Original Research Article

Validation of Electrical Cardiometry Measurements Compared to Transthoracic Echocardiography in Fluid Responsiveness in Sepsis

Abstract

Background: Severe sepsis and septic shock patients have a broad range of hemodynamic characteristics. Greater understanding of the hemodynamics profile and responding to therapy could contribute to more effective treatment that consequently lowering mortality and morbidity. The current research work was designed to investigate the non-invasive diagnostic accuracy and agreement of electrical cardiometry (EC) with transthoracic echocardiography (TTE) for fluid responsiveness in sepsis.

Methods: This prospective cohort study was assessed on 25 patients showing clinical criteria of sepsis and developed hypotension. All patients were subjected to simultaneous measurement by EC and TTE. Fluid was administered if stroke volume (SV) measured by TTE increased by > 10% after the fluid challenge up to 30 mL/kg else vasopressor infusion started.

Results: EC significantly predicted fluid responsiveness in sepsis compared to TTE with 81.4% sensitivity and 90% specificity. There was an insignificant difference between SV index (SVI), cardiac index (CI), SV, and cardiac output (CO) estimated by TTE and by EC. The mean bias between SV measured by TTE and by EC was 0.25 ± 3.4 ml. The mean bias between TTE and by EC was 0.10 ± 1.78 mL/m^2 in SVI, 0.01 ± 0.35 L/min in CO and 0.009 ± 0.18 L/min/m^2 in CI.

> **Comment [A1]:** Consider the following:
>
> A better understanding of the hemodynamic profile and response to therapy can lead to more effective treatment and consequently a lower mortality and morbidity.

> **Comment [A2]:** Consider:
>
> … was initiated …

> **Comment [A3]:** Do not start a sentence with an abbreviation.

Conclusions: EC significantly predicted fluid responsiveness in sepsis compared to TTE with good agreement between measurements of EC and TTE.

Keywords: Sepsis, Fluid Responsiveness, Electrical Cardiometry, Transthoracic Echocardiography

Introduction:

Sepsis and septic shock are significant disorders that influence millions of individuals around the world each year. Early detection and early management of sepsis enhance better outcomes [1].

Fluid administration is a critical aspect of supportive treatment for sepsis. Recent recommendations for sepsis proposed protocolized strategies to fluid resuscitation, in spite of the absence of solid clinical or physiological data supporting these approaches[2]. In consideration of the risks of both over-and under-resuscitation, it is critical to distinguish individuals who will get benefit from more intravenous fluid treatment after boluses of intravenous fluid. Some of the hemodynamic characteristics of septic shock and severe sepsis patients are very different from one another. As a better result of the understanding of the hemodynamic profile in septic shock as well as the responsiveness to treatments, the mortality, and morbidity of septic shock patients could be reduced[3].

The ultimate hemodynamic monitor should be safe, affordable, non-invasive, simple to be used and evaluate, and capable of continuous, hands-free data collection [4]

The gold standard for measuring stroke volume (SV) is intermittent pulmonary artery catheter (PAC) thermodilution. However, these procedures are invasive and have been associated with health challenges [5].

Transthoracic echocardiography (TTE) is considered the popular non-invasive method; however, it has significant limitations due to the demand for a skilled operator, is technically challenging, and is achieved on an intermittent basis[6].

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Electrical cardiometry (EC) may constantly and non-invasively measure cardiac output (CO) based on thoracic electrical bioimpedance. During the cardiac cycle, the CO assessment was performed by thoracic electrical impedance utilizing the EC strategy that was influenced by erythrocyte orientation and the peak flow velocity in the ascending aorta [7].

We conducted this study to validate EC use for the non-invasive determination of fluid responsiveness compared to TTE in a special category of critically ill patients in whom dynamic fluid responsiveness is of clinical value in the management.

Patients and Methods:

In our prospective cohort observational study, 25 patients aged 19 to 65 years old, of both sexes, with clinical criteria for sepsis and hypotension (mean arterial pressure (MAP) ≤ 65 mmHg) were included. Sepsis was diagnosed by a 2 point elevation in the Sequential Organ Failure Assessment (SOFA) score [8] variables resulting from the infection [MAP 70 mmHg, platelet count 150 X 10^3/l, urine output 0.5 ml/kg/hr, PaO_2/FiO_2 ratio 300, serum creatinine >1.2 mg/dL, Glasgow Coma Scale score <15, serum bilirubin > 1.2 mg/dL].

