

Calibrating Stroke Volume Measurement of Electrical Cardiometry Compared with Transthoracic Echocardiography

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Calibrating Stroke Volume Measurement of Electrical

Cardiometry Compared with Transthoracic Echocardiography

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Electrical cardiometry (EC) is a non-invasive method of continuous left cardiac output (CO) monitoring based on changes of thoracic electrical impedance over the cardiac cycle. Since controversy exists regarding its accuracy, it has been proposed to calibrate EC using a one-time measurement of the left ventricular outflow tract (LVOT) obtained by transthoracic echocardiography (TTE). The goal of this study was to evaluate agreement between stroke volume (SV) measurements obtained by TTE and EC in a heterogeneous adult population, and to evaluate the previously proposed calibration formula for SV, which was obtained for pregnant women. For this prospective study, a total of 102 adult patients (44 female, 58 male between 21 and 84 years), who were scheduled for routine echocardiography for various indications were included and underwent simultaneous TTE and EC. SV (SV_{TTE} and SV_{EC}), CO (CO_{TTE} and CO_{EC}), heart rate (HR_{TTE} and HR_{EC}), envelope time (ET; left ventricular ET, $LVET_{EC}$ and ET_{TTE}), mean and maximum systolic blood flow velocity in $LVOT_{TTE}$ ($LVOT_{TTE_meanSBFV}$ and $LVOT_{TTE_maxSBFV}$, respectively), velocity time integral (VTI_{TTE}), index of contractility ($ICON_{EC}$), thoracic fluid content (TFC_{EC}), area and diameter in $LVOT_{EC}$ ($LVOT_{EC_area}$ and $LVOT_{EC_diameter}$, respectively) were obtained. $LVOT_{EC_area}$, SV_{EC} , and body weight were used to obtain a modified estimate of SV (mSV_{EC}). Correlations and Bland-Altman analysis were performed. Mean percentage error limits of <30% were defined as clinically acceptable. There was no correlation between SV_{TTE} and SV_{EC} . A weak, but significant correlation was detected between SV_{TTE} and mSV_{EC} ($r=0.32$, $p=0.01$). The Bland Altman analysis revealed a mean percentage error of 58%. The mean percentage error remained above 30% even after controlling for gender. In a heterogeneous adult patient population, SV and CO derived from EC did not agree with measurements obtained from TTE. Using $LVOT_{area}$ to calibrate EC derived SV did not improve agreement to a clinically acceptable level.

30 **Keywords:** electrical cardiometry, stroke volume, impedance cardiography, non-invasive
31 cardiac output monitoring, transthoracic echocardiography

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Introduction

Cardiac output (CO) is a key variable when describing and treating the cardiovascular system. The ideal CO monitor would be safe, non-invasive, low-cost, painless, and easy to interpret and would allow for continuous, hands-free acquisition of accurate data. Electrical cardiometry (EC), a more recent version of impedance cardiography, meets many of the criteria for an ideal monitor and previously published research suggests that EC successfully trends CO [1-6], but its accuracy in measuring absolute values of stroke volume (SV) has been inconsistent in published research [7-11].

EC calculates SV (SV_{EC}) by estimating mean systolic blood flow velocity (SBFV) and duration (corrected flow time, FTc) and is then multiplied by a patient constant called 'volume of electrically participating tissue' (VEPT), as suggested by the company of the ICON[®] device (*Eq. 1*):

$$SV_{EC} \text{ (mL)} = VEPT * \text{mean SBFV} * FTc \quad (1)$$

CO monitors are typically validated against a reference standard, which has traditionally been thermodilution using a pulmonary artery catheter. Given the risks associated with the use of pulmonary artery catheters, transthoracic echocardiography (TTE), which is safe, painless and non-invasive, lends itself as a valuable substitute technique for measuring CO. Main disadvantages of TTE to measure CO are non-continuous single point estimation and the need for a highly trained provider to obtain velocity time integral (VTI) measurements [12]. VTI is calculated from the mean SBFV times left ventricular ejection time (LVET). Similarly to EC, SV estimate by TTE (SV_{TTE}) is based on a measurement of the mean

SBFV and envelope time (ET). In contrast to EC, instead of using an abstract and proprietary patient constant that largely is based on patients' weight, the measured parameter left ventricular outflow tract area (LVOT_{area}) is used and calculated, as a physiological equation, as follows (Eq. 2):

$$SV_{TTE} \text{ (mL)} = LVOT_{area} \text{ (cm}^2\text{)} * VTI \text{ (cm)} \quad (2)$$

Recently, Martin and colleagues compared SV parameters derived from TTE and EC in a sample of 44 pregnant volunteers and found excellent agreement between duration of systole (LVET and ET) and heart rate (HR) as measured by the two methods [13]. SV_{EC} was also shown to have a highly significant correlation with VTI as well as with SV_{TTE} . However, with a percentage error of 42% in Bland-Altman analysis, absolute agreement between SV_{TTE} and SV_{EC} was poor. Considering that both methodologies used measures for blood velocity and systolic ejection time in order to estimate what is essentially a VTI, Martin and colleagues hypothesized that agreement between TTE and EC could be significantly improved by calibrating SV_{EC} (essentially using it as an index of VTI, rather than of stroke volume per se) using the LVOT_{area} derived from a one-time TTE measurement. This measurement of the LVOT diameter is obtained from the parasternal long axis view and requires rather basic TTE skills. Based on a multiple linear regression model and log-linear transformation, the following calibration formula for modified SV_{EC} (mSV_{EC}) was derived [13] (Eq. 3):

$$mSV_{EC} = 2.2 * LVOT_{area} \text{ (cm}^2\text{)}^{(0.705)} * SV_{EC} \text{ (mL)}^{(0.388)} * \text{weight (kg)}^{(0.21)} \quad (3)$$

