Cardiac output measurements during high-risk caesarean section using electrical bioreactance or arterial wave form analysis: an assessment of agreement

J Gutierrez [1]*, H Perry [1,2]*, M Columb [3], S Bampoe [4], B Thilaganathan [1,2], A Khalil [1,2].

* Denotes joint first author with equal contribution to manuscript.

1. Fetal Medicine Unit, Department of Obstetrics and Gynaecology, St George's University Hospitals NHS Foundation Trust, Blackshaw Road, London, SW17 0QT, UK.
2. Vascular Biology Research Centre, Molecular and Clinical Sciences Research Institute, St George's University of London, Cranmer Terrace, London SW17 0RE, UK.
3. Manchester University Hospitals Foundation Trust, Wythenshawe, M23 9LT.
4. Centre for Anaesthesia and Perioperative Medicine. University College London. London, WC1E 6BT, UK.

Correspondence Author:
Professor Asma Khalil MBBCh, MD MRCOG, MSc (Epi), DFSRH, Dip (GUM)
Fetal Medicine Unit
Department of Obstetrics and Gynaecology
St. George's University Hospitals NHS Foundation Trust
Blackshaw Road, London, SW17 0QT, UK.
E-mail: akhalil@sgul.ac.uk

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ABSTRACT

Background: Maternal haemodynamics change significantly during Caesarean Section complicated by massive haemorrhage or severe hypertensive disease. Cardiac output (CO) monitoring aids early, goal-directed haemodynamic therapy. The aim of this study was to record haemodynamic changes observed during Caesarean section using invasive (LiDCO*rapid)* and non-invasive (NICOM®) devices and to assess agreement between the two devices in measuring CO.

Methods: Simultaneous hemodynamic measurements were taken from the two devices using standardized techniques in women undergoing Caesarean section at high-risk of haemodynamic instability. Agreement was assessed using Bland-Altman plots and the Agreement/Tolerable Index (ATI). Agreement analyses were performed for repeated measures in subjects and using centiles.

Results: 307 paired data from 10 patients were analysed. The mean bias (LiDCO*rapid* – NICOM®) was 3.05 $L.min^{-1}$ (95% CI 1.89 to 4.21). Limits of Agreement ranged from -1.58 $L.min^{-1}$ (95% CI -4.47 to -0.14) to 7.68 $L.min^{-1}$ (95% CI 6.24 to 10.56). The resulting agreement interval was 9.26 $L.min^{-1}$ which returned 2.3 as the ATI.

Conclusion: The LiDCO*rapid* and NICOM® hemodynamic monitors exhibit large mean differences indicating that they should not be considered clinically interchangeable. There is an unacceptable level of agreement (ATI>2) conferring an extreme risk of clinical misclassification with massive hemorrhage.

INTRODUCTION

Maternal haemodynamics can change significantly during caesarean section due to the effects of neuraxial sympathetic blockade, vasodilatory general anaesthetic agents, changes in aorto-caval compression upon supine positioning or at the time of delivery of the fetus, and also in response to massive haemorrhage.[1,2] In routine practice, maternal heart rate and blood pressure (BP) are measured to monitor these changes. However, measurement of stroke volume, cardiac output (CO) and systemic vascular resistance provides a more nuanced assessment of haemodynamic changes and is desirable, particularly in cases of massive haemorrhage or hypertensive disease, in order to guide targeted haemodynamic therapy.

Pulmonary artery catheterisation is considered the gold-standard of CO monitoring and has been performed in an obstetric population.[3–5] However, in practice, this invasive procedure is not practical peri-operatively and carries significant risk to the pregnant women. Several less invasive and non-invasive methods have been developed as alternatives.[6–9] In cases where CO monitoring is required, this is commonly performed using a radial arterial line to give continuous BP recording via waveform analysis. LiDCO*rapid* (LiDCO, Cambridge, UK) is a CO monitor that converts the arterial pressure waveform into volume measurements using an algorithm (PulseCO) to estimate CO, which has been validated against lithium indicator dilution assessment. LiDCO*rapid* has not been validated in pregnancy. NICOM® (Cheetah Medical, Boston, MA, USA) is a completely non-invasive device which uses thoracic bioreactance technology to estimate hemodynamic indices. We have previously shown good agreement of NICOM® readings with echocardiography in the third trimester of pregnancy.[9]

The aim of this study was to record haemodynamic changes observed during Caesarean section at high risk of haemodynamic instability using invasive (LiDCO*rapid*) and non-invasive (NICOM®) monitors and to assess the agreement between the two devices in measuring CO.

