of low or high TTE CO estimates. The variation in bias of NICOM® we found, goes someway to explaining the wide limits of agreement.

Repeatability and Reproducibility

Intraobserver repeatability assessment was performed in 67 subjects. Three USCOM® Doppler acquisitions of acceptable quality were obtained for intraobserver repeatability assessment. The intra-class correlation coefficient for USCOM® CO estimation was 0.969 (95% CI 0.953-0.980). Each patient had two, complete NICOM® profiles obtained. The intra-class correlation coefficient for NICOM® CO estimation was 0.953 (95% CI 0.927-0.969).
The interobserver reproducibility of USCOM® was assessed in 40 subjects, across the three trimesters. This varied from 0.899 (95% CI 0.790-0.952) in the first trimester (27 cases), 0.969 (95% CI 0.88-0.992) in the second trimester (10 cases), and 0.965 (95% CI 0.185-0.990) in the third trimester (3 cases). The intra-class correlation coefficient for CO was 0.896 (95% CI 0.812-0.944). As NICOM® is a user-independent device, interobserver reproducibility was not assessed.

Discussion

USCOM® and NICOM® demonstrated good agreement with echocardiography in the third trimester. The level of agreement between USCOM® and echocardiography in the third trimester meets the recommended level of clinical acceptability (7). The MPD for USCOM® ranged from 28.8% (third trimester) to 43.8% (postpartum). MPD at earlier gestations was 38%, comparable to previously published data in non-pregnant patients (12). NICOM® has near clinically acceptable agreement in the third trimester (MPD of 32%), however we found no agreement outside of the third trimester.

Interpretation of study findings and comparison with the existing literature

A meta-analysis (12) of USCOM® validation studies outside of pregnancy reported a mean bias of -0.39 L/min, precision of 1.27L/min, 95% LOA of -2.879 L/min and +2.099 L/min with a MPD of 42.7% (see Table 4 for a summary of validation studies). In one study (13) comparing USCOM® to 3-dimensional TTE in advanced pregnancy, the authors reported a bias of +0.4L/min, precision of 1.0 L/min, 95% LOA of -1.4 L/min to +2.3 L/min and a MPD of 31.4%, comparable to the findings in our study. The level of agreement in the current study was higher than previously reported in the non-obstetric population.

NICOM® in the third trimester has a MPD approaching 30% and therefore shows potential to be used intrapartum and at advanced gestations. NICOM® has many positive attributes, including its simplicity of use, operator-independence and ability to provide continuous hemodynamic profiles in an intra-operative/intrapartum situation. The levels of agreement we observed would indicate that NICOM® cannot be used interchangeably with echocardiography at earlier gestations or postnatally. Several NICOM® validation studies (Table 4) display highly variable levels of accuracy and precision. Early validation studies

For Peer Review

reported strong correlations (r=0.84-0.90) between bioreactance and pulmonary artery catheterization derived CO estimates (14), however Bland Altman analysis was lacking. Importantly, the differences between the different techniques are acceptable as long as different technology-specific reference ranges are employed.

Study strengths and limitations

The cross sectional area used to deduce stroke volume is obtained by different methodologies. The strength of using echocardiography is that the LVOT is measured in individual patients. USCOM® employs an algorithm, based only on patient's height, to provide the outflow tract diameter. Measurement of flow in the region of the aortic annulus as performed by TTE provides the highest accuracy (15, 16). Whilst the USCOM® estimation provides an easy and reproducible method enabling its bedside application, it does not factor in weight or body surface area (BSA), thus representing a potential source of error in CO estimation. Pregnancy is associated with significant changes in BSA, and this could be associated with changes in aortic dilatation (17-19).

Echocardiography and USCOM® utilize different Doppler modalities. PW Doppler enables a recording of velocity at any specific point within the cardiac anatomy, unlike continuous wave (CW) Doppler, which cannot ascertain the precise location at which that velocity was obtained. Training in the correct application of USCOM® is important in order to obtain the transaortic VTI. Inaccurate recordings (eg in the ascending aorta) can be a significant source of error.

Finally, it is plausible that the hyperdynamic circulation will result in greater noise artefact, which will be included in the USCOM® CW Doppler spectrum. This may result in "over-reading" of the VTI, and hence produce a falsely elevated CO estimation than that provided by PW Doppler techniques. This may potentially explain the positive bias in the obstetric population, as compared to the negative bias reported in the non-obstetric population.

Clinical / Research Implications

Our data demonstrate that USCOM® and NICOM® show good agreement at advanced gestations. In clinical practice, their application will be in the management of critical illness in advanced pregnancy (eg septic shock, hemorrhage or preeclampsia). Both technologies have favorable characteristics that make them suitable for bedside application. They are simple to use with measurements obtained in minutes, by both medical and non-medical personnel (20) with minimal training required to achieve operative proficiency.

This cross comparison study, and the results we have found at earlier gestations, does pose a question about the accuracy and precision of non-invasive monitors, and the interpretation of their findings, when used outside of the third trimester, hence thorough validation must be performed prior to interpreting published maternal hemodynamics data. Importantly, the indices obtained using non-invasive devices will not be directly comparable to those of TTE and hence device-specific reference ranges need to be constructed. One of the most relevant applications of this technology will be to display trends in haemodynamics. The inherent assumptions made by the machine algorithms should be of little relevance when assessing trends within a patient, as the "error" is likely to remain constant. Future studies should evaluate the ability of these devices to accurately assess hemodynamic trends in both routine and pathological obstetric cases.

For Peer Review

Conclusion

There is an unquestionable need for non-invasive hemodynamic monitoring in the management of the critically ill obstetric patients and for goal-directed therapy. However, the need and desire to utilize non-invasive technology should not be compromised by poorly reproducible, inaccurate or unvalidated measurements. Our findings suggest that both USCOM® and NICOM® perform well in advanced pregnancy and have excellent repeatability and reproducibility.

For Peer Review

References

1. Melchiorre K, Sharma R, Thilaganathan B. Cardiovascular implications in preeclampsia: an overview. Circulation. 2014;130(8):703-14.
2. Ghossein-Doh C, Spaanderman MM, Al Doulah R, van Kuijk SM, Peeters LL. Cardiac adaptation to the next pregnancy in formerly pre-eclamptic women bound to develop recurrent pre-eclampsia. Ultrasound Obstet Gynecol. 2015.
3. Valensise H, Vasapollo B, Gagliardi G, Novelli GP. Early and late preeclampsia: two different maternal hemodynamic states in the latent phase of the disease. Hypertension. 2008;52(5):873-80.
4. Melchiorre K, Sutherland GR, Liberati M, Thilaganathan B. Preeclampsia is associated with persistent postpartum cardiovascular impairment. Hypertension. 2011;58(4):709-15.
5. Ueland K, Gills R, Hansen J, WYANT GM. Maternal cardiovascular dynamics. I. Cesarean section under subarachnoid block anesthesia. Survey of Anesthesiology. 1969;13(1):67-70.
6. Ackerman WE, Porembka DT, Juneja MM, Kaczorowski DM. Use of a pulmonary artery catheter in the management of the severe preeclamptic patient. Anesthesiology review. 1991;17(4):37-40.
7. Critchley LH, Critchley JJH. A Meta-Analysis of Studies Using Bias and Precision Statistics to Compare Cardiac Output Measurement Techniques. Journal of Clinical Monitoring and Computing. 1999;15(2):85-91.
8. Critchley LA, Lee A, Ho AM. A critical review of the ability of continuous cardiac output monitors to measure trends in cardiac output. Anesth Analg. 2010;111(5):1180-92.
9. Robson SC DW, Moore M, Hunter S. Combined Doppler and echocardiographic measurement of cardiac output: theory and application in pregnancy. . BJOG. 1987;94:1014–27.
10. Easterling TR, Watts DH, Schmucker BC, BENEDETTI TJ. Measurement of cardiac output during pregnancy: validation of Doppler technique and clinical observations in preeclampsia. Obstetrics & Gynecology. 1987;69(6):845-50.
11. Quinones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography. 2002;15(2):167-84.
12. Chong SW, Peyton PJ. A meta-analysis of the accuracy and precision of the ultrasonic cardiac output monitor (USCOM). Anaesthesia. 2012;67(11):1266-71.
13. McNamara H, Barclay P, Sharma V. Accuracy and precision of the ultrasound cardiac output monitor (USCOM 1A) in pregnancy: comparison with three-dimensional transthoracic echocardiography. Br J Anaesth. 2014;113(4):669-76.
14. Keren H, Burkhoff D, Squara P. Evaluation of a noninvasive continuous cardiac output monitoring system based on thoracic bioreactance. Am J Physiol Heart Circ Physiol. 2007;293(1):H583-9.
15. Dittmann H, Voelker W, Karsch KR, Seipel L. Influence of sampling site and flow area on cardiac output measurements by Doppler echocardiography. Journal of the American College of Cardiology. 1987;10(4):818-23.
16. Zoghbi WA, Quinones MA. Determination of cardiac output by Doppler echocardiography: a critical appraisal. Herz. 1986;11(5):258-68.
17. Wolak A, Gransar H, Thomson LE, Friedman JD, Hachamovitch R, Gutstein A, et al. Aortic size assessment by noncontrast cardiac computed tomography: normal limits by age, gender, and body surface area. JACC Cardiovascular imaging. 2008;1(2):200-9.
18. Campens L, Demulier L, De Groote K, Vandekerckhove K, De Wolf D, Roman MJ, et al. Reference values for echocardiographic assessment of the diameter of the aortic root and ascending aorta spanning all age categories. The American journal of cardiology. 2014;114(6):914-20.
19. Davis AE, Lewandowski AJ, Holloway CJ, Ntusi NA, Banerjee R, Nethononda R, et al. Observational study of regional aortic size referenced to body size: production of a cardiovascular

For Peer Review

magnetic resonance nomogram. Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance. 2014;16:9.
20. Boyle M, Steel L, Flynn GM, Murgo M, Nicholson L, O'Brien M, et al. Assessment of the clinical utility of an ultrasonic monitor of cardiac output (the USCOM) and agreement with thermodilution measurement. Critical Care and Resuscitation. 2009;11(3):198-203.

Conflicts of Interest

None declared

Acknowledgements

We would like to thank both USCOM® and NICOM® for the loan of their invaluable equipment in order for us to conduct vital research studies in this field. We would also like to thank the research midwives and sonographers at St George's Hospital who helped us recruit our study participants.