By applying this formula, agreement between SV_{TTE} and mSV_{EC} significantly improved and percentage error decreased to 22% in their study. However, data was derived from a very specific patient population including only non-laboring pregnant women at 24 weeks or greater gestational age. Furthermore, validity of the mSV_{EC} formula was only supplied by bootstrapping and cross-validation, rather than using a prospective evaluation cohort. Therefore, the primary aim of the present study was (a) to compare SV estimates derived from EC and TTE in non-pregnant, female and male adult outpatients undergoing routine echocardiography assessment and (b) to evaluate whether agreement between both methods can be improved by calibrating SV_{EC} measurements with a one-time $LVOT_{area}$ measurement obtained from TTE and then applying Martin's formula to calculate the mSV_{EC} .

Methods

Study population

This prospective, cross-sectional study was approved by the ethic committee of the Medical University of Vienna (Vienna, Austria) (EK1139/2015) and registered with ClinicalTrial.gov (NCT02702063 08/03/2016).

A convenience sample of female and male adult patients routinely scheduled for TTE was recruited at the Echocardiography Laboratory of the Department of Cardiology at the Medical University of Vienna (Vienna, Austria) between April 2015 and March 2016. Exclusion criteria included age younger than 18 or older than 85 years, and patients presenting with moderate to severe aortic regurgitation, congenital heart disease with

intracardiac shunt, or arrhythmia (atrial fibrillation). Written informed consent was obtained from all patients prior study start.

Of the 159 patients, who were considered for enrollment during the study period, six patients declined (n=3), refused (n=1), or were not able to sign informed consent (n=2) and 51 patients were excluded due to incomplete or unevaluable measurements (n=26), due to logistic reasons (n=2), or for the following medical reasons: atrial fibrillation (n=7), high grade aortic regurgitation (n=2), obstruction of the LVOT (n=1), previously unknown arrhythmia (n=11), suspected raised intraabdominal pressure (n=1), or newly detected shunt disease (n=1); leaving a total of 102 patients, who were included in the study.

All methods were performed in accordance with the relevant guidelines and regulations.

Measurements

All measurements were performed at the Echocardiography Laboratory of the Department of Cardiology at the Medical University of Vienna (Vienna, Austria) by the same certified cardiac sonographers. Weight (kg) and height (cm) were used to calculate body mass index (BMI = kg/cm²). TTE and EC measurements were obtained simultaneously during one of three consecutive measurement sessions and the mean values of the three sessions were used for analysis.

Electrical cardiometry (EC)

EC measurements including SV_{EC} (mL) and CO_{EC} (L/min) were obtained using the ICON[®] monitor (Osypka Medical, Inc, La Jolla, California, USA and Berlin, Germany). Four electrocardiogram electrodes (Ambu[®] Blue Sensor VL, Ballerup, Denmark) were placed

on the bare skin of patients on the left neck below the ear, above the midpoint of the left clavicle, along the left mid-axillary line at the level of the xiphoid process, and five cm caudal from the third electrode.

Patient's characteristics including age (years), gender (female/male), height (cm), and weight (kg) were entered into the monitor. Times of the monitor and TTE machine were synchronized prior to data collection. The monitor was programmed (a) to capture moving averages of EC variables based on the previous 10 cardiac cycles and (b) to record those averages every 10 seconds. As per manufacturer recommendations, only EC data with a signal quality index (SQI) of ≥ 70 were included in the analysis. EC and TTE measurements were reviewed by one of two attending physicians certified in echocardiography (R.T. or C.O.) and who were blinded to measurements. Additionally, both reviewers evaluated 20% of scans to confirm measurement accuracy.

SV measured by EC was calculated using both equations:

$$SV_{EC} = VEPT * \text{mean SBFV} * FTc \quad (1)$$

$$mSV_{EC} = 2.2 * LVOT_{\text{area}} (\text{cm}^2)^{(0.705)} * SV_{EC} (\text{mL})^{(0.388)} * \text{weight (kg)}^{(0.21)} \quad (3)$$

Transthoracic echocardiography (TTE)

The left ventricular outflow tract (LVOT) was measured in the left parasternal long axis view as the distance between the inflection points at the base of the aortic valve cusps and calculated as $LVOT_{\text{area}} (\text{cm}^2) = \pi \times (LVOT_{\text{diameter}} (\text{mm}) / 2)^2$. LVOT measurements were repeated three times, and the mean value was used for SV calculations. VTI was obtained from the apical five-chamber view by placing the pulsed wave Doppler sampling cursor in

the middle of the LVOT immediately proximal to the aortic valve. During each measurement session the mean of three high quality VTIs was calculated. The SV_{TTE} (mL) was then derived as product of the $LVOT_{area}$ (cm^2) with mean VTI (cm). HR was measured in beats per minute (bpm). CO_{TTE} was obtained by the machines' built-in program according to the formula: CO_{TTE} (L/min) = $LVOT_{area}$ (cm^2) x VTI (cm) x HR (bpm). One pair of data for each patient including the following parameters was evaluated: SV (SV_{EC} and SV_{TTE} in mL), CO (CO_{EC} and CO_{TTE} in L/min), HR (HR_{EC} and HR_{TTE} in bpm), $LVET_{EC}$ (in m/sec), ET_{TTE} (in m/sec); TTE measured LVOT area ($LVOT_{TTE_area}$ in cm^2), diameter ($LVOT_{TTE_diameter}$ in cm), SBFV ($LVOT_{TTE_meanSBFV}$ and $LVOT_{TTE_maxSBFV}$ in m/sec), VTI_{TTE} (in cm), index of contractility ($ICON_{EC}$), thoracic fluid content (TFC_{EC}), and diameter of the $LVOT_{EC}$ ($LVOT_{EC_diameter}$) was measured. $LVOT_{area}$, SV_{EC} , and body weight (kg) was used to obtain a modified estimate of SV (mSV_{EC}).