METHODS

Study design and patient selection

This was a prospective cohort study of patients undergoing a caesarean section at St George's Hospital, London for suspected morbidly-adherent placenta or severe preeclampsia, in whom invasive blood pressure monitoring was indicated. Women with known structural heart disease were excluded. Written informed consent was gained from all participants and ethical approval for the study was obtained (12/LO/0810). All patients were weighed and had their height measured before the procedure. All patients had the procedure performed under combined spinal-epidural anaesthesia, in the same operating theatre and by the same core group of surgeons and anaesthetists. The primary outcome was difference in CO between the two devices.

Haemodynamic measurements

For the NICOM® monitor, sensors were placed on the front of the patient's thorax as per the recommended use. The participants' details, including current height and weight were entered. Maternal heart rate, stroke volume and CO were measured. Radial mean arterial pressure was entered every two minutes in order to obtain readings of systemic vascular resistance. For the LiDCO*rapid* monitoring, a 20-gauge radial arterial line was sited under local anaesthetic using an aseptic technique. The line was flushed, and continuous arterial waveform BP monitoring established. Patient information, including current height and weight were entered. Following insertion of the combined spinal-epidural, both machines were calibrated according to the respective manufacturer protocols with the patient lying still in a supine position on a 30-degree left-lateral tilt before recording was commenced. Baseline readings were noted and then paired concurrent measurements were recorded at

2-minute intervals from the start of the procedure for a 60-minute period or until the procedure was completed, if sooner. As well as haemodynamic parameters, we recorded the following variables: time of start of procedure, time of delivery of the baby and placenta, weight of the baby, total blood loss, amount, rate and type of intravenous fluid or blood product administered, the time, dose and type of vasopressors administered.

Statistical analysis

Agreement between the two devices was assessed using Bland-Altman plots. Normality of distributions was assessed using normal probability plots and the D'Agostino omnibus test. As the data recorded represent multiple observations in each patient, variation both between and within subject were taken into consideration. Thus, the limit of agreement and its corresponding 95% confidence intervals were calculated using the method of variance estimates recovery (MOVER)[10]. Percentage error was calculated using the ratio of limit of agreement (1.96xSD) to the mean CO. A percentage error less than ±30% was considered acceptable. In order to evaluate the global deviation of the devices from each other, the mean percentage difference was calculated as the mean percentage value of the ratio of the absolute value of differences between the methods to the mean cardiac output of the measurement.[11] In order to interpret the clinical implications of the agreement in CO, a tolerability interval, which separates extreme values that could result in opposing interventions, was established a priori as 4L/min based on the difference between the upper and lower bounds of the normal range of maternal CO values at term, as previously described.[12–14] An agreement tolerability interval-ratio (ATI) was calculated by dividing the range of the limits of agreement by the pre-defined tolerability interval (4L/min).

Interpretation of the resulting ratio was performed as per the current guidance: acceptable agreement <1, marginal agreement = 1-2 and unacceptable agreement >2.[14]

