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RESEARCH

FoCUS and non-invasive hemodynamics monitoring in neonatal sepsis

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Abstract

Sepsis is one of the most encountered pathologies in the neonatal intensive care unit (NICU) and is associated with significant morbidity and mortality, especially in preterm neonates. In this study, we aimed to assess early hemodynamic status in preterm neonates diagnosed with sepsis by electrical cardiometry and compare its utility to functional echocardiography in NICU. This is a case–control prospective observational study that enrolled 70 septic preterm neonates (34 0/7 to 36 6/7 weeks gestational age) who were admitted to Tanta University NICU and met the criteria for diagnosis of neonatal sepsis; meanwhile, cases with septic shock were excluded. A non-sepsis group of 70 newborns matched for gestational age and sex was included as a control group. Bedside focused cardiac ultrasound (FoCUS) and electrical cardiometry monitoring were performed on the 2nd day of the clinical diagnosis of sepsis. Stroke volume (SV), cardiac output (CO), and cardiac index (CI) measurements by both echocardiography and electrical cardiometry were significantly higher in the sepsis group compared to the non-sepsis group. Systemic vascular resistance (SVR) and systemic vascular resistance index (SVRI) were significantly lower in the septic group compared to the non-sepsis group. Correlations between electrical cardiometry and focused cardiac ultrasound parameters were significantly positive regarding SV, CO, CI, SVR, and SVRI in all the studied groups.
Conclusions: Electrical cardiometry could be considered a useful and promising tool for early assessment of hemodynamics in preterm neonates with sepsis coinciding with echocardiography.

What is Known:
- *Preterm infants diagnosed with sepsis can develop cardiovascular instability due to the unique features of their cardiovascular function and reserve.*
- *Prompt identification of patients with progression of sepsis severity may be accomplished through frequent clinical assessments and monitoring of the changes in their physiological indices (heart rate, BP, urine output, capillary refill time, and neurologic status) and biochemical variables (blood gas, lactate, electrolytes, and creatinine).*

What is New:
- *Electrical cardiometry could be considered a useful and promising tool for the early assessment of hemodynamics in preterm neonates with sepsis coinciding with echocardiography.*

Keywords Neonatal sepsis · Electrical cardiometry · Focused cardiac ultrasound

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Abbreviations

ASD	Atrial septal defect
CI	Cardiac index
CO	Cardiac output
EC	Electrical cardiometry
ECG	Electrocardiogram
FoCUS	Focused cardiac ultrasound
GA	Gestational age
Hb	Hemoglobin
HR	Heart rate
I/T	Immature/total ratio
IDM	Infant of diabetic mother
IUGR	Intra-uterine growth restriction
MBP	Mean blood pressure
NICU	Neonatal intensive care unit
PDA	Patent ductus arteriosus
PFO	Patent foramen ovale
PLT	Platelets count
SV	Stroke volume
SVR	Systemic vascular resistance
SVRI	Systemic vascular resistance index
TLC	Total leukocytes count

Introduction

Neonatal sepsis is a systemic infection occurring in infants ≤ 28 days of life, and it is an important cause of morbidity and mortality of newborns. Moreover, studies have shown an increased rate of neonatal infection in association with lower gestational age and lower birth weight [1, 2].

The neonatal cardiovascular response to sepsis varies from that perceived in older children and adults and may result in a hyperdynamic or a hypodynamic circulation. Sepsis-induced cardiovascular dysfunction includes myocardial dysfunction and vasoregulatory failure that could lead to systemic vasodilation or vasoconstriction [3].

Functional echocardiography is a non-invasive method for assessing myocardial function and hemodynamic parameters as the cardiac output (CO) in infants. However, it is operator-dependent and requires a specific technique. Electrical cardiometry (EC) is a feasible bedside non-invasive tool that measures thoracic electrical bioimpedance (TEB) and hemodynamic parameters such as stroke volume (SV) and cardiac output (CO), contractility (expressed as contractility index, ICON), systemic vascular resistance (SVR), and thoracic fluid content [4].

This study aimed to assess early hemodynamic status in septic preterm neonates by using electrical cardiometry and comparing its utility to functional echocardiography in the NICU. We hypothesized that electrical cardiometry could facilitate continuous bedside hemodynamic monitoring in septic preterm infants and help in the early management of any instability.

Methods

This case–control prospective observational study was conducted in the NICU of Tanta University Hospitals after it was approved by the local ethical committee of The Faculty of Medicine, Tanta University (No. 33069/04/19). Written parental consent was obtained prior to cases enrollment. The study included 70 preterm newborns (gestational age ranged from 34 0/7 to 36 6/7 weeks calculated from the first day of the last normal menstrual period and by using the New Ballard score [5]) who met the diagnostic criteria of neonatal sepsis, as defined by Haque [6]. A control group or a non-sepsis group of 70 healthy neonates, matched for gestational age and sex, was also enrolled. The study was conducted over a 2-year duration. Exclusion criteria included neonates with intra-uterine growth restriction (IUGR), infant of diabetic mother (IDM), infants with major congenital anomalies or structural heart diseases, neonates with evidence of perinatal asphyxia with Apgar score < 5 at 5 min, neonates with skin lesions and inability to tolerate adhesive skin leads, neonates with hydrops fetalis, cases on high frequency mechanical ventilation, surgical cases, and infants with septic shock.

The study was conducted in accordance with the Helsinki Declaration. The manuscript was prepared following STROBE guidelines [7].

All the enrolled neonates underwent full history taking and thorough clinical examination.

Echocardiography

The first echocardiographic assessment included a full morphologic and hemodynamic assessment of cardiac anatomy and physiology by using a segmental approach [8].