For Peer Review

Figure Legends

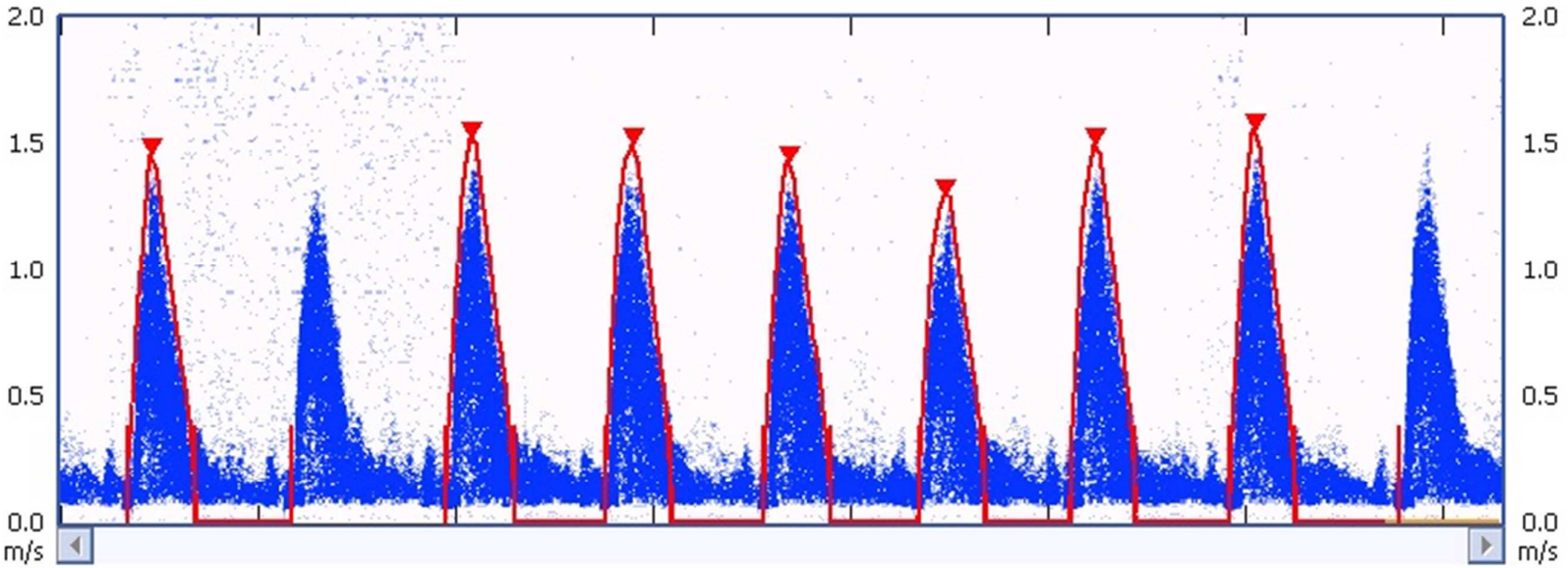
Figure 1 USCOM® (UltraSound Cardiac Output Monitor, USCOM Ltd, Australia) acquisition from a study participant demonstrating the Doppler profile of transaortic blood flow. Doppler profiles with a red envelope (flowtracer) were analysed having been deemed acceptable by the study investigator.

Figure 2 2-d transthoracic echocardiographic measurement of the left ventricular outflow tract (LVOT) diameter in the parasternal long axis view, at the level of the aortic valve (AV) annulus in early systole. In this example, the LVOT was measured at 1.8cm, which would give a cross sectional area (CSA) of 2.54cm^2. The CSA is calculated by the formula: CSA = 0.785 x (LVOT)^2.

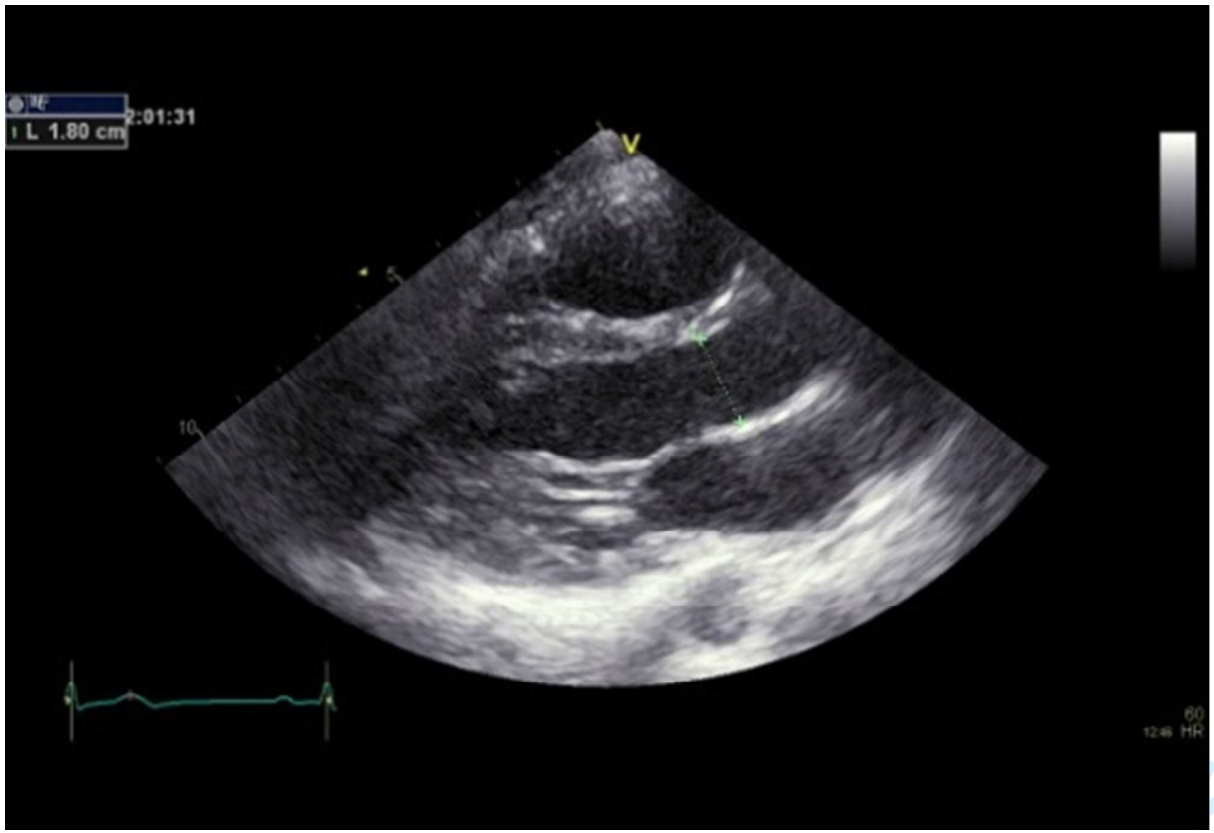
Figure 3 Measurements of the left ventricular outflow tract velocity-time integral (LVOT VTI) were obtained from the apical five-chamber view. A pulsed wave (PW) Doppler sample was positioned at the centre of LVOT, 3-5mm proximal to the aortic valve. VTI x CSA = Stroke volume.