The patients or their relatives were requested for written informed consent. Our research work was done after the Ethical Committee approval from Tanta University Hospitals (approval code: 33017/03/19) and registration of clinicaltrials.gov (ID: NCT03938220).

Patients with shock for any other reason, preexisting cardiac illness, heart rate greater than 140 beats/min, rhythm other than sinus rhythm, chronic renal failure, and morbid obesity were excluded.

The following investigations were done [complete blood count, C- reactive protein, procalcitonin, serum lactate, liver, and renal function tests, arterial blood gases, electrocardiogram, and blood culture]. Patients with definitively diagnosed sepsis and experienced hypertension underwent simultaneous EC and TTE measurements. Sepsis was

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Comment [A16]: Should be in 'present tense'!!!!~ This the INTRODUCTION and not 'Patients & Methods'. Revise appropriately.

Comment [A17]: Sentences should be arranged into 2 or 3 paragraphs. In doing this, sentences must be appropriately ordered and linked to offer contextual coherence.

Comment [A18]: May also consider:

The study was conducted to validate … … … …

OR

The main aim of the study was to … … …

Comment [A19]: Any reasons for this sample size in this observational study??? How was this sample size arrived at?

The following may be helpful:
Xiaofeng Wang, Xinge Ji, Sample Size Estimation in Clinical Research: From Randomized Controlled Trials to Observational Studies, Chest, Volume 158, Issue 1, Supplement, 2020, Pages S12-S20,

Comment [A20]: It will be good to state the obvious reasons why these tests are necessary.

managed based on the surviving sepsis campaign guidelines in 2016 [9] and its update 2018 [10].

Fluid resuscitation consisted of a 30 ml/kg lactated ringer IV infusion given over the first 3 hours (5 mL/kg/30 min) and was monitored by fluid receptiveness[11] (the patient was considered a fluid responder if SV evaluated by TTE rises by more than 10% following the fluid replacement [11]. If the patient fails to respond to fluids, the infusion of vasopressor (0.05–0.3g/kg/min norepinephrine) was initiated.

Electrical cardiometry:

Measurements were performed using an ICON ® hemodynamic monitoring system (ICON Cardiotronics, Inc., La Jolla, CA 92307; Osyka Medical GmbH, Berlin, and Germany, model C3, Serial no: 1725303). There were four EC sensors used (1st: 5 cm from the base of the neck, 2nd: on the base of the neck, 3rd: lower thorax at xiphoid process level, and 4th: 5 cm down the 3rd electrode at anterior axillary).

Transthoracic echocardiography:

Measurements were carried out using Philips ® (CX50 – Extreme edition) prepared with phased array transducer. The patient was in the supine position.

SV of the left ventricle was estimated through:

a) We measured the left ventricular outflow tract (LVOT) diameter and the aortic valve in the parasternal long-axis view. Then, we freeze the screen at the best aortic valve view during mid-systole (when the valves are wide open), and LVOT was measured at the aortic annulus at the base of the leaflets.

b) LVOT VTI: at the apical five-chamber view, we visualized LVOT and the aortic valve. Next, the pulse wave Doppler gate was placed at the LVOT at the aortic annulus or the base of the aortic valve leaflets. VTI tracing was improved by integrating the pulse wave Doppler

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Comment [A21]: Write-up is not sequential. Section should be re-organised to be sequential.

Comment [A22]: Should be a new paragraph after re-phrasing sentences.

Comment [A23]: Superscript:

ICON®

Comment [A24]: Hemodynamic Monitoring System

Comment [A25]: May consider:

'There were four EC sensors used as follows: …. … '.

Comment [A26]: Consider:

(a) Measurement of the Left Ventricular Outflow Tract (LVOT) diameter and the aortic valve in the parasternal long-axis view. During the procedure, LVOT was measured at the aortic annulus at the base of the leaflets after the screen is frozen at the best aortic valve view during mid-systole.