Statistical Analysis

Patients' details were presented using descriptive statistics. Distribution of continuous data was assessed by a visual inspection of histograms and the Kolmogorov-Smirnov-test. Categorical data were expressed by frequencies with percentages and continuous data as means with standard deviation (SD; parametric) or as medians with ranges (non-parametric). Chi-square tests were performed to analyze categorical variables. The ratio of $LVET_{EC}$ and ET_{TTE} was calculated. Scatter plots and Pearson's correlation coefficients (r) were used to assess correlations between TTE and EC measurements. Effect sizes were categorized according Rea and Parker (1992) (negligible: ≤ 0.10 , weak: 0.10-0.20, moderate: 0.20-0.40, relatively strong: 0.40-0.60, strong: 0.60-0.80, very strong: 0.80-

1.00). Bland-Altman analysis was used to assess agreement between TTE and EC measurements by calculating means and SDs of the bias (difference between TTE and EC measured values) and the mean of both measured values (TTE value plus EC value divided by 2), upper and lower 95% limits of agreement (LoA; $\pm 1.96 \times \text{SD}$ of the bias), 30% LoA ($\pm \%$ of the mean of both measured values), and percentage errors (PE in %) were calculated as $1.96 \times \text{SD}$ of the bias divided by the mean of both measured values times 100. The mean PE limit of $\pm 30\%$ is clinically acceptable and in accordance with previous data[14]. Statistical significance level was set at $p < 0.05$ (two-tailed). Statistical analyses were performed using SPSS Statistics 25 (IBM® Corporation, Armonk, NY, USA).

Results

Demographic data of 102 patients with various indications for echocardiography such as coronary heart disease, valvular disease or heart failure are presented in Table 1. Age was similar between female (58.2 ± 17.9 years) and male (58.6 ± 16.6 years) patients ($p = 0.894$) and between underweight (56.9 ± 19.2 years) and normal weighted (59.6 ± 15.3 years) patients ($p = 0.447$). Significant more male (67.2%) than female (43.2%) patients were overweight or obese ($p = 0.017$).

Table 1 Demographics

<i>Characteristics</i>	TOTAL (n=102)
Age (years)	58.4 ± 17.1 61 (21-84)
Gender (female/male)	44 (43.1%) / 58 (56.9%)
Weight (kg)	76.5 ± 17.1

Height (cm)	170.4 ± 9.3
BMI (kg/cm ²)	26.2 ± 5.0
BMI groups	
underweight (<18.5)	5 (4.9%)
normal (18.5-24.9)	39 (38.2%)
overweight (25.0-29.9)	33 (32.4%)
obese (≥30.0)	25 (24.5%)

Abbreviation: BMI, body mass index.

All data collected from TTE and EC as well as correlations between TTE and EC measurements are presented in Table 2. Comparisons between TTE and EC measurements showed a very strong, relatively strong, and moderate correlation with HR, ET, and mSV, respectively. SV and CO did not correlate between TTE and EC (Table 2).

Table 2 Transthoracic echocardiography (TTE) and electrical cardiometry (EC) measurements of 102 patients.

	EC	TTE	Correlation
	mean±SD median (range)	mean±SD median (range)	correlation coefficient p-value ^a (effect size)
SV (mL)	73.5 ± 18.5 71.3 (41.2 – 149.3)	77.4 ± 20.5	r=0.027 p=0.784 (no correlation)
modified SV (mL)	69.1 ± 12.9 67.8 (43.1 – 105.5)	76.7 (29.0 – 140.2)	r=0.304 p=0.002 (moderate)
CO (L/min)	5.2 ± 1.4 5.1 (2.5 – 10.3)	5.3 ± 1.4 5.1 (2.7 – 11.0)	r=0.093 p=0.353 (no correlation)
HR (beats/min)	71.1 ± 12.5 69.4 (48.5 – 113.2)	69.8 ± 12.6 68.3 (36.8 – 111.7)	r=0.950 p<0.001 (very strong)
Time	<u>LVET_{EC} (ms)</u>	<u>ET_{TTE} (ms)</u>	
Envelope time	296.1 ± 23.7 298.8 (219.7 – 339.7)	306.8 ± 39.6 311.3 (214.3 – 434.3)	r=0.576 p<0.001 (relatively strong)
LVET _{EC} (ms) / ET _{TTE} (ms)	1.0 ± 0.1 1.0 (0.7-1.3)		-
LVOT _{TTE_meanSBFV} (ms)	-	0.7 ± 0.1 0.7 (0.5 – 1.2)	-
LVOT _{TTE_maxSBFV} (ms)	-	1.1 ± 0.2 1.0 (0.6 – 1.7)	-
LVOT _{TTE_diameter} (cm)	-	21.0 ± 1.7 21.0 (17.0-27.0)	-
LVOT _{TTE_area} (cm ²)	-	3.5 ± 0.6	-

		3.5 (2.3 – 5.7)	
Device specific outcome	<u>ICON_{EC}</u> 48.1 ± 20.6 43.2 (15.8 – 121.8)	<u>VTI_{TTE} (cm)</u> 22.4 ± 5.6 22.3 (10.3 – 37.6)	r=0.103 p=0.305 (no correlation)
TFC _{EC}	29.8 ± 12.8 27.3 (18.0 – 126.0)	-	-

Abbreviations: CO, cardiac output; ET, envelope time; HR, heart rate; ICON, index of contractility; LVET, left ventricular ejection time; LVOT, left ventricular outflow tract; SBFV, systolic blood flow velocity; SV, stroke volume; TFC, thoracic fluid content; VTI, velocity time integral.