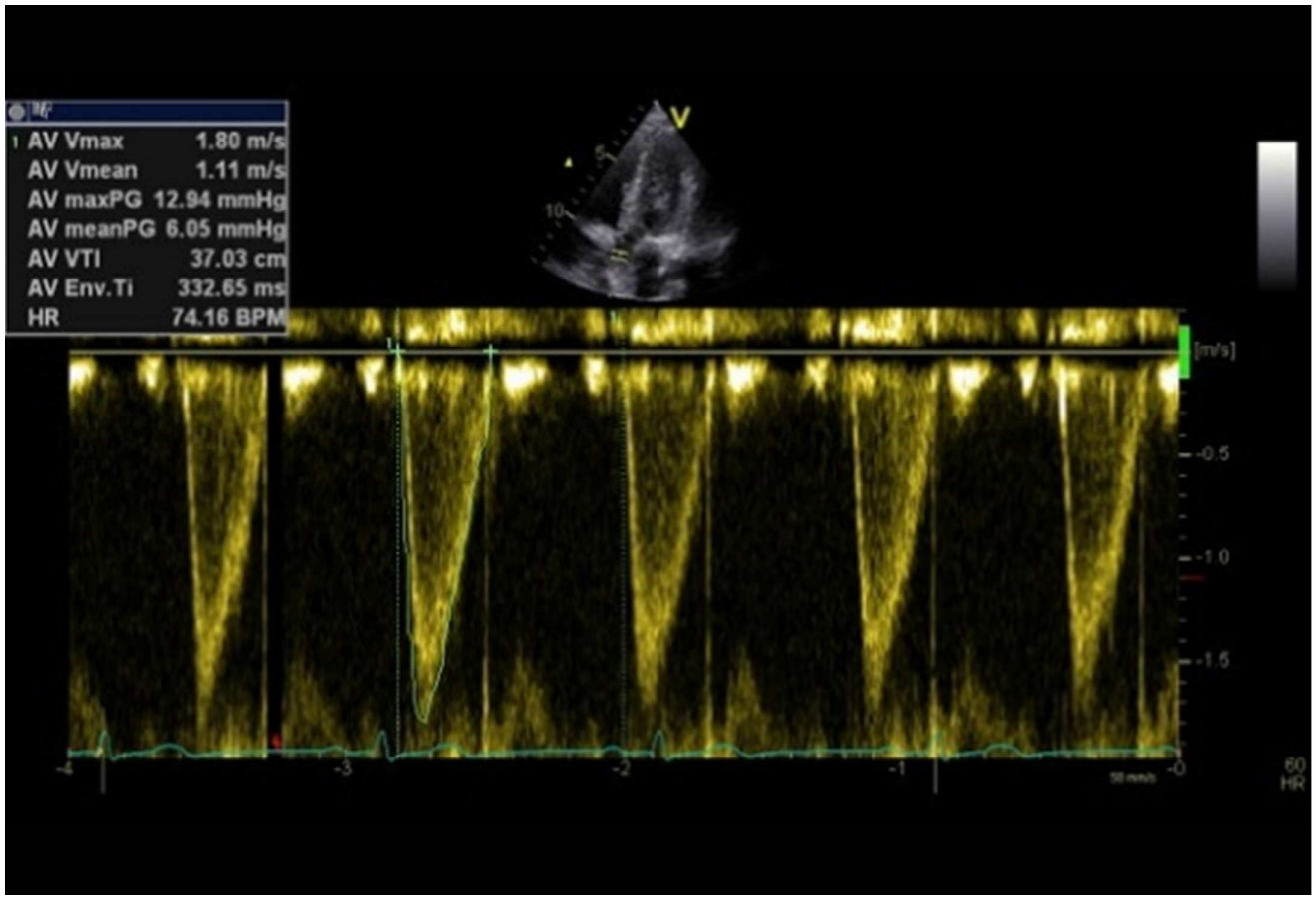
Figure 4 Recruitment flowchart

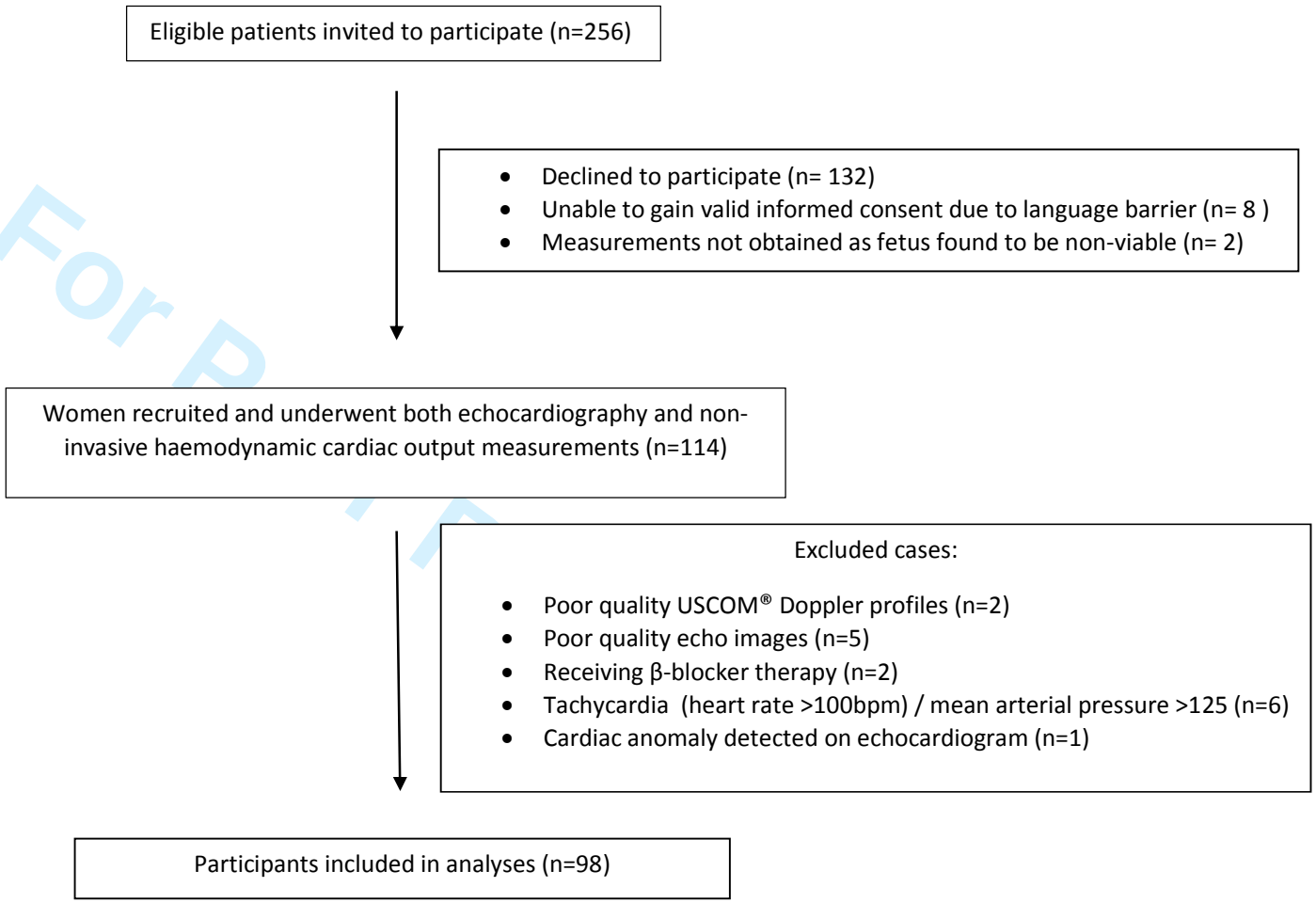
For Peer Review



Review


2:01:31
L 1.80 cm
V
5
10
60
12:46 HR


AV Vmax 1.80 m/s
AV Vmean 1.11 m/s
AV maxPG 12.94 mmHg
AV meanPG 6.05 mmHg
AV VTI 37.03 cm
AV Env.Ti 332.65 ms
HR 74.16 BPM
[m/s]
-0.5
-1.0
-1.5
-4
-3
-2
-1
-0
60
HR


Eligible patients invited to participate (n=256)
Declined to participate (n= 132)
Unable to gain valid informed consent due to language barrier (n= 8)
Measurements not obtained as fetus found to be non-viable (n= 2)
Women recruited and underwent both echocardiography and non-invasive haemodynamic cardiac output measurements (n=114)
Excluded cases:
Poor quality USCOM® Doppler profiles (n=2)
Poor quality echo images (n=5)
Receiving β-blocker therapy (n=2)
Tachycardia (heart rate >100bpm) / mean arterial pressure >125 (n=6)
Cardiac anomaly detected on echocardiogram (n=1)
Participants included in analyses (n=98)

	First Trimester (n=29)	Second Trimester (n=25)	Third Trimester (n=21)	Postpartum (n=23)
Maternal Age / years (SD)	31 (6.3)	33 (3.5)	34 (5.5)	30 (5.1)
Nulliparity, n (%)	18 (62%)	23 (92%)	7 (33%)	n/a
Caucasian, n (%)	22 (76%)	21 (84%)	18 (86%)	13 (56%)
Maternal weight at booking (kg), mean (SD)	65.3 (9.6)	68.6 (14)	70.4 (14)	71.2 (15.9)
Maternal BMI at booking (kg/m^2), mean (SD)	23.1 (5.7)	24.3 (7.3)	26.3 (5.3)	26.4 (5.4)
Maternal mean arterial pressure at booking (mmHg), mean (SD)	83 (18)	85 (8)	93 (20)	86 (10)
Maternal weight at assessment (kg), mean (SD)	65.5 (10)	74.5 (15)	85.4 (13.3)	76.6 (16)
Maternal BMI at assessment (kg/m^2), mean (SD)	24.2 (3.8)	27.3 (5.5)	31.9 (4.9)	28.3 (5.3)
Maternal mean arterial pressure at assessment (mmHg), mean (SD)	85 (19)	84.3 (9)	96.7 (8)	89 (14)

Table 1 Baseline characteristics of the study cohort

For Peer Review

	First Trimester	Second Trimester	Third Trimester	Postpartum
USCOM®	0.366	0.364	0.569*	0.176
NICOM®	0.048	-0.086	0.664*	0.610*

Table 2 Correlation coefficients for NICOM® (Non-Invasive Cardiac Output Monitor, NICOM® (Cheetah Medical, USA) and USCOM® (UltraSound Cardiac Output Monitor, USCOM Ltd, Australia) vs echocardiography (LVOT-VTI method) for each study group. Correlation coefficients that reached statistical significance ($p<0.05$) are highlighted (*).

For Peer Review

	First Trimester	Second Trimester	Third Trimester	Postpartum
Bias (L/min) USCOM®	0.738	0.896	0.861	0.439
Precision (L/min)	1.041	1.091	0.788	1.357
95% LOA (L/min)	-1.304 +2.779	-1.242 +3.034	-0.683 +2.407	-2.221 +3.099
MPD (%)	38.1	38.1	28.8	43.8
Bias (L/min) NICOM®	-0.97	-0.354	0.581	-0.009
Precision (L/min)	1.61	1.555	0.857	1.319
95% LOA (L/min)	-4.12 +2.18	-3.403 +2.696	-1.099 +2.261	-2.593 +2.575
MPD (%)	70.6	61	32.2	44.1

Table 3 Accuracy and precision statistics for USCOM® (UltraSound Cardiac Output Monitor, USCOM Ltd, Australia) and NICOM® (Non-Invasive Cardiac Output Monitor, Cheetah Medical, USA) vs 2d transthoracic echocardiography (TTE) using the left ventricular outflow tract – velocity time integral (LVOT-VTI) method for cardiac output (CO) estimation. Bias = mean difference between two methodologies, precision = standard deviation of the bias, 95% limits of agreement (LOA) = bias ± 1.96 SD, Mean percentage difference (MPD) = LOA/mean CO between two methodologies x 100.

For Peer Review

Table 4 A summary of accuracy and precision statistics from a selection of published validation studies of both USCOM® (UltraSound Cardiac Output Monitor, USCOM Ltd, Australia) and NICOM® (Non-Invasive Cardiac Output Monitor, Cheetah Medical, USA) in the non-obstetric population. Only studies which reported on complete accuracy and precision statistics (and not just correlation coefficients) are included. The two NICOM® studies reported cardiac index (L/min/m^2) instead of cardiac output (L/min).

Investigators	Year	Patient Population	Reference Method	Non Invasive Device used	Bias (L/min or L/min/m^2)	Precision (L/min or L/min/m^2)	95% Limits of Agreement (L/min or L/min/m^2)	Mean Percentage Difference (%)
Knirsch	2008	Paediatric Cardiology	PAC Thermodilution	USCOM®	-0.13	1.34	-1.47 +1.21	36.4
Tan	2005	ICU	PAC Thermodilution	USCOM®	-0.18	0.82	-1.43 +1.78	35.7
Thom	2009	ICU	PAC Thermodilution	USCOM®	-0.09	1.47	-3.01 +2.83	51.7
Wong	2008	Liver transplant	PAC Thermodilution	USCOM®	-0.39	0.93	-1.47 +2.25	25.6
Kober	2013	Cytoreductive surgery in ovarian carcinoma	PAC Thermodilution	NICOM®	0.26	0.85	-1.39 +1.92	50.7
Kupersztych-Hagege	2013	ITU	PAC Thermodilution	NICOM®	-0.09	2.55	-2.2 +4.1	82

For Peer Review

	First Trimester	Second Trimester	Third Trimester	Postpartum
Bias (L/min) USCOM®	0.916	1.051	0.7401	0.488
Precision (L/min)	0.863	1.158	0.790	1.322
95% LOA (L/min)	-0.775 +2.607	-1.218 +3.321	-0.808 +2.288	-2.103 +3.079
MPD (%)	32	39.7	29.8	45.5
Bias (L/min) NICOM®	-0.801	-0.200	0.458	0.010
Precision (L/min)	1.561	1.408	0.887	1.305
95% LOA (L/min)	-3.861 +2.259	-2.966 +2.560	-1.281 +2.197	-2.548 +2.568
MPD (%)	69.8	54.2	33.2	43.7

Table 1 Supplementary Material

Accuracy and precision statistics for USCOM® (UltraSound Cardiac Output Monitor, USCOM Ltd, Australia) and NICOM® (Non-Invasive Cardiac Output Monitor, Cheetah Medical, USA) vs 2d transthoracic echocardiography (TTE) using the single-plane Simpson's method for cardiac output (CO) estimation. This method involves deducing ventricular volumes by tracing the endocardial border in diastole and systole in the apical four-chamber view. Bias = mean difference between two methodologies, precision = standard deviation of the difference, 95% limits of agreement (LOA) = bias ± 1.96 SD, Mean percentage difference (MPD) = LOA/mean CO between two methodologies x 100.