Trend-ability was assessed using polar plot analysis.[15,16] A Polar plot is based on polar coordinates, meaning that changes in Cardiac output (ΔCO) are represented by an angle and a radius to display the direction of change and concordance. The angle represents the degree of agreement to the line of identity (LiDCo*rapid* = NICOM®) while the radius represents the magnitude of the underlying change (in L/min) between 2 consecutive measurements of CO. ΔCO < 0.5 L/min were excluded as they may be attributable to noise and do not contribute significantly to the trend analysis [17]. Mean polar angle (angular bias) and 95% Radial limits of agreement (RLoA) were calculated. An angular bias of ±5º and RLoA of ±30º are deemed consistent with good trend-ability. ΔCO plotted within ±30° has been proposed as reflecting acceptable trending. Thus, concordance rate (CR), defined as the percentage of data pairs plotted within ±30º, was calculated. Interpretation of the resulting CR was performed as per the current recommendation: >95% good trending, 90-95% marginal trending and <90% poor trending.[16] Analyses were conducted using Number Cruncher Statistical Systems (NCSS), version 12, NCSS Inc., Kaysville UT, Prism version 7, GraphPad Software Inc., La Jolla CA, and SigmaPlot version 14.0 SigmaPlot (Systat Software, San Jose, CA). Statistical significance was defined as $P < 0.05$ (two-sided).

RESULTS

Ten women were included in the study and their demographic details and intra-operative details are shown in Table 1. Seven women had a Caesarean for morbidly-adherent placenta and three for severe preeclampsia. We recorded 307 sets of paired hemodynamic data across in these 10 women. There were 4 incidences of loss of paired measurement data across the dataset. These all occurred in the same patient. In the Bland-Altman plot analysis of CO measurements, the mean bias, defined as the mean difference between NICOM® and LiDCO*rapid* CO measurements, was 3.05 L/min (95% CI 1.89 to 4.21). The limits of agreement (Figure 1) extended from a lower bound of -1.58 L/min (95% CI -4.47 to -0.14) to an upper bound of 7.68 L/min (95% CI 6.24 to 10.56). The mean percentage difference was 42.21% (95% CI 39.58 to 44.85) demonstrating a large percentage difference between the two devices. Visual inspection of the Bland-Altman plot demonstrates heteroscedasticity with poorer agreement with increasing CO, or in a hyperdynamic state. Logarithmic transformation reduces this effect, suggesting a proportionality error (Figure 2).

Based on the calculated limits of agreement and using a difference in CO of 4L/min between devices as resulting in a significant difference in clinical intervention, the resulting agreement interval was 9.26L/min giving an ATI of 2.3 (9.26L/min divided by 4 L/min), indicating unacceptable agreement between the two devices (Figure 1).

Trend-ability analysis returned an angular bias of -7.36° and 95% RLoA of (53.13° to -52.13°) indicating poor trend-ability. After excluding 188 data pairs due to changes below 0.5l/m, the resulting CR was 63.30% which indicates poor trending. The polar plot analysis

for the whole cohort is shown in Figure 3. Individual patient plots are shown in supplementary Figure 1.

Visual inspection of trends in intra-operative CO measurement in individual cases demonstrated concordant hemodynamic measurements between the two devices in eight out of the 10 patients (supplementary Figure 2). Two patients with major obstetric haemorrhage demonstrated discordance in CO indices at a time of clinical hemodynamic instability (Figure 4). In these patients, the NICOM® bioreactance monitor demonstrated lower CO reading reflective of massive haemorrhage, whereas LiDCO*rapid* showed paradoxical findings of increased CO.

DISCUSSION

Summary of study findings

Our study demonstrates unacceptable agreement in CO measurement between NICOM® and LiDCO*rapid* monitors in pregnant women with high-risk of hemodynamic instability undergoing Caesarean section. This suggests that these devices should not be used interchangeably as misclassifying low versus high CO states would confer significant clinical risks during volume resuscitation. The level of disagreement was greatest at higher CO levels, typical of the relative hyperdynamic state of pregnancy. Our analyses show that there is a systematic proportionality error across the range of observed measurements. Furthermore, individual case review of this series suggests that NICOM® bioreactance monitoring provides readings which are a better reflection of the hemodynamic picture in major obstetric haemorrhage (decrease in CO) compared to LiDCO*rapid*.

Interpretation of study findings and comparison with the existing literature

Several studies have been performed using invasive and non-invasive devices during caesarean section[18–23], but none have compared a non-invasive device to the current clinical standard of monitoring maternal haemodynamic parameters during high-risk caesarean section. Furthermore, most published studies have relied on percentage error or difference to evaluate or compare monitors, even though such a comparison is inappropriate when there is lack of a 'gold standard' invasive monitoring. We overcame the latter limitation by measuring agreement in CO assessment with a pre-defined tolerability index specifically developed for use where there is lack of such a 'gold standard'.