^a Pearson correlation

Correlations and Bland Altman plots regarding SV obtained (SV_{TTE} , SV_{EC}) or calculated (modified SV_{EC}) from TTE and EC measurements are shown in Figure 1. While modified SV_{EC} significantly correlated with SV_{TTE} , SV_{EC} did not (Table 2; Figure 1 A and C, respectively). The mean percentage error between TTE and EC measurements regarding SV was slightly lower using the modified formula (mSV_{EC} : 55.2%) compared to the obtained SV (SV_{EC} : 70.8%); however, it was still above the clinically acceptable level of 30%.

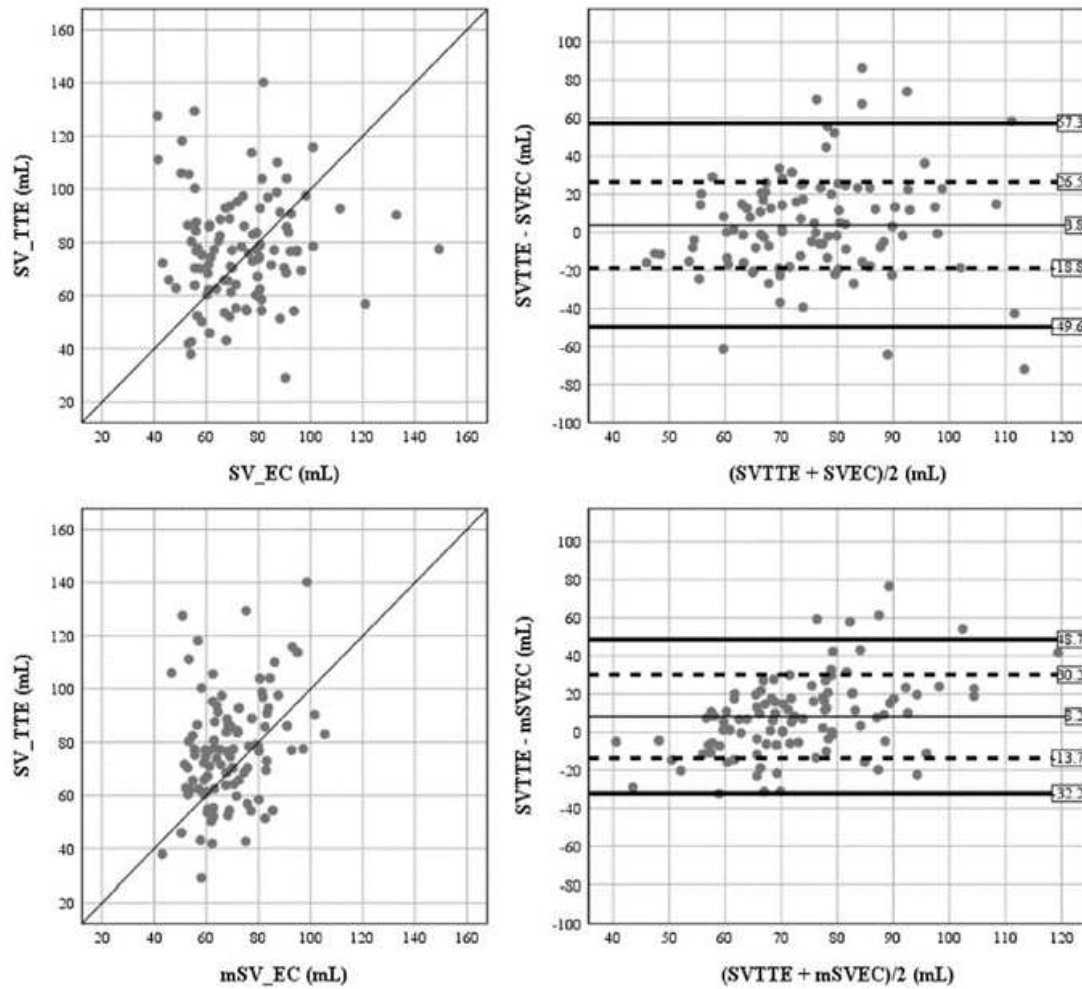
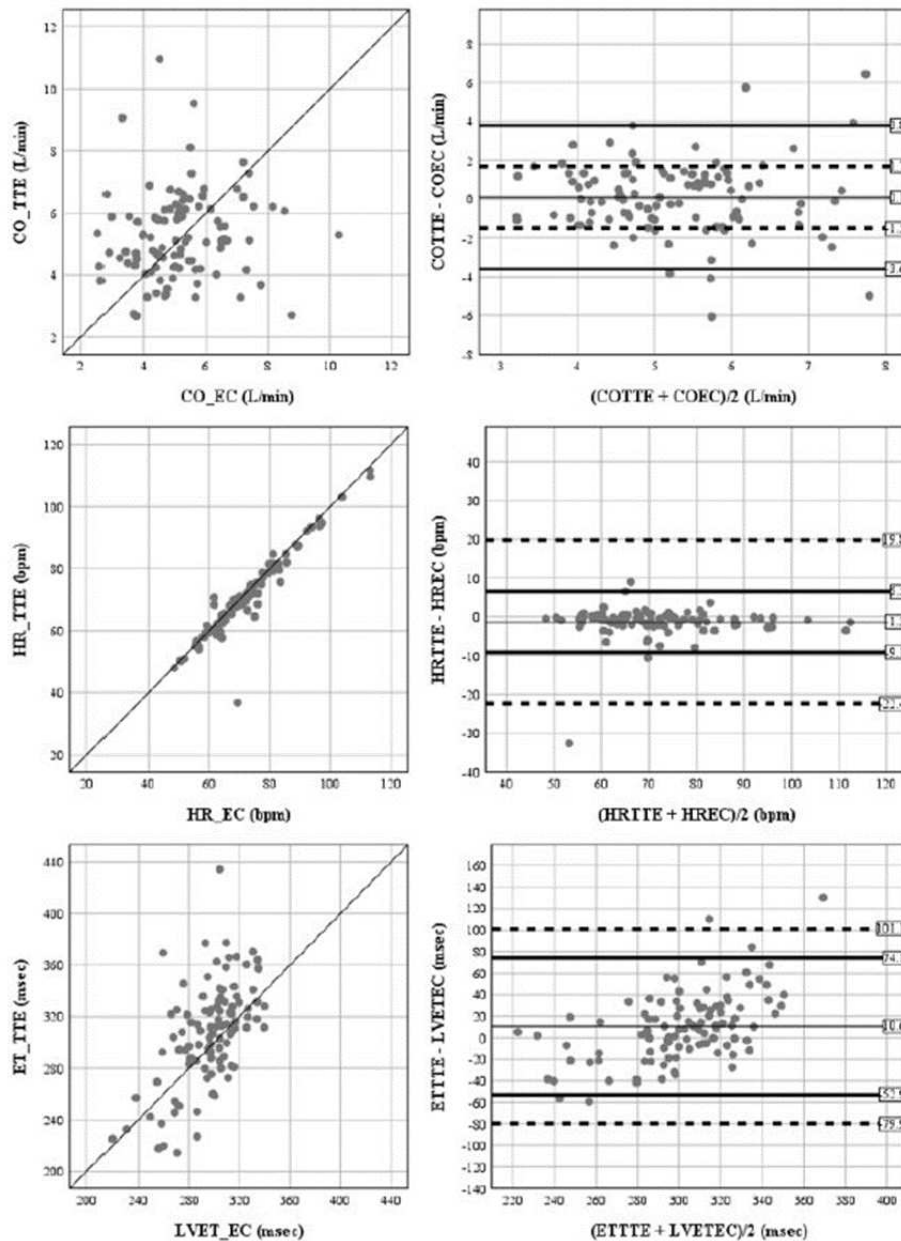