For Peer Review

	1st Trimester	2nd Trimester	3rd Trimester
NICOM vs Echo (LVOT-VTI)	-0.139	-0.188	0.575*
USCOM vs Echo (LVOT-VTI)	0. 406*	0.158	0.552*

Table 2 Supplementary Material

For all pregnant patients, we calculated the body surface area (BSA) using the weight and height obtained at assessment. The LVOT-VTI cardiac output was indexed using the BSA obtained, to deduce a cardiac index (L/min/m^2). Table 2 gives the correlation coefficients for NICOM® (Non-Invasive Cardiac Output Monitor, Cheetah Medical, USA) and USCOM® (UltraSound Cardiac Output Monitor, USCOM Ltd, Australia) vs TTE cardiac index (CI) estimates for each trimester. Correlation coefficients that reached statistical significance ($p<0.05$) are highlighted (*).

For Peer Review

	1st Trimester	2nd Trimester	3rd Trimester
Bias (L/min/m²) USCOM®	0.388	0.570	0.517
Precision (L/min/m²)	0.590	0.754	0.462
95% LOA (L/min/m²)	-0.769 +1.546	-0.909 +2.050	-0.387 +1.422
MPD (%)	36.8	45.6	32.1
Bias (L/min/m²) NICOM®	-0.630	-0.157	0.256
Precision (L/min/m²)	0.976	0.894	0.465
95% LOA (L/min/m²)	-2.543 +1.282	-1.910 +1.596	-0.655 +1.167
MPD (%)	72.9	61.2	33.9

Table 3 supplementary material

For all pregnant patients, we calculated the body surface area (BSA) using the weight and height obtained at assessment. The LVOT-VTI cardiac output was indexed using the BSA obtained, to deduce a cardiac index (L/min/m^2). Table 3 shows the accuracy and precision statistics for cardiac index agreement between NICOM® (Non-Invasive Cardiac Output Monitor, Cheetah Medical, USA) and USCOM® (UltraSound Cardiac Output Monitor, USCOM Ltd, Australia).

For Peer Review

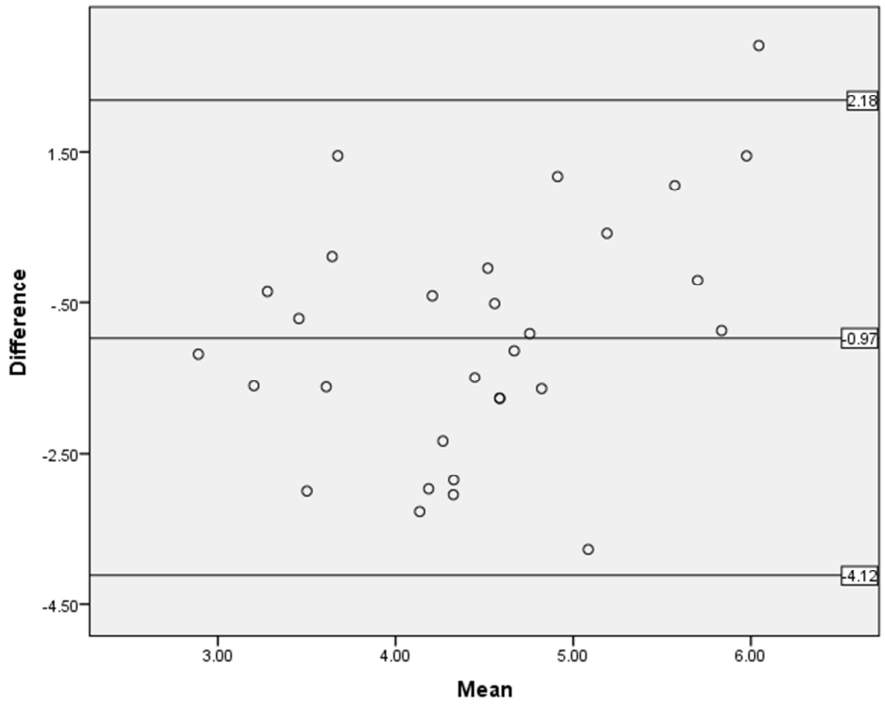


Fig 1 (Supplementary material) Bland Altman Plot demonstrating the mean bias and 95% limits of agreement (LOA) between NICOM® (Non-Invasive Cardiac Output Monitor, Cheetah Medical, USA) and transthoracic echo (TTE) CO estimates obtained by the left ventricular outflow tract – velocity time integral (LVOT-VTI) method in the first trimester.

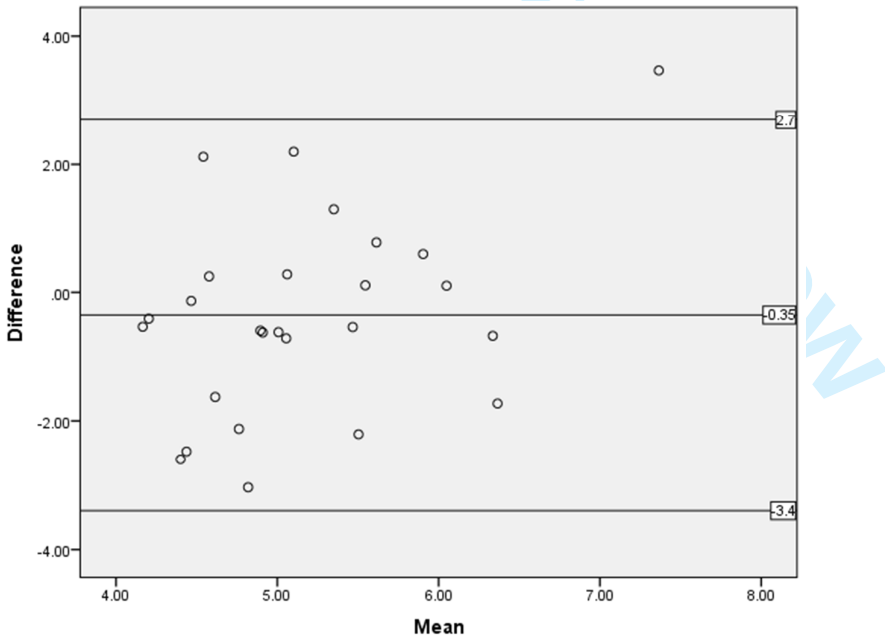


Figure 2 (supplementary material) Bland Altman Plot demonstrating the mean bias and 95% limits of agreement (LOA) between NICOM® (Non-Invasive Cardiac Output Monitor, Cheetah Medical, USA) and transthoracic echo (TTE) CO estimates obtained by the left ventricular outflow tract – velocity time integral (LVOT-VTI) method in the second trimester.

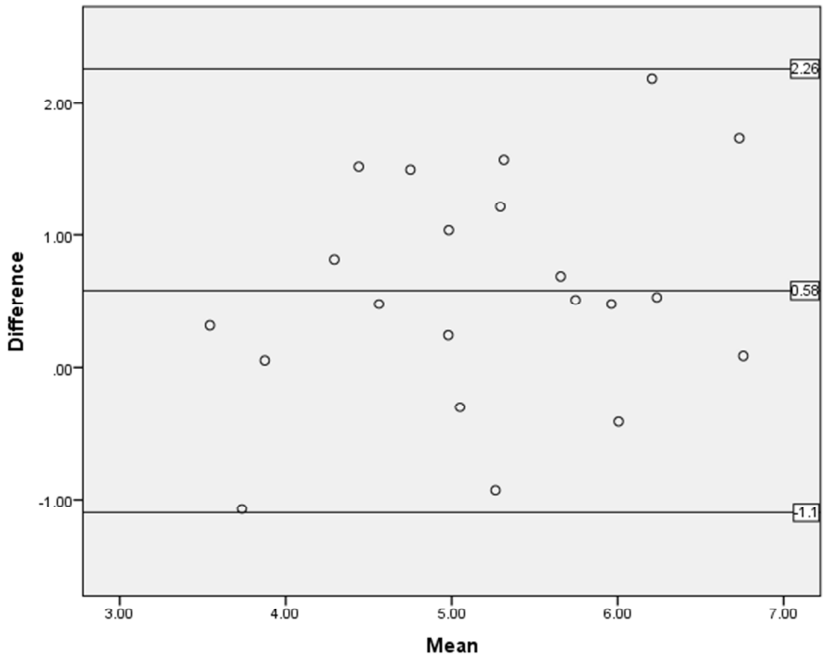


Figure 3 (supplementary material) Bland Altman Plot demonstrating the mean bias and 95% limits of agreement (LOA) between NICOM® (Non-Invasive Cardiac Output Monitor, Cheetah Medical, USA) and transthoracic echo (TTE) CO estimates obtained by the left ventricular outflow tract – velocity time integral (LVOT-VTI) method in the third trimester.

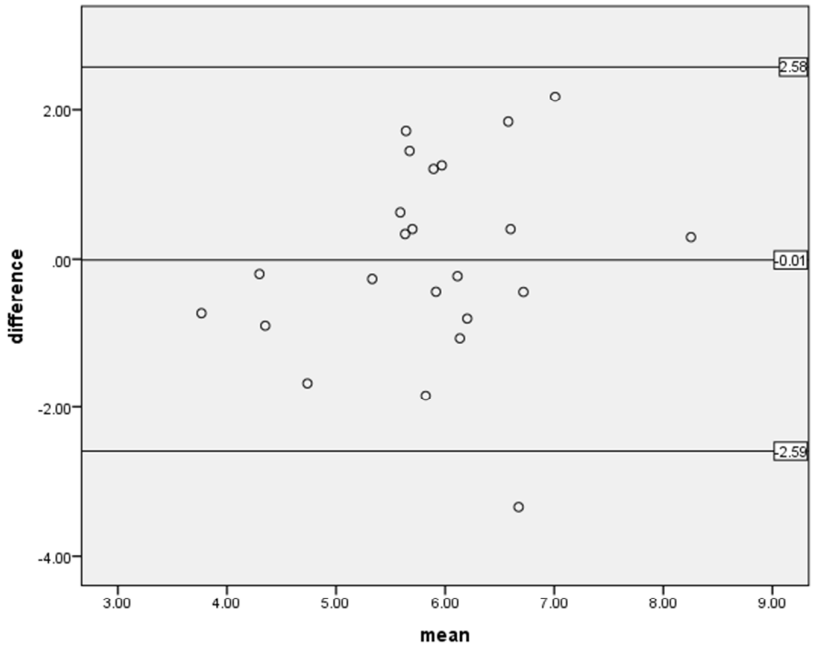


Figure 4 (supplementary material) Bland Altman Plot demonstrating the mean bias and 95% limits of agreement (LOA) between NICOM® (Non-Invasive Cardiac Output Monitor, Cheetah Medical, USA) and transthoracic echo (TTE) CO estimates obtained by the left ventricular outflow tract – velocity time integral (LVOT-VTI) method in the postpartum group.