Comment [A27]: Always make sure these abbreviations are first defined before subsequent appearances in the text.

Left ventricular outflow tract velocity time integral (LVOT VTI) … … …

gate and LVOT as close together as feasible. Then, the outline of one of the systolic waveforms was freezed and traced.

At the same previous view of PW Doppler, we just moved the cursor from one peak of a wave to another, and the machine calculated the HR and CO automatically.

MAP and TTE and EC measurements [SV, cardiac output (CO), cardiac index (CI), and stroke volume index (SVI)] were recorded immediately earlier the fluid resuscitation and every 30 min till MAP > 65 mmHg.

The primary outcome was the diagnostic accuracy of EC in predicting fluid responsiveness. The secondary outcomes were agreements of measurements of EC with TTE.

Sample Size Calculation:

The sample size was computed by MedCalc ® programme version 18.2.1 (MedCalc Software, Ostend, Belgium) as at least 21 patients (at least 7 fluid responder and at least 14 fluid non-responder). The sample size was determined using the subsequent criteria: 0.05 alpha error and a power of 99 %. Depending on a prior study [12], the area under the curve (AUC) for EC's ability to predict fluid responsiveness was 0.927, and the ratio of fluid non-responders to responders was 2:1.

Statistical analysis

SPSS v25 (IBM Inc., Chicago, IL, USA) was utilized for statistical analysis. The mean and standard deviation (SD) described the quantitative data, whereas the frequency and percentage (%) described the qualitative variables. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were used to clarify the diagnostic performance. Agreement: a) Measurements of TTE and EC were compared by paired Student's T test b) Modified Bland Altman plots of TTE and EC measurements were done to calculate the bias and its SD. A two-tailed P value < 0.05 was considered significant.

Results:

Comment [A28]: … … frozen … …

Comment [A29]: See above comment and re-phrase sentences in this section accordingly. Consider:
Left ventricular outflow tract velocity time integral (LVOT VTI) was obtained by tracing the … …

Comment [A30]: This should be moved to the beginning of this section, PATIENTS AND METHODS.

Table 1 shows the patient characteristics and laboratory data of the studied patients.

Mean arterial blood pressure changes for all included subjects are shown in Figure 1

SV and SVI changes measured by TTE and EC for all participants are shown in Figure 2

CO and CI changes measured by TTE and EC for all participants are shown in Figure 3

EC significantly predicted fluid responsiveness in sepsis compared to TTE with 81.4% sensitivity, 90% specificity, 96.6% PPV, and 58.1% NPV.

There was an insignificant difference between SVI, SV, CO, and CI measured by TTE and by EC. Table 2

The mean bias between SV measured by TTE and by EC was 0.25 ± 3.4 mL. The mean bias between SVI measured by TTE and by EC was 0.10 ± 1.78 mL/m^2. The mean bias between CO measured by TTE and by EC was 0.01 ± 0.35 L/min. The mean bias between CI measured by TTE and by EC was 0.009 ± 0.18 L/min/m^2. Figure 4

Discussion

SV may be constantly and non-invasively measured via EC, which utilizes thoracic electrical bioimpedance. The EC principle uses variations in thoracic electrical impedance that is primarily driven by erythrocyte orientation and peak flow velocity in the ascending aorta over the cardiac cycle to estimate SV [13].

In our study, EC significantly predicted fluid responsiveness in sepsis compared to TTE. This was in agreement with Soliman [12], who showed that cut-off 12.5% for delta CO by TTE for prognosis the fluid receptiveness in severe sepsis and hypotension patients with sensitivity 90%, and specificity 70%. Fluid resuscitation (30 ml/kg) was injected, and the response to the fluid was determined as MAP > 65 mmHg with lactate level <4 mmol/L, CO measured by EC, in managing the fluid therapy. However, they didn't compare EC with TTE as in our study.

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Comment [A31]: The authors are advised to consult instructions relating to manuscript preparation of JAMMR, particularly presentation and display of results.

Comment [A32]: Do not start sentences with abbreviations!

Consider:

Stroke volume (SV) …

Comment [A33]: Consider this for the PATIENTS AND METHODS section. Discuss the results obtained in light of the main objective of this study.