Xiao *et al.* used LiDCOr*apid* to support goal-directed fluid therapy during caesarean section in both a low-risk cohort and a cohort of women with stable hypertensive disease.[19,20] They found LiDCO*rapid* monitoring resulted in less maternal hypotension and vasopressor requirement, suggesting that the trend of CO observations can be clinically useful. However, their study was significantly limited by the lack of any cases of obstetric hemorrhage or uncontrolled hypertension. Dyer *et al.* used LiDCOPlus (a lithium-dilution calibrated arterial waveform monitor) and a bioimpedance device to observe the effect of different vasopressor regimes. They found good correlation between the devices in terms of CO monitoring although again, their cohort included only low-risk women without major obstetric haemorrhage.[18] The discordance of LiDCO*rapid* hemodynamic measurements with hemorrhage has been reported previously in a non-pregnant population. Asamoto *et al.* reported poor agreement between LiDCO*rapid* and pulmonary artery catheter measurements during cardiac and transplant surgery.[24] They found that LiDCO*rapid* underestimated CO index in high CO conditions. Whilst we noted overestimation by LiDCO*rapid* at lower CO, this finding of inaccuracy during hemodynamic instability is clinically important. NICOM® monitors have been validated in pregnant and non-pregnant populations[9,25–29] and used reliably in a small observational study during Caesarean section[30] and in numerous studies of pregnant populations, including healthy controls and those with hypertensive disease.(Table 2)[8,29 30] NICOM® has been compared to pulmonary artery catheterisation in a stable cardiac population, demonstrating good agreement at normal CO, with poorer agreement at the extremes of the range.[33] We found no studies of NICOM in an unstable adult population, however an animal model study of paediatric haemorrhagic shock demonstrated poor agreement between NICOM and pulmonary artery catheterisation.[34]

Possible reasons for the divergence in CO recording between the two devices could be due to the different methods by which they calculate CO. LiDCO*rapid* relies on the invasive arterial line to obtain the BP waveform. There are many factors that can affect the accuracy of the displayed waveform, and therefore, the accuracy of those variables that are derived from the waveform. Secondly, the algorithm it uses to calculate CO was not based on a pregnant population, which has a unique haemodynamic profile compared to the general population. This may lead to both systematic bias in the CO calculation as well as the unreliable readings seen in periods of instability. Conversely, as NICOM® uses a direct, central measurement, it is less susceptible to interference. Limitations of NICOM® include inaccuracy in cases of aortic insufficiency or anatomical abnormalities. Additionally, because the area under the pulse wave is proportional to the product of peak flow and ventricle ejection time, low flow conditions may result in less precise CO measurements.[35]

Study limitations and strengths

The main strength of our study is that we were able to obtain paired recordings of the two devices in pregnant women undergoing the same procedure under the same conditions, thereby reducing the impact of confounding factors. A second strength is that our comparison took place in precisely the clinical situation where close and accurate haemodynamic monitoring is required, rather than in stable, low risk patients without major haemorrhage. This allowed us to note the discordance between devices at periods of hemodynamic instability, something other studies were not designed to detect. Performing the study in a different population, with minimal blood loss may have shown acceptable

agreement between the devices, as other authors have found.[18] Finally, use of ATI as a more reliable method of assessing agreement that is clinically relevant, makes our results more interpretable and valid compared to Bland-Altman analysis. A limitation of our study is that neither of the devices have been validated against an invasive technique of measuring CO in pregnancy, with only limited studies of LiDCO*rapid* outside of pregnancy[24]. Therefore, while they can reflect changes and trends in CO, the values displayed may not represent the true patient's CO. A second limitation is the relatively small number of patients in our study, which was unavoidable given the paucity of such clinical cases.