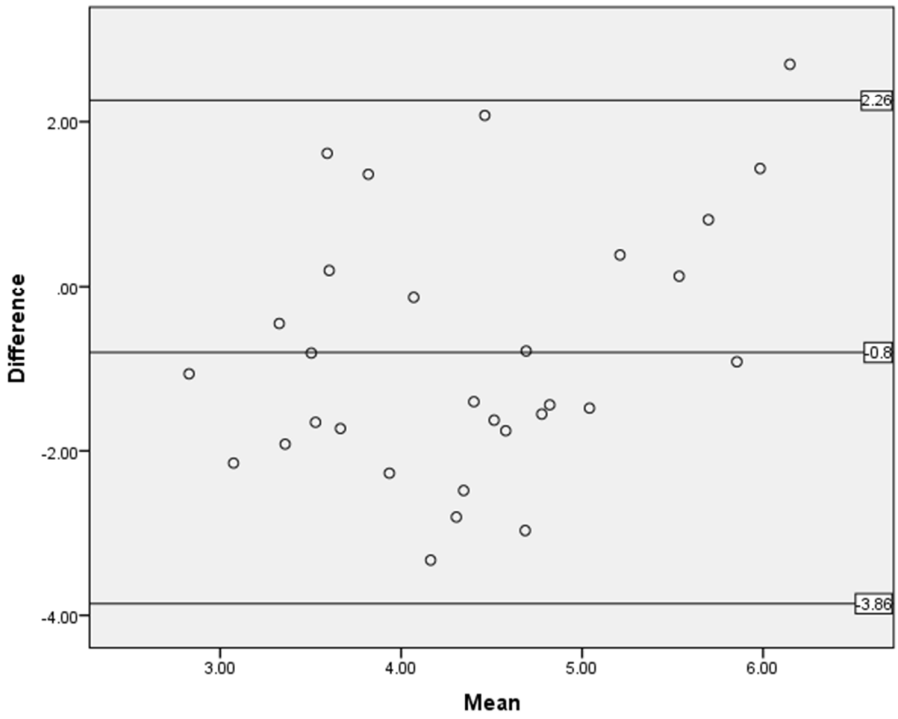


Figure 5 (supplementary material) Bland Altman Plot demonstrating the mean bias and 95% limits of agreement (LOA) between NICOM® (Non-Invasive Cardiac Output Monitor, Cheetah Medical, USA) and transthoracic echo (TTE) CO estimates obtained by the single-plane Simpson rule, in the first trimester.

Peer Review

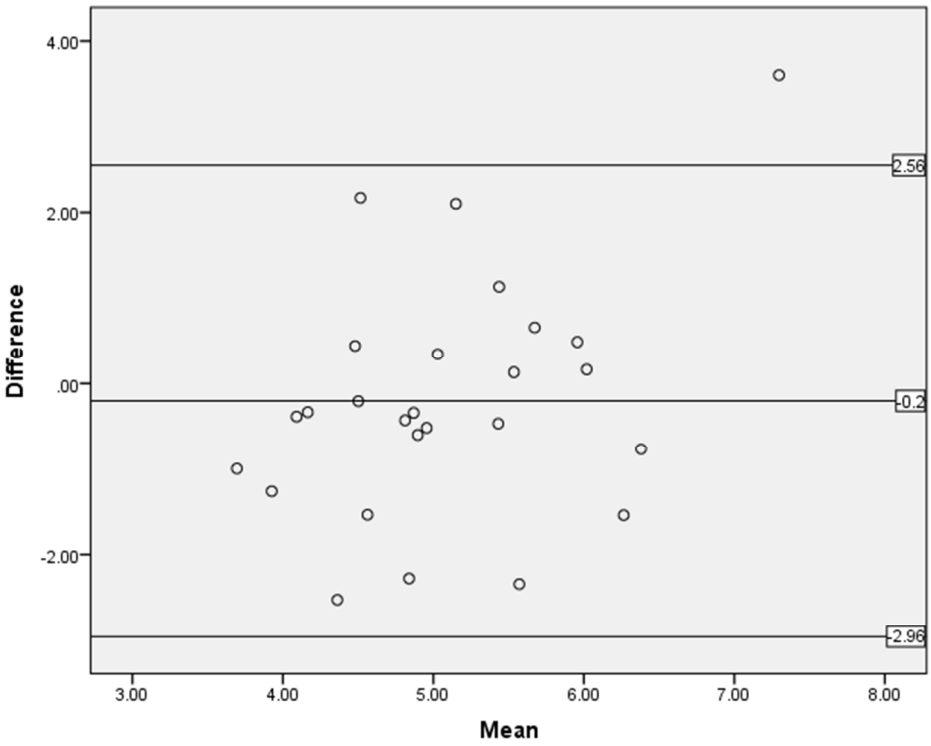


Figure 6 (supplementary material) Bland Altman Plot demonstrating the mean bias and 95% limits of agreement (LOA) between NICOM® (Non-Invasive Cardiac Output Monitor, Cheetah Medical, USA) and transthoracic echo (TTE) CO estimates obtained by the single-plane Simpson rule, in the second trimester.

For Peer Review

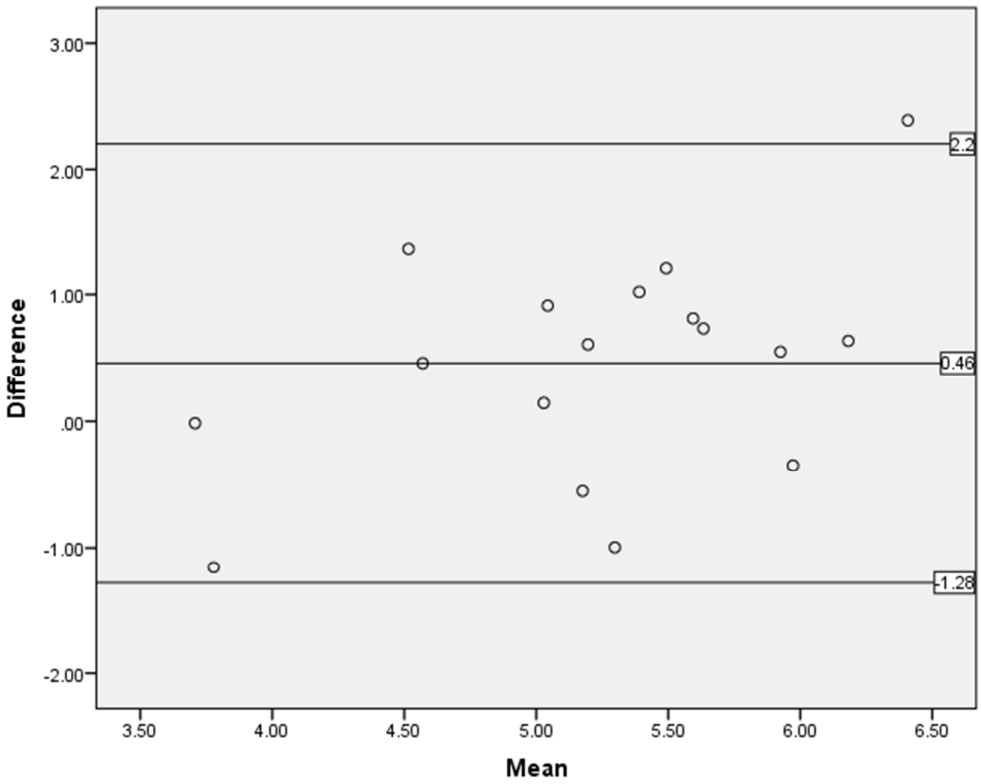


Figure 7 (supplementary material) Bland Altman Plot demonstrating the mean bias and 95% limits of agreement (LOA) between NICOM® (Non-Invasive Cardiac Output Monitor, Cheetah Medical, USA) and transthoracic echo (TTE) CO estimates obtained by the single-plane Simpson rule, in the third trimester.

For Review

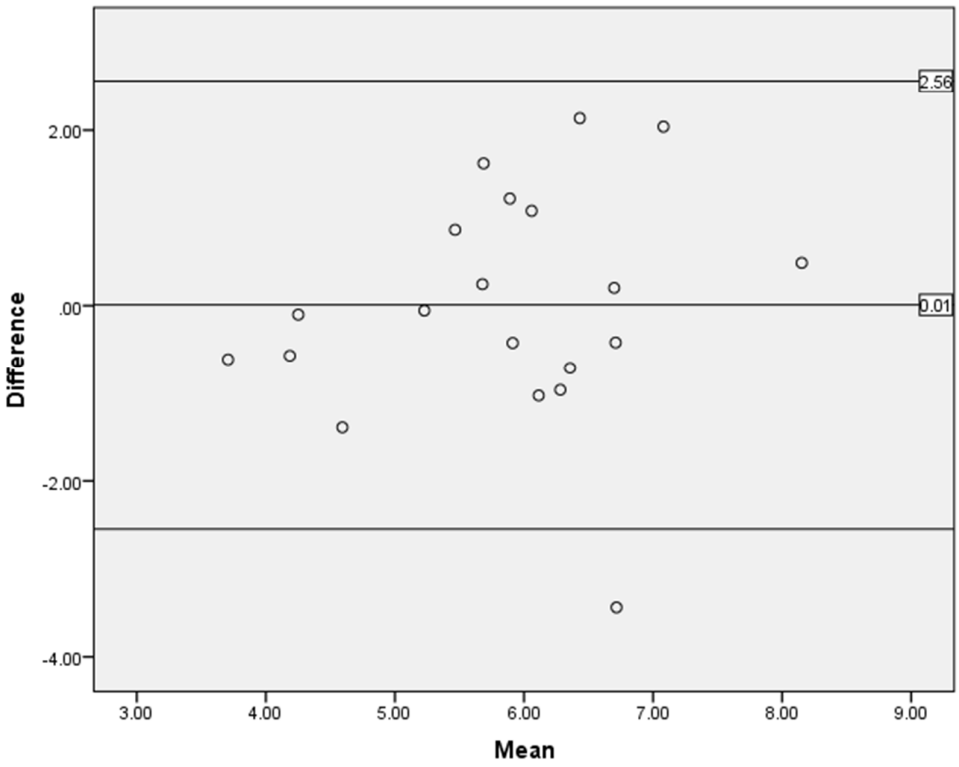


Figure 8 (supplementary material) Bland Altman Plot demonstrating the mean bias and 95% limits of agreement (LOA) between NICOM® (Non-Invasive Cardiac Output Monitor, Cheetah Medical, USA) and transthoracic echo (TTE) CO estimates obtained by the single-plane

For Peer Review

Simpson rule, in the postpartum group.