Fig 1 Correlations and Bland Altman plots comparing transthoracic echocardiography (TTE) and electrical cardiometry (EC) regarding stroke volume (SV; Fig. A and B, respectively) and modified SV (Fig. C and D, respectively). While modified SV_{EC} significantly correlated with SV_{TTE} (Fig. C; $r=0.304$, $p=0.002$), SV_{EC} did not (Fig. A; $r=0.027$, $p=0.784$). In Fig. B and C, the thin line presents the bias, thick lines the 95% limit of agreement, and dashed lines the 30% limit of agreement. Bland Altman analysis revealed a mean percentage error of 70.8% and 55.2% with SV and modified SV, respectively.

224 Correlations and Bland Altman plots regarding CO, HR, and ET obtained from TTE and
225 EC measurements are shown in Figure 2. While HR and ET obtained by EC significantly
226 correlated with TTE (Table 2; Fig. C and Fig. D, respectively), CO did not (Table 2; Fig.
227 A). The two mean percentage errors below the clinically acceptable level of 30% were
228 HR with 11.1% and ET with 21.1%; while the mean percentage errors of CO was 71.6%.
229



230

231 **Fig 2** Correlations and Bland Altman plots comparing transthoracic echocardiography
 232 (TTE) and electrical cardiometry (EC) regarding cardiac output (CO; A and B,
 233 respectively), heart rate (HR; C and D, respectively), and envelope time (ET; E and F,
 234 respectively). While HR and ET obtained by EC significantly correlated with TTE (Fig.
 235 C: $r=0.950$, $p<0.001$ and Fig. D: $r=0.576$, $p<0.001$, respectively), CO_{EC} did not (Fig. A;
 236 $r=0.093$, $p=0.353$). In Fig. B, C and F, the thin line presents the bias, thick lines the 95%
 237 limit of agreement, and dashed lines the 30% limit of agreement. Bland Altman analysis
 238 revealed a mean percentage error of 71.6%, 11.1%, and 21.1% with CO, HR, and ET,
 239 respectively.

Subgroup analysis

Values obtained with TTE did only significantly correlate between ET and age as well as height, while EC values significantly correlated with age (SV, CO, ET), weight (mSV), height (SV, mSV, CO), and BMI (mSV). Correlations are shown in Table 3.

Table 3 Correlations of transthoracic echocardiography (TTE) and electrical cardiometry (EC) measurements regarding age, weight, height, and body mass index.

Correlation		SV (mL)	mSV (mL)	CO (L/min)	HR (bpm)	ET (ms)
Age (years)	TTE	r=0.028 p=0.782	-	r=-0.062 p=0.534	r=-0.165 p=0.097	r=0.251 p=0.011
	EC	r=-0.303 p=0.002	r=-0.156 p=0.118	r=-0.356 p<0.001	r=-0.166 p=0.095	r=0.224 p=0.023
Weight (kg)	TTE	r=0.128 p=0.199	-	r=0.147 p=0.139	r=0.032 p=0.751	r=-0.159 p=0.111
	EC	r=0.137 p=0.170	r=0.608 p<0.001	r=0.114 p=0.255	r=0.025 p=0.803	r=-0.008 p=0.939
Height (cm)	TTE	r=-0.049 p=0.624	-	r=-0.015 p=0.885	r=0.090 p=0.367	r=-0.297 p=0.002
	EC	r=0.371 p<0.001	r=0.584 p<0.001	r=0.331 p=0.001	r=0.060 p=0.552	r=-0.079 p=0.429
BMI (kg/cm ²)	TTE	r=0.182 p=0.067	-	r=0.185 p=0.062	r=-0.018 p=0.858	r=-0.014 p=0.889
	EC	r=-0.040 p=0.692	r=0.386 p<0.001	r=-0.050 p=0.618	r=-0.013 p=0.894	r=0.040 p=0.692

Abbreviations: BMI, body mass index; CO, cardiac output; ET, envelope time; HR, heart rate; mSV, modified stroke volume; SV, stroke volume.