Clinical and research implications

The best method of measuring agreement between CO monitors, and other devices, has long been an issue of contention in anaesthetic and critical care settings.[14,36] Most authors use the Bland-Altman analysis[37], which offers a good visual assessment of agreement, but does not distinguish if there is acceptable limits of agreement. Critchley *et al.* proposed using a set cut-off percentage difference of 30% as one way of quantifying agreement in this setting.[15] However, even the use of such a limit is clinically uninterpretable when there is no clinical 'gold standard' for comparison. ATI has the advantage of being individualized for a particular clinical situation and related to significant clinical end points such as diagnosis and management of massive obstetric haemorrhage. Our study does not demonstrate any disadvantages in CO trend monitoring with a non-invasive NICOM® device compared to the

invasive LiDCO*rapid* device. In some cases, with massive obstetric haemorrhage, hemodynamic indices obtained by the NICOM® device appeared more in keeping with the clinical picture of severe hypovolaemia than indicated by LiDCO*rapid*. Given the latter findings, and accessibility to non-invasive monitoring, further research in this area is warranted.

Conclusion

The LiDCO*rapid and* NICOM® monitors should not be used interchangeably in an obstetric setting due to unacceptable agreement in CO readings. The ATI evaluation, a clinically-relatable measure of agreement, was poor for these devices.

Author Contributions

AK, BT and SB conceived the idea for the study. JG, HP and SB recruited patients and collected the data. MC provided statistical expertise. HP and JG prepared the first draft of the manuscript. All authors contributed to and approved the final manuscript.

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Declarations of Interest

The authors report no conflicts of interest.

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FIGURE LEGENDS

Figure 1. Bland-Altman Plot and ATI calculation of Cardiac Output measurement by NICOM® and LiDCO*rapid.*

Figure 2. Bland-Altman Plot of Cardiac Output measurement by NICOM® and LiDCO*rapid.* with logarithmic transformation.

Figure 3. Polar plot analysis of trend in CO of all 10 patients measured by NICOM® and LiDCO*rapid*.

Figure 4. Discordance in cardiac output (CO) measurement recorded by NICOM® and LiDCO*rapid* in two patients with haemodynamic instability.

Table 1. Demographic and operative details of the pregnant women monitored in this study.

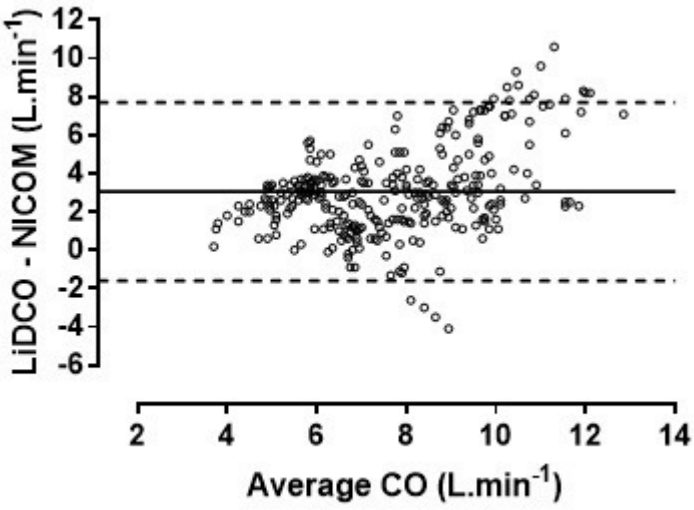
Parameter	**Median (Interquartile Range) or Number (%)**
Maternal age (years)	33.0 (31.8-34.5)
Maternal height (m)	1.60 (1.57-1.76)
Maternal weight (kg)	76.2 (66.1-86.5)
Maternal body mass index (kg/m^2)	28.9 (25.6-32.5)
Ethnicity *Caucasian* *Asian* *AfroCaribbean*	 7 (70%) 1 (10%) 2 (20%)
Nulliparity	2 (20%)
Smoker	3 (30%)
Assisted Conception	3 (30%)
Gestational age at Caesarean section (weeks)	34.6 (32.2-35.9)
Birthweight (g)	2147.0 (2039.8-2562.0)
Estimated blood Loss (ml)	840.0 (463.0-4150.0)
Blood Transfusion	4 (40%)
Admission to HDU	10 (100%)
Admission to ITU	1 (10%)

HDU = obstetric high dependency unit allowing invasive monitoring but not intubation and ventilation. ITU = intensive care unit allowing intubation and ventilation and organ support.