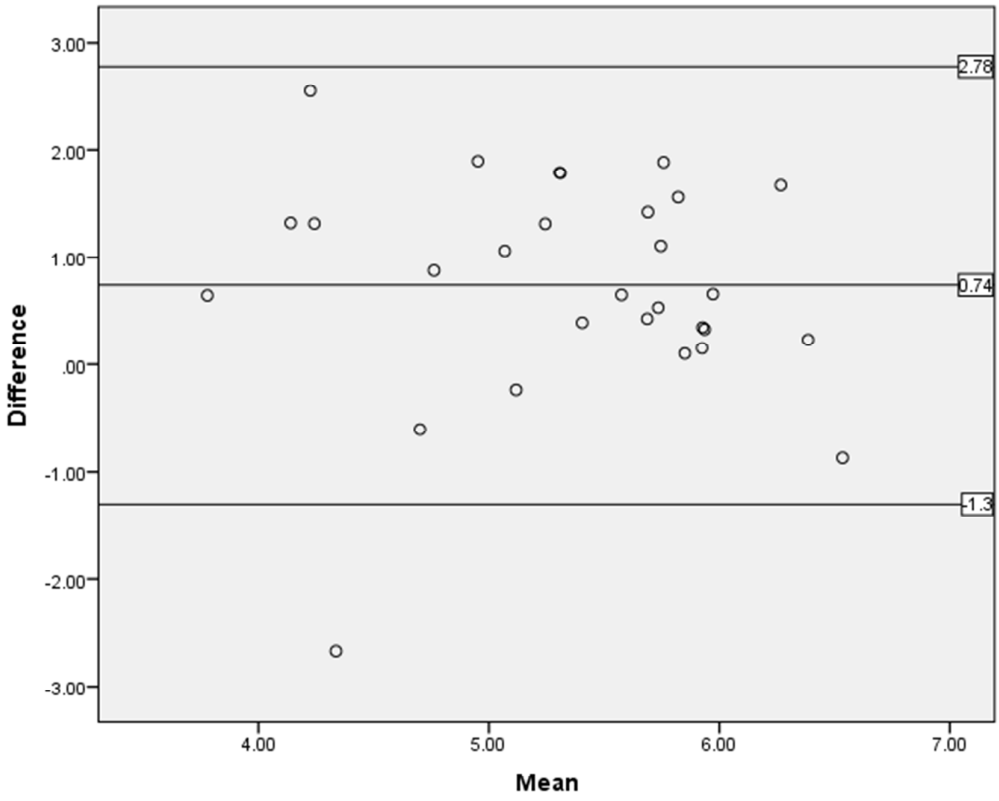


Figure 9 (Supplementary material) Bland Altman plot demonstrating the mean bias and 95% limits of agreement (LOA) between USCOM® (Ultrasound Cardiac Output Monitor, USCOM Ltd, Australia) and transthoracic echo (TTE) CO estimates obtained by the left ventricular outflow tract – velocity time integral (LVOT-VTI) method, in the first trimester.

er Review

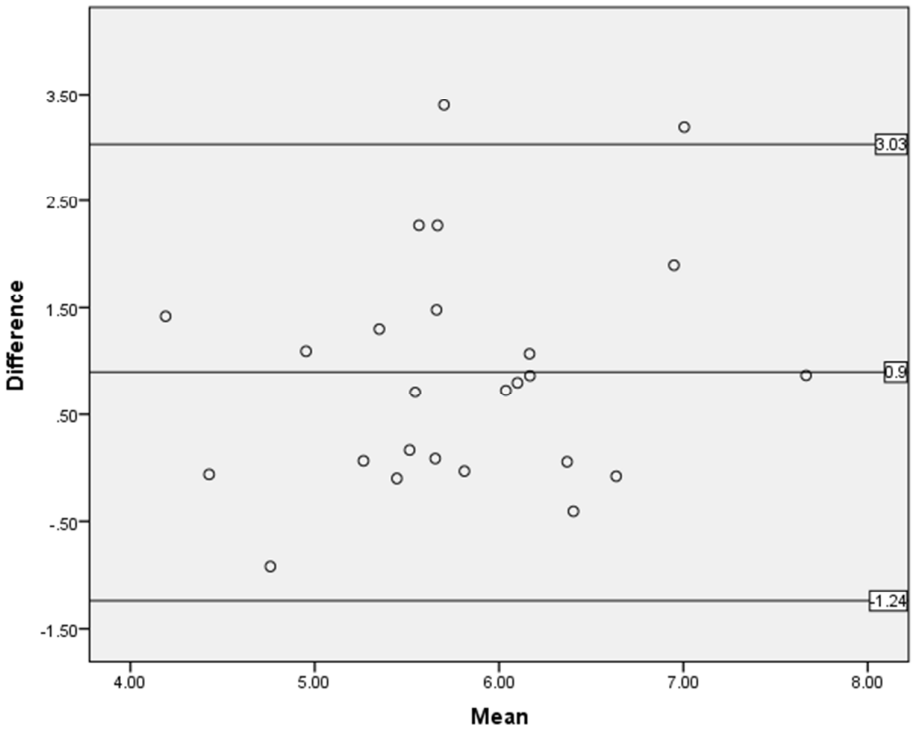


Figure 10 (Supplementary material) Bland Altman plot demonstrating the mean bias and 95% limits of agreement (LOA) between USCOM® (Ultrasound Cardiac Output Monitor, USCOM Ltd, Australia) and transthoracic echo (TTE) CO estimates obtained by the left ventricular outflow tract – velocity time integral (LVOT-VTI) method, in the second trimester.

For Peer Review

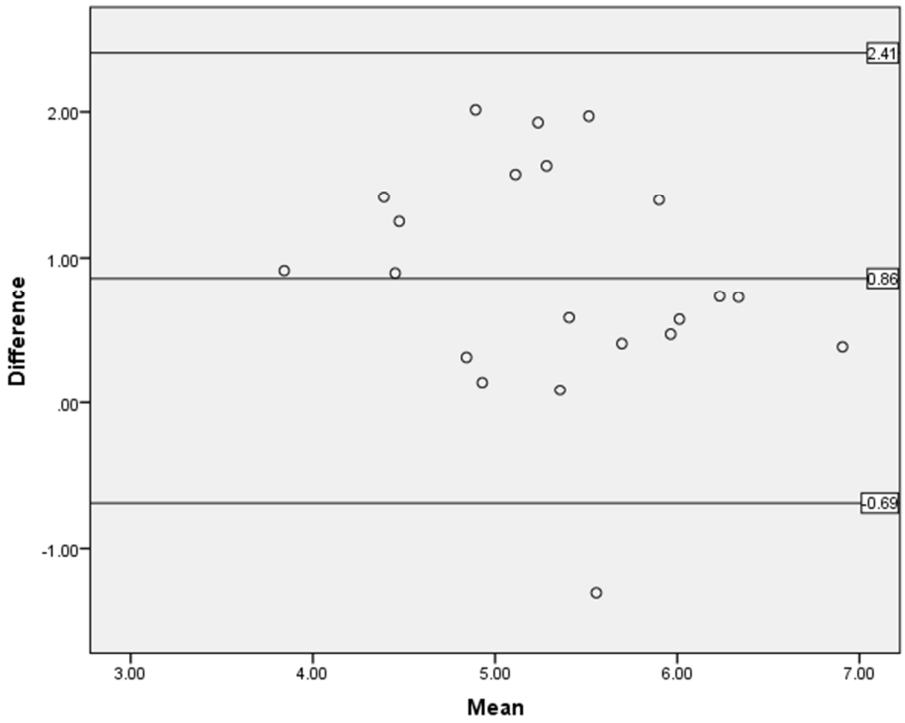


Figure 11 (Supplementary material) Bland Altman plot demonstrating the mean bias and 95% limits of agreement (LOA) between USCOM® (Ultrasound Cardiac Output Monitor, USCOM Ltd, Australia) and transthoracic echo (TTE) CO estimates obtained by the left ventricular outflow tract – velocity time integral (LVOT-VTI) method, in the third trimester.

Peer Review

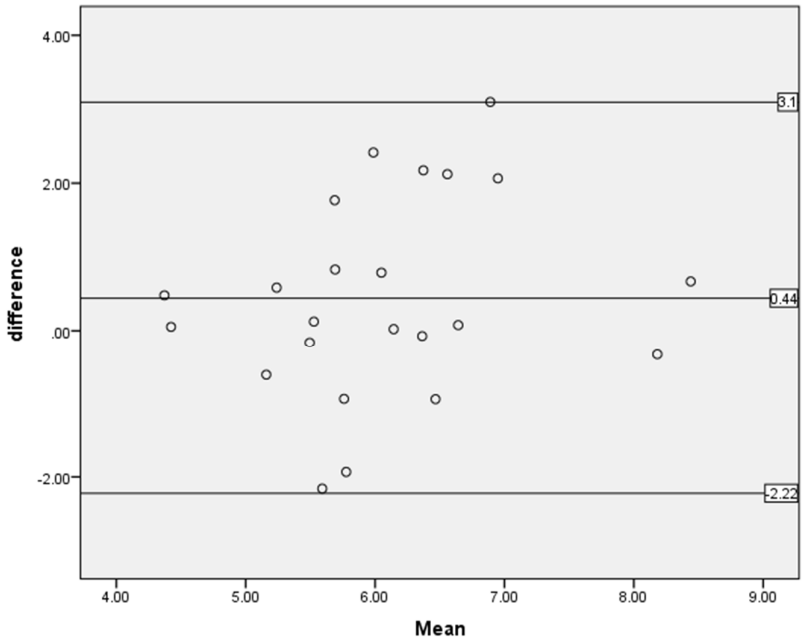


Figure 12 (Supplementary material) Bland Altman plot demonstrating the mean bias and 95% limits of agreement (LOA) between USCOM® (Ultrasound Cardiac Output Monitor, USCOM Ltd, Australia) and transthoracic echo (TTE) CO estimates obtained by the left ventricular outflow tract – velocity time integral (LVOT-VTI) method, in the postpartum group.