Analyses of female (n=44) and male (n=58) patients is presented in Table 4 and showed significant moderate correlation between SV_{TTE} and SV_{EC} in females and males, while mSV_{EC} showed a significant strong correlation with SV_{TTE} in males, but not in females. No correlations were detected between CO_{TTE} and CO_{EC}. All other values correlated between TTE and EC measurements.

Table 4 Transthoracic echocardiography (TTE) and electrical cardiometry (EC) measurements of female (n=44) and male (n=58) patients.

	EC	TTE	Correlation
FEMALE	mean±SD median (range)	mean±SD median (range)	correlation coefficient p-value (effect size)
SV (mL)	69.2 ± 17.0 66.1 (41.2 – 121.0)	80.1 ± 20.0	r=-0.307 p=0.043 (moderate)
modified SV (mL)	62.0 ± 9.3 60.7 (43.1 – 87.6)	77.2 (38.0 – 129.4)	r=0.158 p=0.307 (no correlation)
CO (L/min)ds	4.9 ± 1.4 4.7 (2.5 – 8.2)	5.5 ± 1.5 5.3 (2.7 – 11.0)	r=0.078 p=0.615 (no correlation)
HR (beats/min)	71.2 ± 10.2 70.5 (50.5 – 103.8)	69.9 ± 11.1 69.8 (36.8 – 103.0)	r=0.872 p<0.001 (very strong)
Envelope time	<u>LVET_{EC} (ms)</u> 295.7 ± 22.7 297.3 (238.0 – 339.7)	<u>ET_{TTE} (ms)</u> 320.5 ± 32.6 321.8 (257.0 – 434.3)	r=0.371 p=0.013 (moderate)
Device specific outcome	<u>ICON_{EC}</u> 54.8 ± 21.0 50.9 (15.8 – 121.8)	<u>VTI_{TTE} (cm)</u> 24.9 ± 5.5 23.6 (16.7 – 37.6)	r=-0.326 p=0.031 (moderate)
MALE	mean±SD median (range)	mean±SD median (range)	correlation coefficient p-value^a (effect size)
SV (mL)	76.8 ± 19.1 75.9 (43.2 – 149.3)	75.3 ± 20.8	r=0.285 p=0.030 (moderate)
modified SV (mL)	74.6 ± 12.5 72.2 (51.7 – 105.5)	76.3 (29.0 – 140.2)	r=0.562 p<0.001 (relatively strong)
CO (L/min)	5.4 ± 1.4 5.2 (2.6 – 10.3)	5.1 ± 1.3 4.8 (2.7 – 9.5)	r=0.161 p=0.227 (no correlation)
HR (beats/min)	71.1 ± 14.1 68.1 (48.5 – 113.2)	69.7 ± 13.8 67.2 (48.0 – 111.7)	r=0.986 p<0.001 (very strong)
Envelope time	<u>LVET_{EC} (ms)</u> 296.5 ± 24.6 302.2 (219.7 – 339.3)	<u>ET_{TTE} (ms)</u> 296.4 ± 41.6 296.3 (214.3 – 377.3)	r=0.742 p<0.001 (strong)
Device specific outcome	<u>ICON_{EC}</u> 43.1 ± 18.9 40.1 (17.4 – 108.2)	<u>VTI_{TTE} (cm)</u> 20.6 ± 4.9 20.0 (10.3 – 29.8)	r=0.288 p=0.029 (moderate)

Abbreviations: CO, cardiac output; ET, envelope time; HR, heart rate; ICON, index of contractility; LVET, left ventricular ejection time; LVOT, left ventricular outflow tract; SBFV, systolic blood flow velocity; SV, stroke volume; TFC, thoracic fluid content; VTI, velocity time integral.

Bland Altman plots regarding SV and mSV obtained from TTE and EC measurements are shown in Figure 3. The mean percentage error between TTE and EC measurements regarding SV and mSV was lower in males (61.6% and 45.1%, respectively) than in females (78.7% and 57.1%, respectively). However, all mean percentage errors were above the clinically acceptable level of 30%.