Comment [A34]: … did not …

Also, Rajput et al. [14] found that ROC curve between EC and thermodilution by PAC with a cut-off of 15% demonstrates a sensitivity of 84% and specificity of 63% in cardiac surgical patients.

As compared to thermodilution, transesophageal Doppler echocardiography, and cardiac catheterization, EC has been proven to guide CO and other hemodynamic parameters non-invasively, including crucially diseased patients [15, 16], intraoperative settings [14], pregnant women[17], children with congenital heart disease[18], and obese children [19].

In line with our results, Elgebaly et al. [20] reported that the mean bias(limits of agreement) of CO between EC and TTE was 0.01 (–0.68 to 0.70) at preoperative readings but–0.01 (–1.21 to 1.18) at postoperative readings in patients with age ≥18 years scheduled for elective lung surgery.

Also, Malik et al. [21] studied patients requiring PAC implantation by coronary artery surgery. Contemporary CO measurements from EC and thermodilution by PAC were completed at three predetermined time intervals and correlated to one another. Bland and Altman investigation showed a bias of 0.08 L/min, a precision of 0.15 L/min, with a slight limit of agreement (-0.13 to 0.28 L/min), and the percentage error was 3.59%. They determined that the CO agreement between EC and thermodilution by PAC is clinically accepted and could be applied mutually.

Moreover, Rauch et al. [19] demonstrated that the mean bias in CO (limits of agreement) between EC & TTE was 0.015 l/min (−0.91: 1.21 l/min) in obese children and adolescents.

Our results agreed with Schmidt et al., [22]showed that the mean bias in CO between EC & TEE (limits of agreement) was 0.18 (-0.99 to 1.36 l/min) patients planned for coronary artery surgery necessitating TEE monitoring.

In disagreement with our results, Magliocca et al. [23] compared CO estimation by EC to thermodilution by PAC on 19 patients underwent orthotopic liver transplantation. CO

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measurements were collected at 5-time points: (T1) PAC insertion; (T2) surgical incision; (T3) portal reperfusion; (T4) hepatic arterial reperfusion; and (T5) abdominal closure. Although TDCO increased at T3-T5, EC was ineffective in tracking the variations of CO with adequate accuracy and precision. The mean bias (±SD) of EC was −3.3 L/min (±2.8 L/min), and the percentage error was 77%. They revealed that EC had less accuracy and precision than thermodilution during OLT, despite its good trending ability. This difference may be due to the different types of patients (OLT in their study). The inaccuracy of EC is specifically large when SVR and arterial elastance were diminished throughout the neohepatic phase.

Our results were contrary to Martin et al. [17], who validated EC in pregnant patients compared to TTE on 44 non-laboring, resting pregnant women. SV by EC had a mean bias of -0.83 mL and a mean percentage error of 22 % compared to TTE. They concluded that the bias and mean percentage error of SV and CO were excessively high. This difference may be due to the different populations (pregnant women in their study).

Moreover, Raue et al. [24] indicated that the mean bias in CO measured concurrently by EC and thermodilution PAC was -0.3 l/min in patients with sepsis with hemodynamic instability or severe systemic inflammatory response syndrome, with frequent limits of agreement (-4.1:3.5 l/min). They concluded that EC could not replace PAC. This difference may be due to different hemodynamic conditions [most patients were on inotropic support (90%) and on mechanical ventilation (96.7%)].

Mekis et al. [25] were in contrast to our results. CO levels were determined concurrently with EC and thermodilution PAC in patients prior to and shortly following coronary artery bypass graft surgery, as well as in the ICU. The agreement was clinically acceptable only before skin incision (mean bias was 0.04 ± 0.41 L/min, and the mean error was 25%) while, it was unacceptably high immediately following skin closure (the mean bias was 0.57 ± 0.92 L/min,

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Comment [A41]: Re-phrase or revise completely. Authors may employ the services of an on-line proof-reading resource to assist in the language structure of the manuscript.

Comment [A42]: ... ... to those of ... ...

Comment [A43]: Did you have identical population demographics? Was your population a 'pregnant' population? Explain to rationalize the context.