For Peer Review

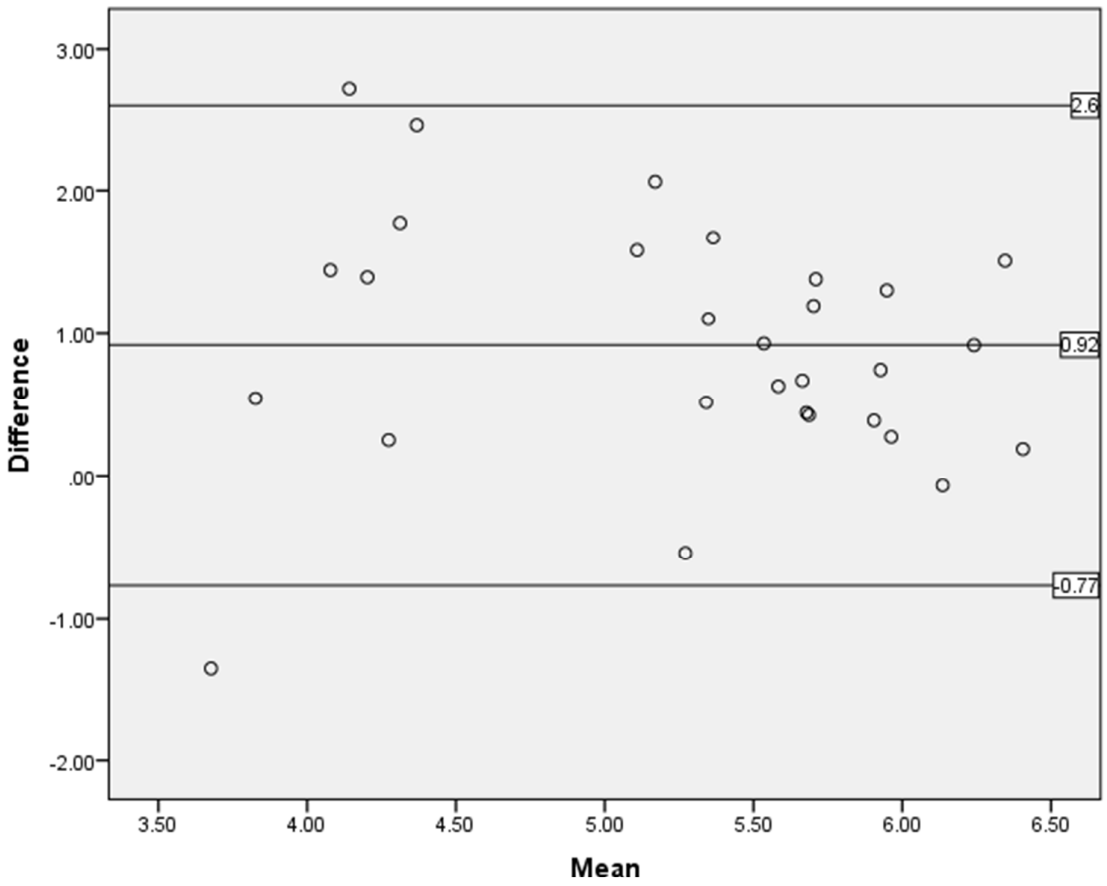


Figure 13 (Supplementary material) Bland Altman Plots demonstrating the mean bias and 95% limits of agreement (LOA) between USCOM ® (Ultrasound Cardiac Output Monitor, USCOM Ltd, Australia) and transthoracic echo (TTE) CO estimates obtained by the single-plane Simpson rule, in the first trimester.

For Review

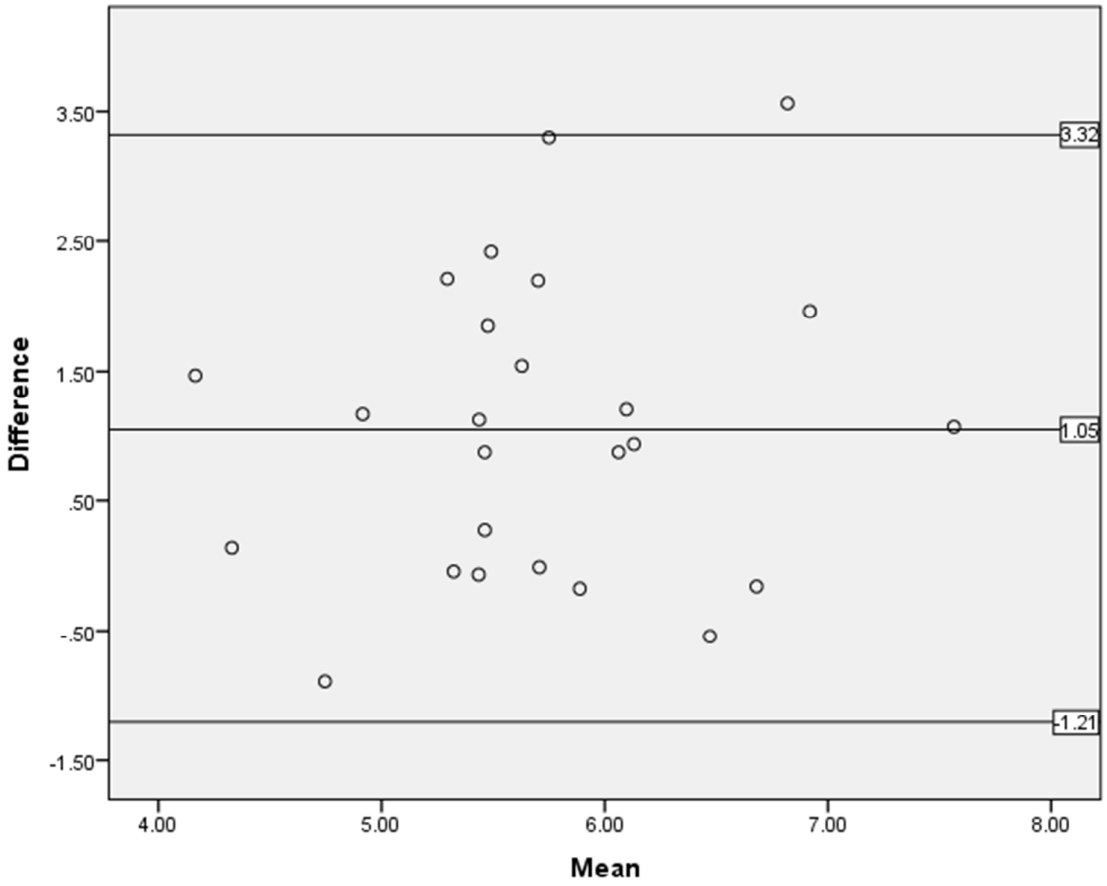


Figure 14 (Supplementary material) Bland Altman Plots demonstrating the mean bias and 95% limits of agreement (LOA) between USCOM® (Ultrasound Cardiac Output Monitor, USCOM Ltd, Australia) and transthoracic echo (TTE) CO estimates obtained by the single-plane Simpson rule, in the second trimester.

For Review

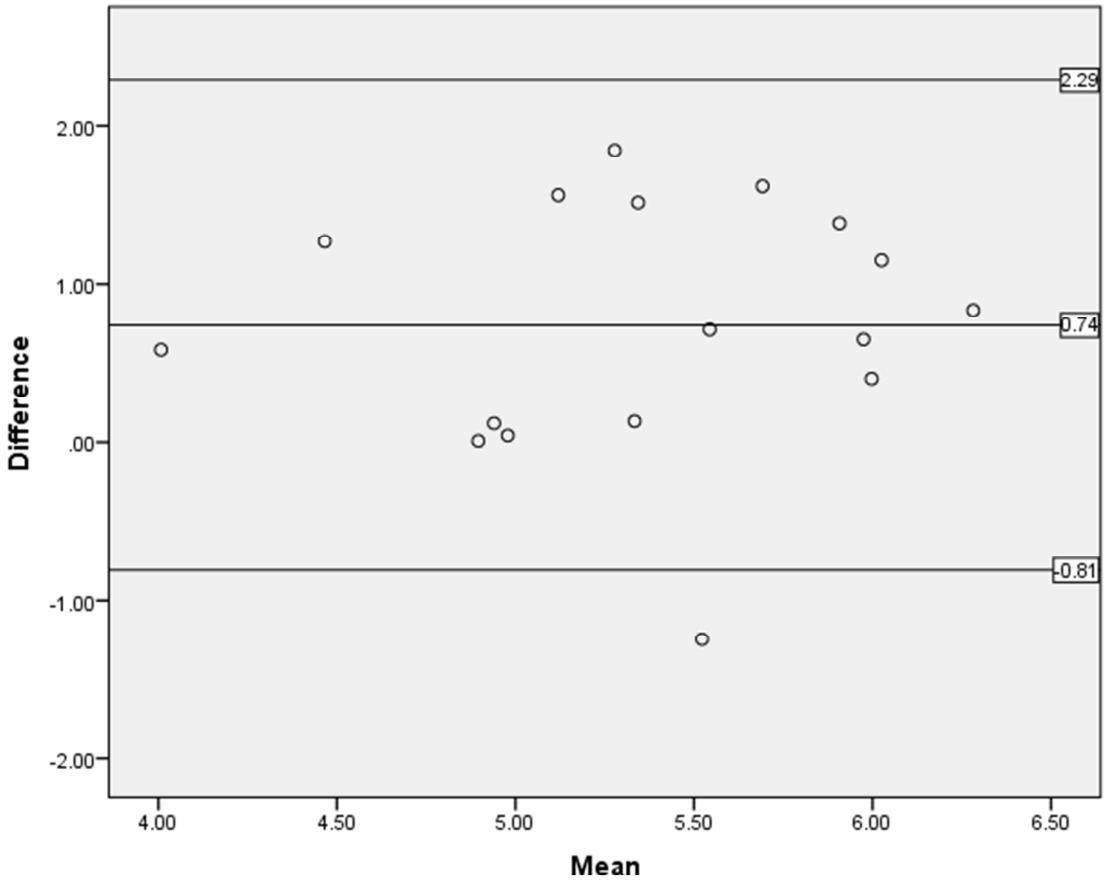


Figure 15 (Supplementary material) Bland Altman Plots demonstrating the mean bias and 95% limits of agreement (LOA) between USCOM ® (Ultrasound Cardiac Output Monitor, USCOM Ltd, Australia) and transthoracic echo (TTE) CO estimates obtained by the single-plane Simpson rule, in the third trimester.