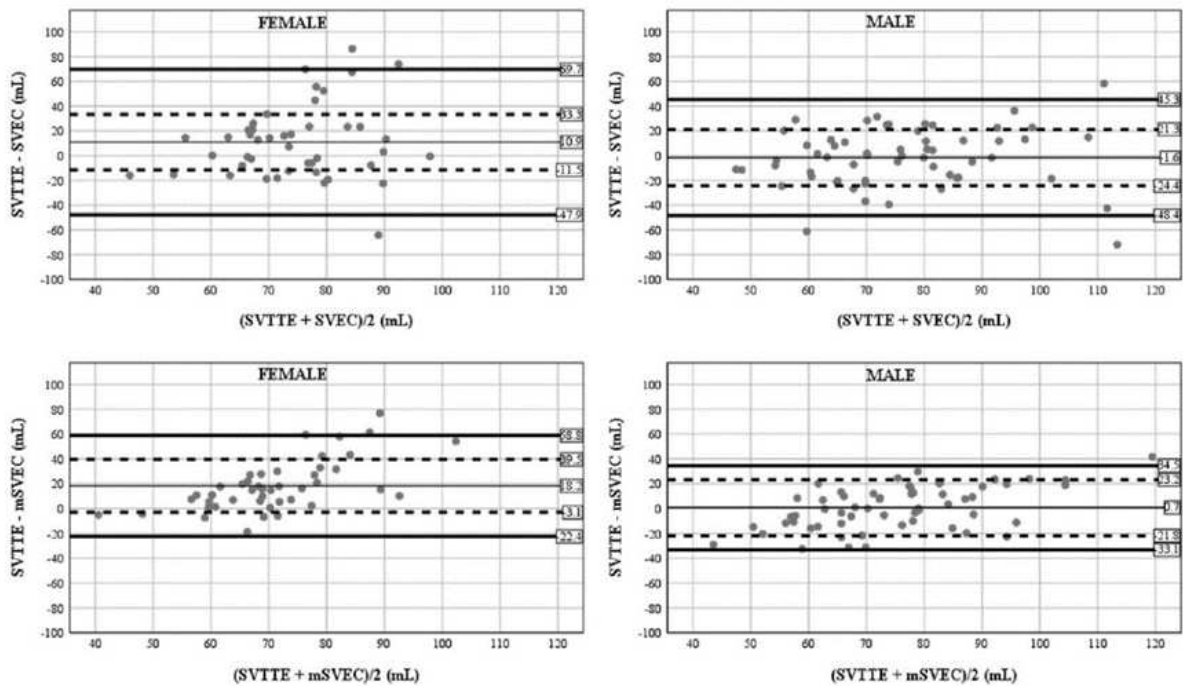


Fig 3 Bland Altman plots of females and males comparing transthoracic echocardiography (TTE) and electrical cardiometry (EC) regarding stroke volume (SV) and modified SV (mSV). The thin line presents the bias, thick lines the 95% limit of agreement, and dashed lines the 30% limit of agreement. Bland Altman analysis revealed a mean percentage error of 78.7% for females and 61.6% for males with SV and of 57.1% for females and 45.1% for males with mSV.

Bland Altman plots regarding CO, HR, and ET obtained from TTE and EC measurements are shown in Figure 4. The mean percentage error for CO and ET between TTE and EC measurements were also higher in females (CO: 75.4%; ET: 20.4%) than in males (CO: 66.2%; ET: 6.7%); while for HR the mean percentage error was higher in males (18.9%) than females (15.0%). However, both, females and males were below the clinically acceptable level of 30% mean PE regarding ET and HR.

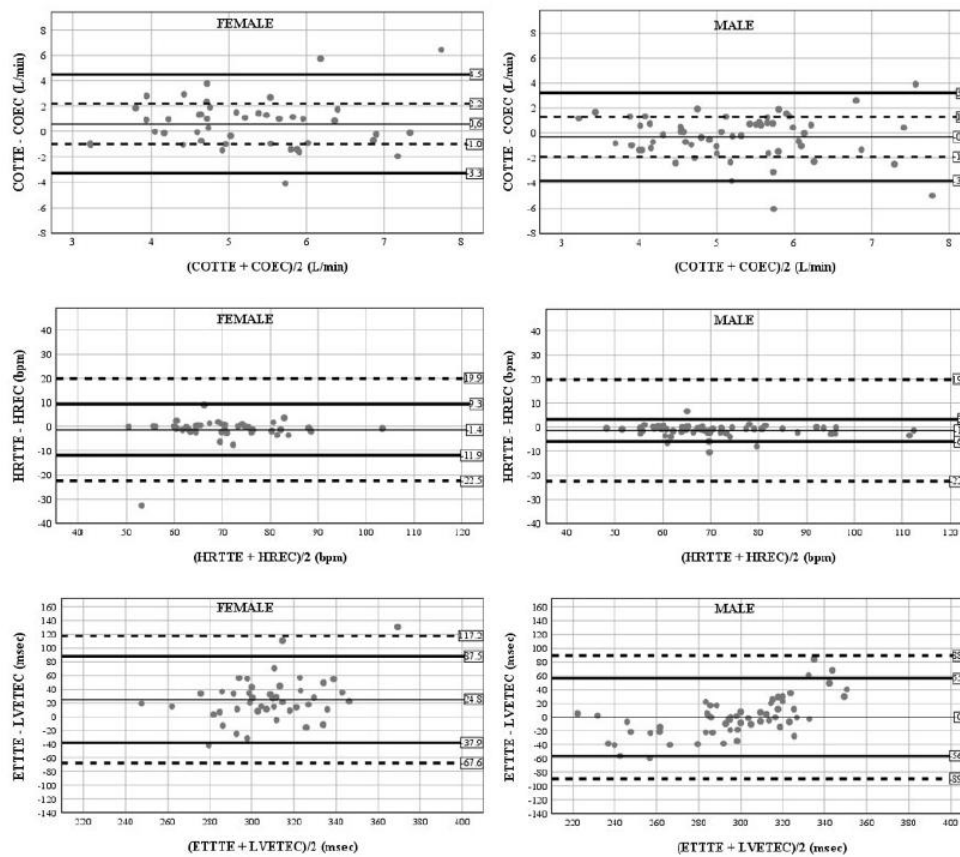


Fig 4 Bland Altman plots comparing transthoracic echocardiography (TTE) and electrical cardiometry (EC) regarding cardiac output (CO), heart rate (HR), and envelope time (ET). The thin line presents the bias, thick lines the 95% limit of agreement, and dashed lines the 30% limit of agreement. Bland Altman analysis revealed a mean percentage error of 75.4% for females and 66.2% for males with CO, 15.0% for females and 18.9% for males with HR, and 20.4% for females and 6.7% for males with ET.