Comment [A44]: Re-phrase or revise!

Comment [A45]: Consider:
The results of Mekis et al. were in contrast to our results.

Comment [A46]: Abbreviations do not begin a sentence!

and the mean error was 42%) and at a borderline level in the ICU (the mean bias was 0.26 ± 0.68 L/min, and the mean error was 32%). Thus, the overall accuracy is not clinically unacceptable. In their study, the thoracic fluid index recorded a statistically significant elevation, whereas the hemoglobin showed an immediate significant drop subsequent to skin closure. Also, this could be due to thermal noise' rises following cardiopulmonary bypass [26]. Moreover, Heringlake et al. [27] showed a bias in CO between PAC and EC of −0.4 L/min and 0.4 L/min and a precision of 3.2 and 3.6 L/min (34.3% and 67.4%) after anesthesia and ICU admission, respectively in patients undergoing elective cardiac surgery with cardiopulmonary bypass and moderate hypothermia. This difference may be due to the different types of patients in their study.

> **Comment [A47]:** Revise/re-phrase completely!!!

Limitations: The sample size was relatively limited. The study was in a single center. The follow-up of patients was limited for a relatively short period. We excluded rhythm other than sinus rhythm or HR > 140 beats/min, chronic renal failure, and earlier cardiac disease. We didn't evaluate the role of hypothermia in bias between the two techniques.

> **Comment [A48]:** What are the requirements for the optimum population/sample size in a study of this nature??? Why only one single medical centre??

> **Comment [A49]:** Any reasons for these exclusions?? This reviewer does not find any discussion to the effect of these exclusions on the study carried out. This is important to do.

Conclusions:

EC significantly predicted fluid responsiveness in sepsis compared to TTE with 81.4% sensitivity, 90% specificity, 96.6% PPV, and 58.1% NPV. Measurements of EC showed good agreement with measurements of TTE.

> **Comment [A50]:** ?????

> **Comment [A51]:** Be very clear! Sensitivity, Specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) were computed but wat is the discussion to indicate this??? Any Gold Standard comparator?
> No 'M x N' matrix table to show the computation of the above performance values and no detailed discussions about their significance.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest

between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

Comment [A52]: Re-write in the correct grammar and in the correct format!
Consider:
'The authors declare that there are no competing interests.'

The authors are advised to consult manuscript preparation instructions of JAMMR.

14. Rajput RS, Das S, Chauhan S, Bisoi AK, Vasdev S. Comparison of Cardiac Output Measurement by Noninvasive Method with Electrical Cardiometry and Invasive Method with Thermodilution Technique in Patients Undergoing Coronary Artery Bypass Grafting. World J Cardiovasc Surg. 2014;4:123-30.

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19. Rauch R, Welisch E, Lansdell N, Burrill E, Jones J, Robinson T, et al. Non-invasive measurement of cardiac output in obese children and adolescents: comparison of electrical cardiometry and transthoracic Doppler echocardiography. J Clin Monit Comput. 2013;27:187-93.

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24. Raue W, Swierzy M, Koplin G, Schwenk W. Comparison of electrical velocimetry and transthoracic thermodilution technique for cardiac output assessment in critically ill patients. Eur J Anaesthesiol. 2009;26:1067-71.

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27. Heringlake M, Handke U, Hanke T, Eberhardt F, Schumacher J, Gehring H, et al. Lack of agreement between thermodilution and electrical velocimetry cardiac output measurements. Intensive Care Med. 2007;33:2168-72.

Comment [A53]: This section must be revised and re-written.

The authors are advised to consult manuscript preparation instructions of JAMMR in order to adopt the appropriate referencing style.