Table 2. A summary of studies using NICOM® in a pregnant and non-pregnant population

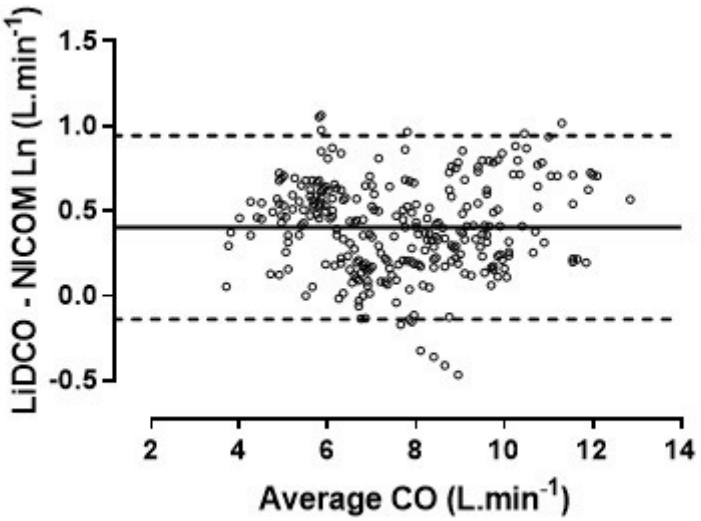
Author	Population	Comparison	Main Findings
Obstetric Studies			
Vinayagam, 2017	524 normotensive and 74 hypertensive pregnant women	Haemodynamic profile using NICOM® and USCOM (a Doppler-based cardiac output monitor)	Moderate correlation in individual parameters. MPD of 34% for CO in the third trimester.
Vinayagam, 2017	98 pregnant or immediately (72hrs) postpartum women	Haemodynamic profile of NICOM® (and USCOM) compared to trans-thoracic echocardiography	NICOM® showed limited agreement to TTE in the first and second trimesters (MPD 71% and 61%) but better agreement in the third trimester (MPD 32%)
Guy, 2017	3013 pregnant women between 35-37 weeks' gestation	Haemodynamic profile using NICOM®. Multivariate regression used to determine significant predictors from demographics and medical history.	Maternal age, weight, weight gain, height, ethnicity, assisted conception and smoking contributed to the prediction of CO.
Stott, 2017	136 pregnant women with current or previous hypertension and 300 healthy controls	Haemodynamic profile using NICOM® in the first half of pregnancy. Reference range created from the healthy cohort using multivariate regression.	Gestational age, ethnicity and body surface area significantly contributed to CO in multivariate regression.
Doherty, 2017	35 pregnant women	Haemodynamic profile of NICOM® compared to trans-thoracic echocardiography	ICC was 0.8 (0.7-0.9) for CO with mean percentage error of +/- 26%
Doherty, 2011	20 pregnant women undergoing Caesarean section	NICOM® monitoring during Caesarean section	Observational study of haemodynamic changes during Caesarean section using NICOM®
Non-Obstetric Studies			
Squara, 2007	110 adult patients after cardiac surgery	Haemodynamic profile using NICOM® compared to thermodilution by pulmonary artery catheter	NICOM® showed good agreement and superior precision to thermodilution.
Weisz, 2014	25 preterm infants undergoing patent ductus arteriosus ligation	Haemodynamic profile using NICOM® compared to echocardiography	NICOM® underestimated SV compared to echocardiography readings but the systematic bias was

			consistent.
Waldron, 2014	100 adult patients undergoing colorectal surgery	NICOM® compared to oesophageal doppler for goal-directed fluid therapy.	Agreement between the two devices was acceptable with no differences in clinical outcomes.
Sun, 2015	60 paediatric patients	Haemodynamic profile using NICOM® compared to echocardiography	There was good agreement in CO measurements between the two devices.