Discussion

In the current study, EC and TTE did not show agreement in terms of SV and CO determination. By applying a calibration formula as proposed by Martin and colleagues in a sample of pregnant women, correlation was improved, but agreement did not reach a clinically acceptable level [13].

The American college of Critical Care Medicine recommends advanced hemodynamic monitoring in managing critically ill patients in the perioperative and intensive care setting, although no detailed recommendation on which invasive or noninvasive devices is given[15, 16]. Explanation for this may lie in the fact that no monitoring system fulfils the demand of an ideal continuous hemodynamic monitoring device [17, 18], which would be noninvasive, easy to handle and interpret, and highly accurate[19]. TTE, and even less TOE, are not to be seen as a monitoring tool in a narrower sense.

In recent years, EC was developed as a very easy to handle, non-invasive and continuous cardiac output measurement device. Electrical cardiometry is approved for advanced hemodynamic monitoring and further hemodynamic parameters in adults, children, and neonates [20, 21].

Several validation studies performed in critically ill pediatric patients demonstrated a high agreement between EC and TTE derived CO-measurements [8, 17, 22, 23]. However, studies performed in adults, and comparing EC technology with pulmonary artery thermodilution or transoesophageal Doppler, resulted in contradicting and inconsistent findings [1, 7, 9, 10, 16, 21, 24-34].

314 Martin and colleagues compared SV parameters derived from EC with TTE in a group of
315 non-laboring pregnant women at 24 weeks or greater gestational age [13]. Apart from
316 excellent correlation in mean LVET and HR, poor absolute agreement in SV measurement
317 with a percentage error of 42% was demonstrated. By applying a calibration formula,
318 agreement improved to a clinically acceptable mean percentage error of 22 %. In our study,
319 comparable in design to that of Martin and colleagues, but with a much more heterogeneous
320 patient sample, correlation between SV measured by TTE and EC was poor. Furthermore,
321 by applying their proposed calibration formula, agreement could not be improved to a
322 clinically acceptable level, unlike the findings in their more homogeneous population. In
323 our study mean percentage error was 58%, which is significantly above the threshold
324 criteria of 30% postulated by Crichley and Crichley for acceptability of agreement with a
325 reference standard [35].

326 In our study, hemodynamic measurements were carried out meticulously following the
327 methodology as described by Martin and colleagues [13]. Transthoracic echocardiography
328 is an approved and accepted hemodynamic monitoring tool in the perioperative setting and
329 its use in clinical practice is recommended by the American Society of Echocardiography
330 (ASE) [36, 37]. Transthoracic echocardiography measurements, which are considered
331 investigator dependent, were performed by a single certified sonographer. Scans were
332 further reviewed by one of two attending physicians certified in echocardiography and
333 blinded to EC measurements.

334 Electrical cardiometry measurements were obtained in the same manner as performed in
335 the study by Martin and colleagues, using the ICON monitor with the placement of the
336 electrodes on the patient's left side[13]. In order to prevent variation in the placement of

EC electrodes, all EC measurements were carried out by the same investigator (MW). To further reduce measurement errors, only EC data with a signal quality index (SQI) of $\geq 70\%$ were assessed, and participants with cardiac arrhythmia were excluded. Therefore, we believe that the inconsistency of our results with those of Martin et al cannot be explained by inaccuracies in hemodynamic measurements.

One possible explanation for our inconsistent findings may lie in the different patient population studied. Martin and colleagues studied a very specific patient cohort of non-laboring pregnant women at 24 weeks or greater gestational age. In contrast, we studied a group of non-pregnant adult outpatients of both sexes undergoing routine diagnostic TTE.

Specifically, one may speculate that the anatomic and physiologic changes of pregnancy could significantly influence thoracic impedance assessed with cardiometry. This includes changes in thoracic and cardiac anatomy, fluid content (lung water), an increase in blood volume, and hemodynamics (increases in CO, SV, HR and a reduction in systemic vascular resistance) [38-40]. Additionally, the presence or absence of breast tissue in a mixed sample of both male and female patients may affect thoracic impedance measurements.

Pregnant women obviously are a unique group of patients who have similarities amongst themselves while at the same time differing greatly as a group from non-pregnant adults of both sexes.

Another source of possible disagreement between the two patient groups is that our patient population may have included more patients with low ejection fractions and low cardiac contractility, which may affect systolic blood acceleration and the ICON parameter, although this possibility was not analyzed in the current trial.

359 To analyze a gender effect, calculations were performed separately in females and males.
360 In the male patient group, mean percentage error improved to 43.9% using the calibration
361 formula. In contrast, in the female patient group, correlation even further deteriorated. As
362 a consequence, contradicting findings to Martin and colleagues cannot be explained by
363 gender. In addition, we hypothesized that discrepancies might be explained by intake of
364 hemodynamically active medications. However, excluding patients taking beta-blockers or
365 antihypertensive agents did not improve measurement agreement.

366 In conclusion, SV and CO measurements obtained with EC did not correlate with
367 measurements obtained with TTE in our patient population. Furthermore, using Martin's
368 technique to calibrate the SV_EC did not meaningfully improve agreement between EC
369 and TTE.

370 Our study did show two areas of agreement with Martin's study: The duration of systole
371 as measured by EC (LVET) had a clinically acceptable percentage error when compared
372 to the Envelope Time (26.4 %) and ICON in both studies was negatively correlated with
373 weight, as had previously been shown[32]. Further research is needed to modify calibration
374 formula suitable in a more generalized non-pregnant population.

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Data availability

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

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