Table 1: Patients characteristics and laboratory investigations of all subjects (n = 25)

Patient characteristics		
Age (years)		44.76 ± 9.18
Sex	Male	13 (52%)
	Female	12 (48%)
BMI (kg/m^2)		29.32 ± 4.51
Laboratory investigations		
Hb (gm/dL)		10.96 ± 1.62
Platelet count ($*10^3$ cells/dL)		257.6 ± 71.02
TLC ($*10^3$ cells/dL)		15.12 ± 1.79
CRP (mg/L)		82.08 ± 21.65
Lactate (mmol/L)		3.89 ± 1.31
pH		7.22 ± 0.07
PaO$_2$ (mmHg)		101.92 ± 10.48
PaCO$_2$ (mmHg)		31.88 ± 3.32
HCO$_3$ (mEq/L)		13.2 ± 2.8

Data are presented as mean $\pm$ SD or frequency (%). BMI: Body mass index, Hb: hemoglobin, TLC: total leucocytic count, CRP: C-reactive protein, PaO$_2$: arterial oxygen tension, PaCO$_2$: carbon dioxide tension

Table 2: Difference between SV (mL), SVI (mL/m^2), CO (L/min) and CI (L/min/m^2) measured by transthoracic echocardiography and by electrical cardiometry (EC)

	Measured by TTE	Measured by EC	P value
SV	77.12±15.88	77.92±15.82	0.703
SVI	40.03±8.63	40.44±8.59	0.717
CO	8.23±1.45	8.33±1.48	0.620
CI	4.26±0.75	4.31±0.76	0.622

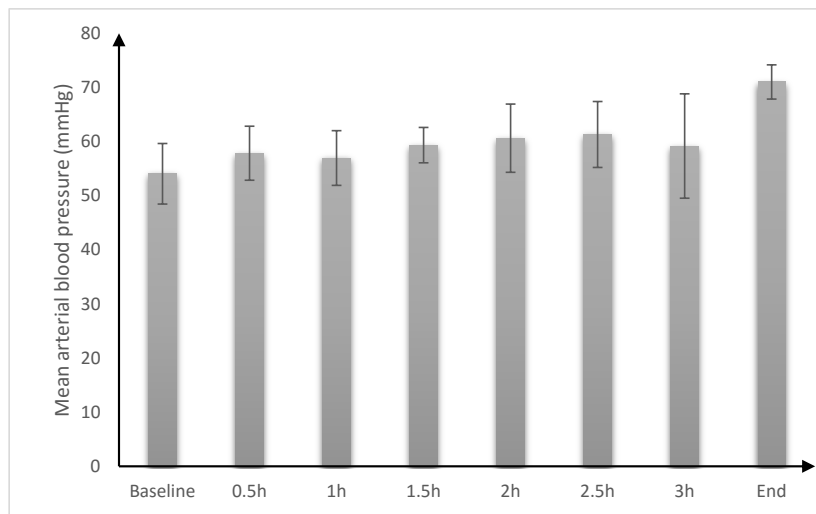SV: Stroke volume, SVI: Stroke volume index, CO: Cardiac output, CI: Cardiac index

Figure 1: Mean arterial blood pressure (mmHg) variations of the studied patients

(A)