$$\frac{Range = 9.6\,L/min}{Interval = 4.0\,L/min} = ATI\ 2.3$$

figure1jpeg.jpg



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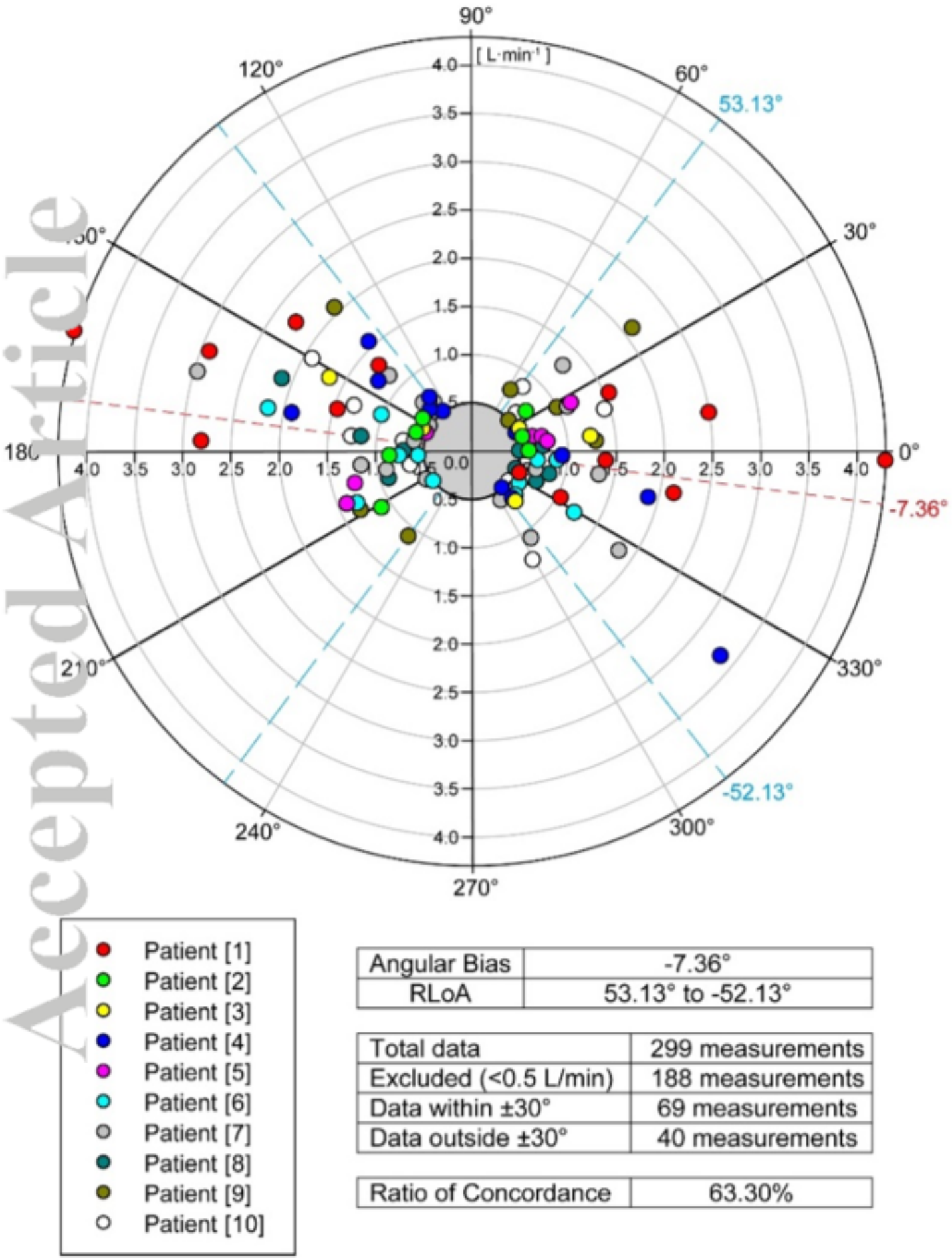