For Review

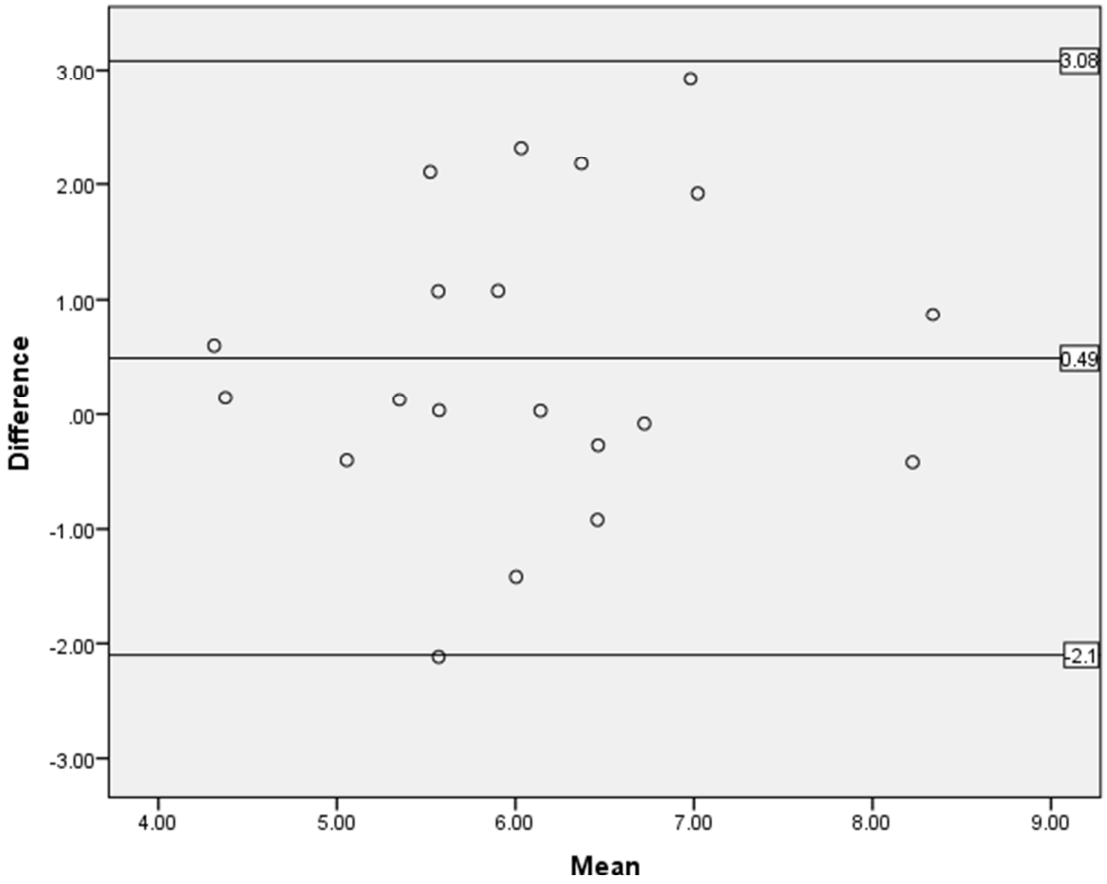


Figure 16 (Supplementary material) Bland Altman Plots demonstrating the mean bias and 95% limits of agreement (LOA) between USCOM ® (Ultrasound Cardiac Output Monitor, USCOM Ltd, Australia) and transthoracic echo (TTE) CO estimates obtained by the single-plane Simpson rule, in the postpartum group.

For Review

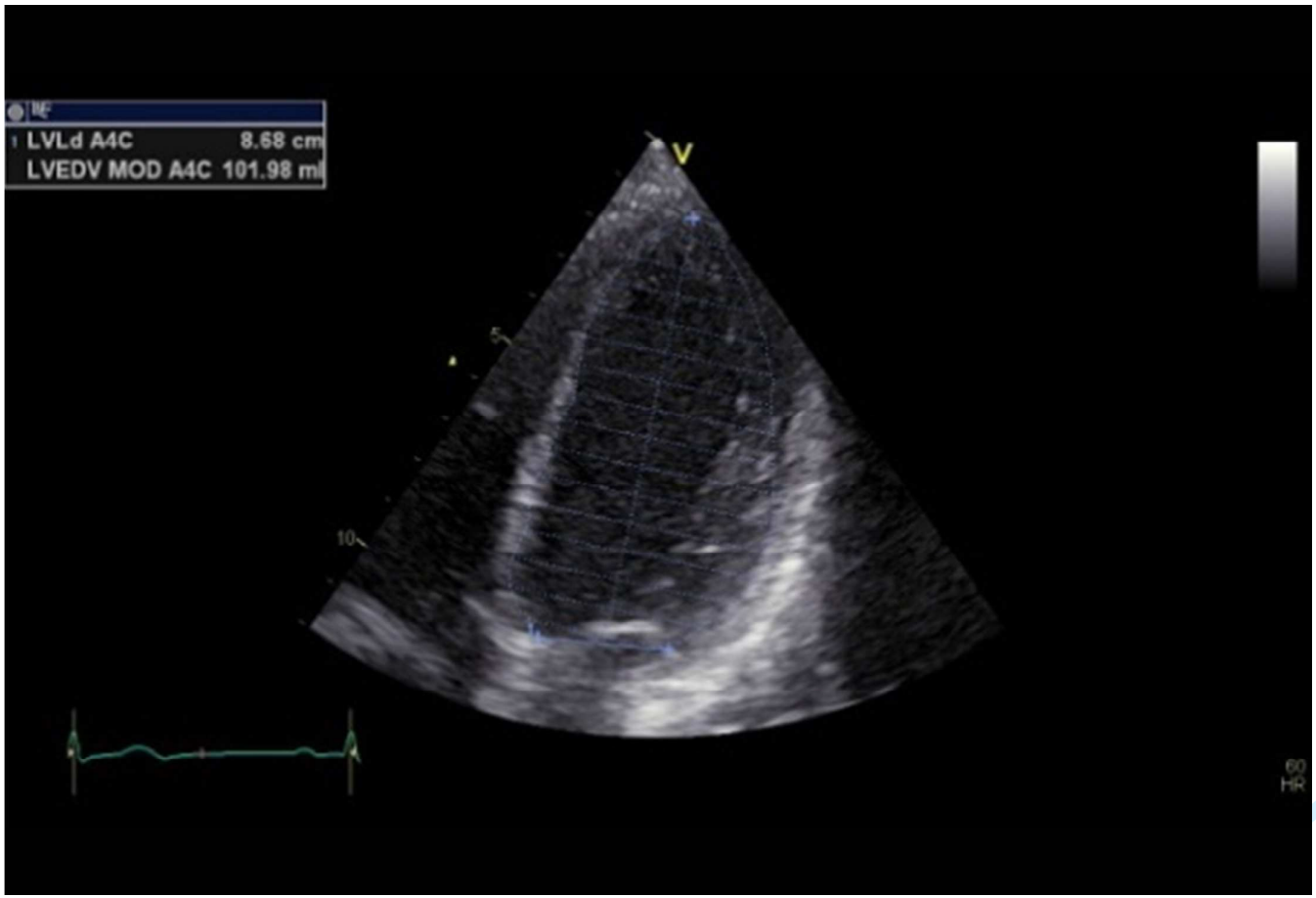


Figure 17 (supplementary material) Left ventricular end diastolic volume (LVEDV) was automatically calculated by tracing the endocardial border in diastole in the apical four-chamber view. In this example, the LVEDV was 101.98 mls. The single-plane Simpson's method involves mathematically dividing the ventricle along its long axis into a series of discs of equal height. The ventricular volume is then represented by the sum of the volume of each of the discs.

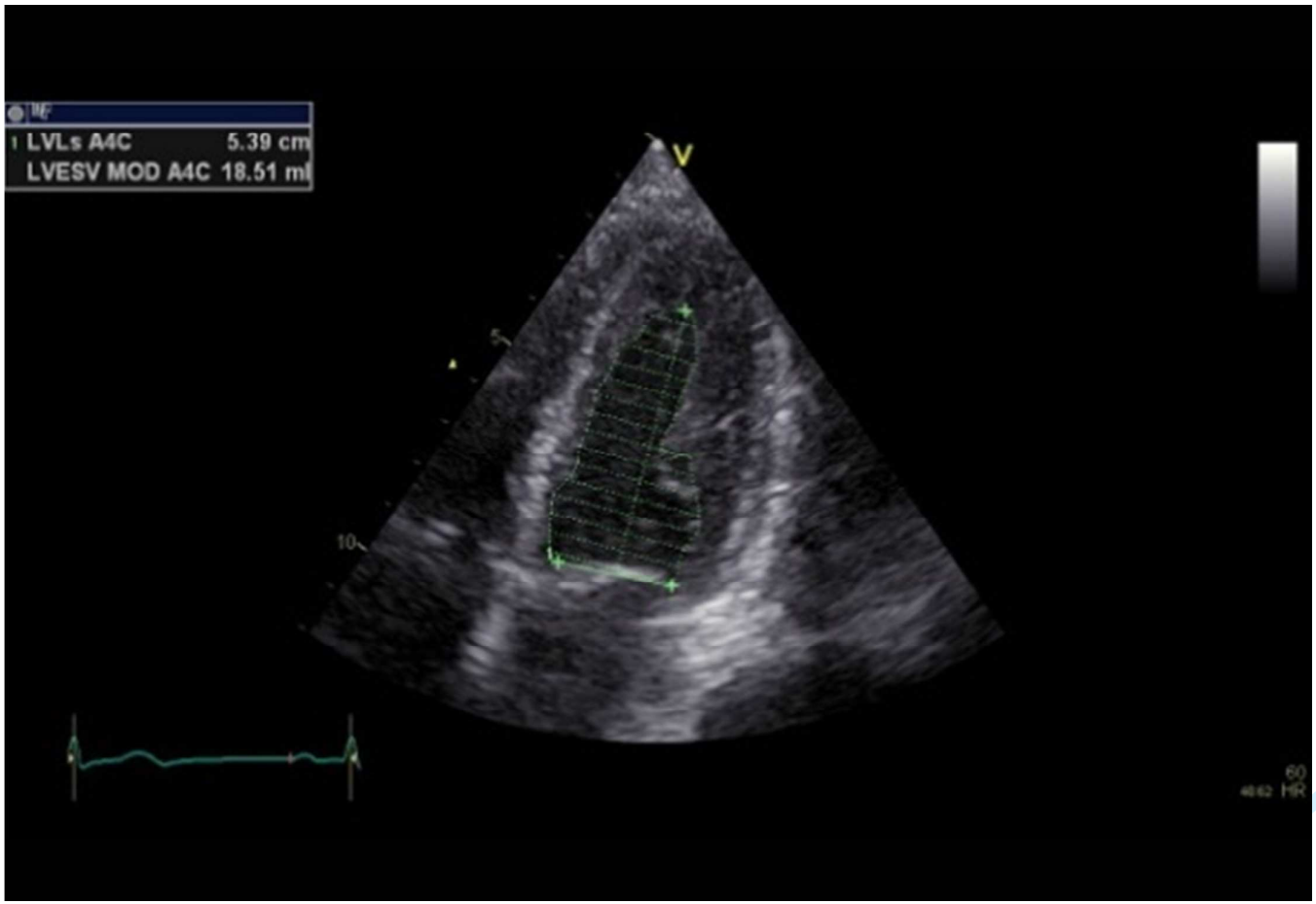


Figure 18 (supplementary material) Left ventricular end systolic volume (LVESV) was automatically calculated by tracing the endocardial border in systole in the apical four-chamber view. In this example, the LVESV was 18.51 mls. The stroke volume is deduced by LVEDV – LVESV; in the examples shown, the stroke volume would be equivalent to 83.47 mls.