(B)
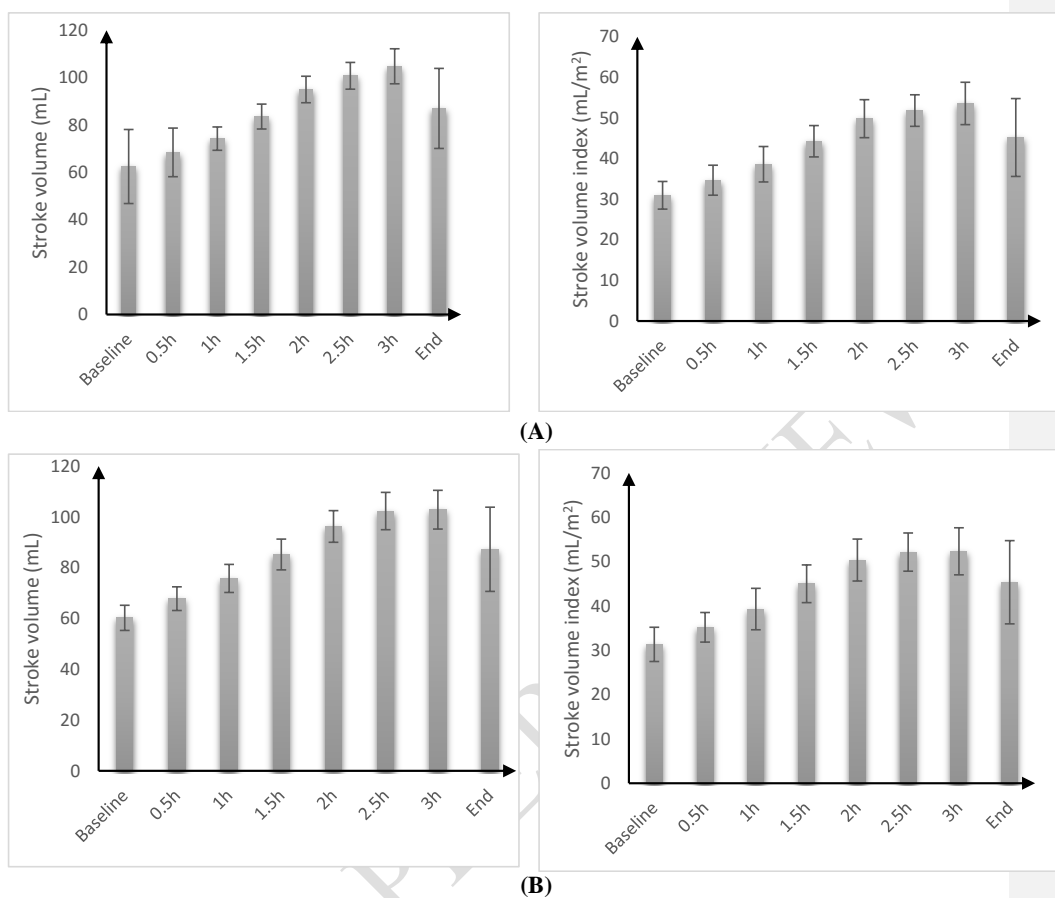
Figure 2: Stroke volume and stroke volume index changes measured by (A) transthoracic echocardiography and by (B) electrical cardiometry of the studied patients
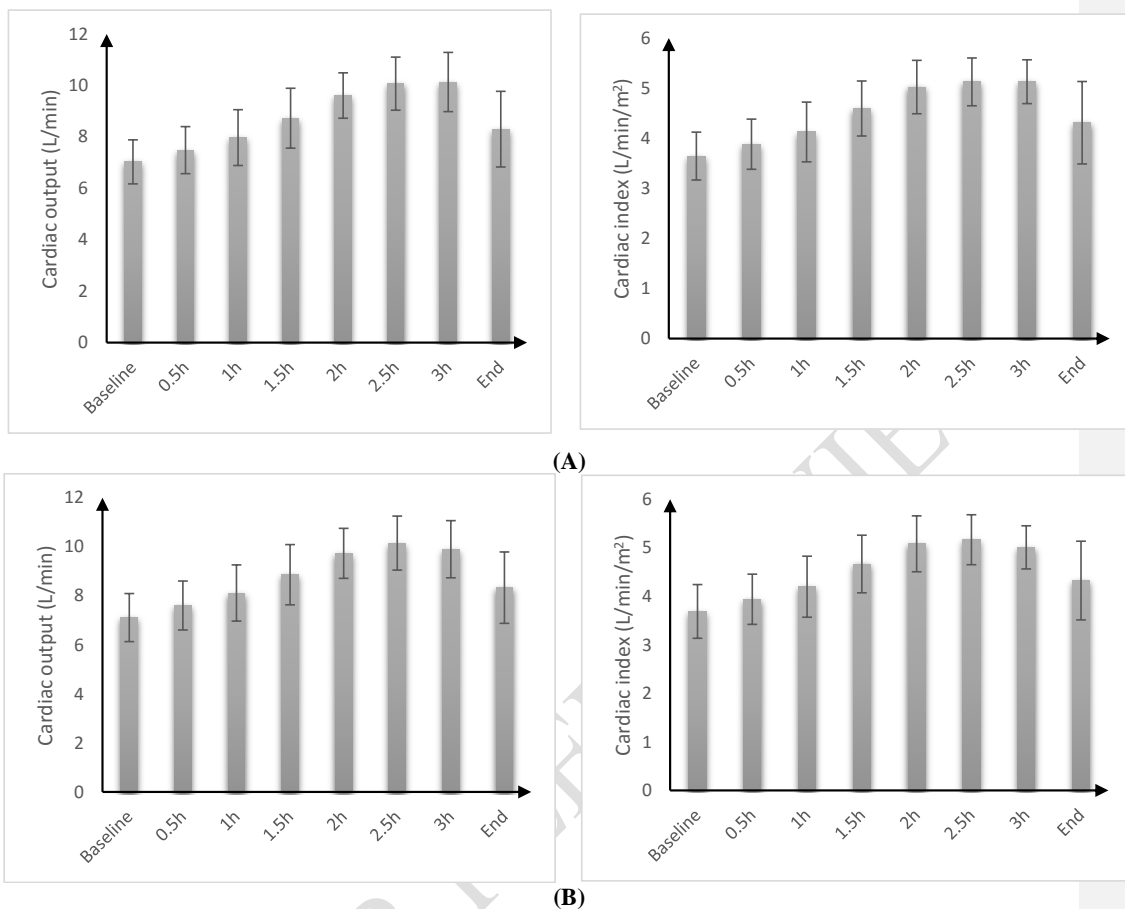
(A)