Angular Bias	-7.36°
RLoA	53.13° to -52.13°

Total data	299 measurements
Excluded (<0.5 L/min)	188 measurements
Data within ±30°	69 measurements
Data outside ±30°	40 measurements

Ratio of Concordance	63.30%

Figure3.png

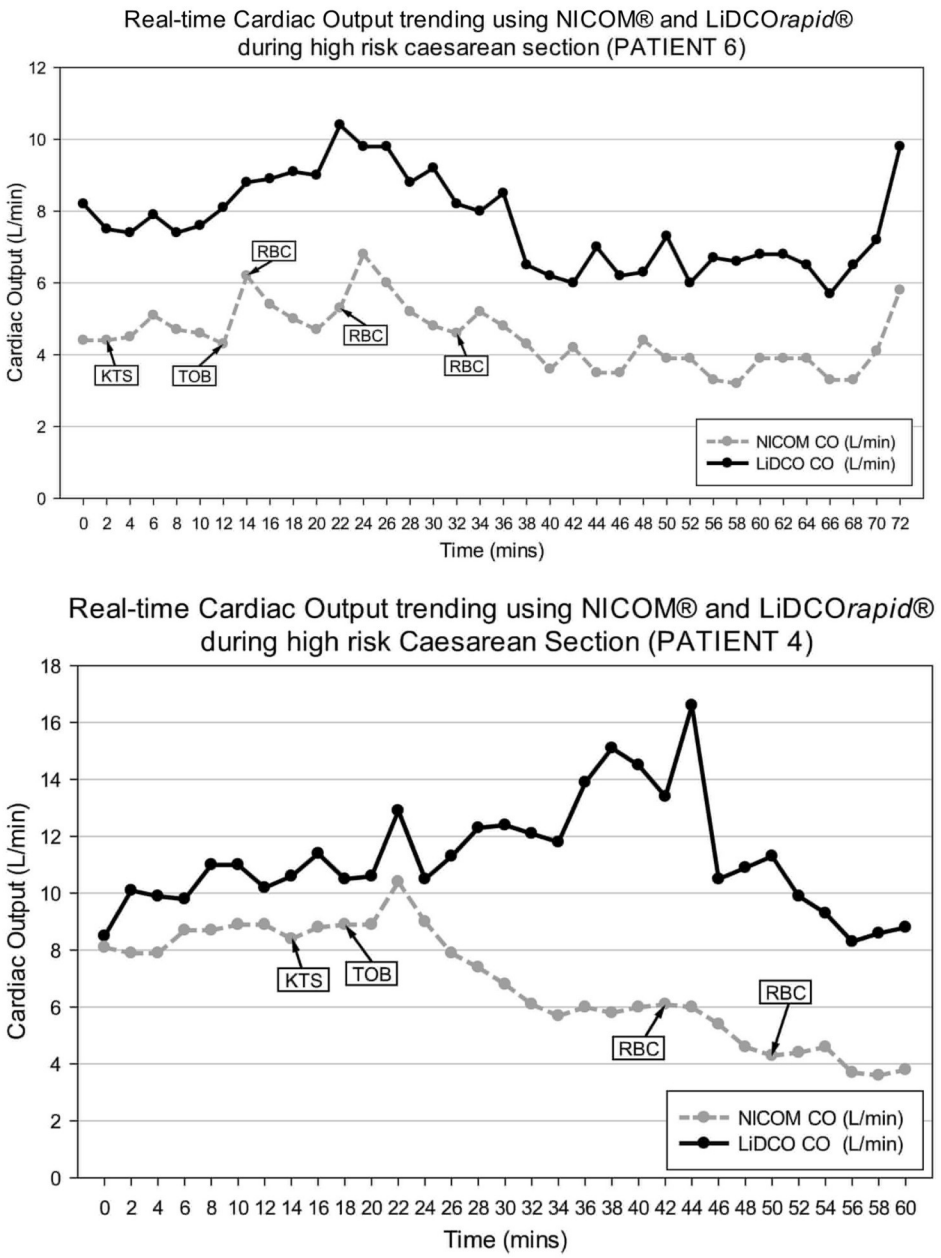

figure4jpeg.jpg