(B)

Figure 3: Cardiac output and cardiac index changes measured by (A) transthoracic echocardiography and (B) electrical cardiometry of the studied patients
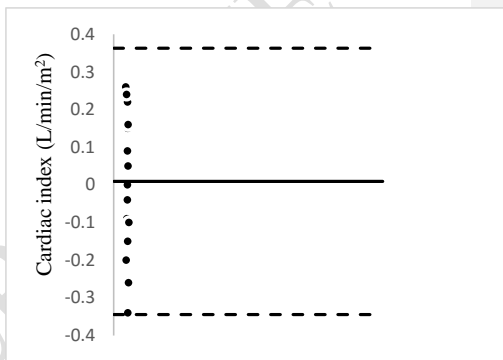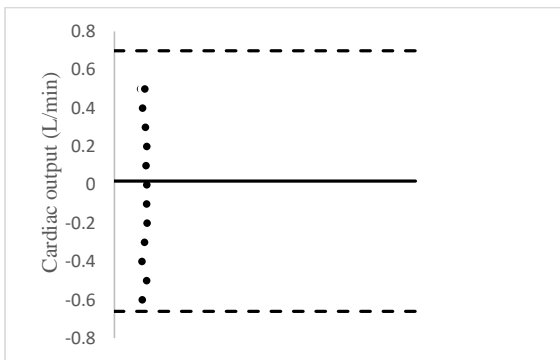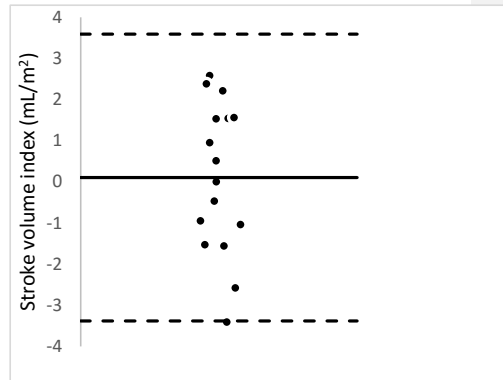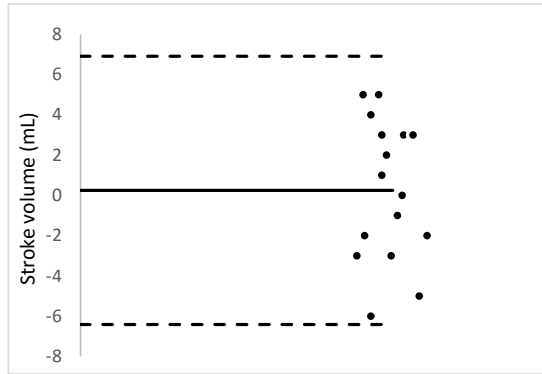
Figure 4: (A) Agreement between stroke volume, (B) stroke volume index, (C) cardiac output and (D) cardiac index measured by transthoracic echocardiography and by electrical cardiometry