Assessment was performed based on the American Society of Echocardiography guidelines [9] and by using Vivid 7, GE Healthcare, Horten, Norway, to get all the important cardiac views including the standard apical, parasternal, and subcostal views so as to obtain all the quantitative and qualitative parameters.

These parameters included the left ventricle outflow tract area (LVOT) and the velocity time integral (VTI) of aortic blood flow, and both were used to calculate stroke volume (SV) (SV = VTI × LVOT area), cardiac output (CO) (CO = SV × heart rate), cardiac index (CI) (CI = CO/body surface area), systemic vascular resistance (SVR) (SVR = 80 × [Mean Arterial Pressure(MAP)-Central Venous Pressure(CVP)]/CO), and systemic vascular resistance index (SVRI) (SVRI = SVR × BSA) [10, 11].

Electrical cardiometry (EC)

Hemodynamic status was assessed using bedside electrical cardiometry in comparison with echocardiography on the 2nd day of the clinical sepsis diagnosis. A portable handheld EC monitor, routinely applied in our clinical activity (ICON®, Osypka, San Diego-CA, USA), was used according to the manufacturer's recommendations. Briefly, a high frequency and low amperage current is released through the thorax by two skin electrodes (placed on the forehead and the left thigh); two other electrodes were placed (the left side of the neck and thorax) as far as possible from conventional electrocardiography (ECG) electrodes to receive the signal modified by thoracic impedance. Changes in the impedance are correlated to the ECG captured at the same time [12]. The EC device was connected to the sensor cable, and individual patient data including age, sex, length, weight, non-invasive blood pressure, heart rate (HR), oxygen saturation (SPO2), and hemoglobin level (Hb) were input. The device then continuously displayed the hemodynamic parameters as CO, CI, SV, SVR, and SVRI [13].

EC assessment was performed to all the enrolled neonates in the supine position and during sleep when possible to reduce undesired movements and agitation. Phototherapy, when applied, was discontinued temporarily during this assessment.

Study outcomes

- Primary outcomes were to
  - assess the early hemodynamic status in healthy preterm neonates by electrical cardiometry and FoCUS;
  - assess the early hemodynamic status in preterm neonates diagnosed as sepsis by electrical cardiometry and FoCUS
- Secondary outcomes were to
  - evaluate the utility of EC monitoring by comparing the results obtained by its use and FoCUS measurements in septic and healthy preterm neonates.

Statistical analysis

Sample size was calculated with a confidence level of = 95% and a power of 80%. Based on a previous study [14], the sensitivity of echocardiography to evaluate cardiac output and cardiac abnormality, as compared with gold standard investigations, is approximated to be 90% among the healthy preterm neonates and the sensitivity of echocardiography expected to be 70% among the septic preterm neonates (due to expected limitations); the least sample size for both of the cases and control groups was ($N = 70$).

Statistical analysis was performed with the Statistical Package for the Social Sciences version 20.0 (SPSS Inc., Chicago, IL, US). Continuous data are presented as mean ± standard deviation or median (interquartile 25–75) for non-normally distributed variables, whereas discrete data are given as absolute values and percentages. Group means of the continuous variables were compared with Student's t-test. Continuous variables were compared between day 2 of sepsis and the last day before discharge using paired samples t-test or Wilcoxon's rank-sum test when appropriate. Categorical variables were compared with chi-squared test or the Fisher exact test when appropriate. Correlations were assessed using Pearson's correlation test. A p-value of < 0.05 was considered statistically significant with a confidence interval of 95%. For agreement, Bland–Altman plot and one sample t-test were used (echo and EC) (if significant, then there is fixed bias).

Results

No statistically significant difference was found between both groups regarding sex, gestational age, postnatal age, and mode of delivery. However, weight and body surface area (BSA) were significantly lower in the sepsis group than the non-sepsis group. Additionally, SPO2/FIO2 ratio was significantly lower in the septic group while serum lactate level was significantly higher in those septic neonates (Table 1).

Cardiac output (CO), stroke volume (SV), and cardiac index (CI), measured by both echocardiography and electrical cardiometry, were significantly higher in the sepsis group than in the non-sepsis group. Meanwhile, systemic vascular resistance (SVR) and systemic vascular resistance index (SVRI) were significantly lower in the sepsis group than in the non-sepsis group, measured with both echocardiography and electrical cardiometry (Table 2).

In the sepsis group, measurements obtained by electrical cardiometry (EC) including stroke volume (SV), cardiac output (CO), cardiac index (CI), systemic vascular resistance (SVR), and systemic vascular resistance index (SVRI) showed a statistically significant positive correlation with the corresponding parameters assessed by FoCUS, as shown in Figs. 1, 2, 3, 4, and 5.

Agreements were calculated by the Bland–Altman analysis (inserted as an online supplement).

Table 1 Comparison between the two studied groups according to different parameters

	Sepsis (n = 70)	Non-sepsis (n = 70)	p
Sex			
Male	36 (51.4%)	30 (42.9%)	0.310
Gestational age (weeks)			
Mean ± SD	35.2 ± 0.8	35.3 ± 0.9	0.545
Post natal age (days)			
Mean ± SD	8.9 ± 5.2	8.6 ± 5	0.751
5-APGAR (min)			
Median (Min.–max.)	10 (9–10)	10 (9–10)	0.612
Weight (kg)			
Mean ± SD	2.4 ± 0.3	2.6 ± 0.3	0.001*
BSA (kg/m$^{2)}$			
Mean ± SD	0.2 ± 0	0.2 ± 0	0.003*
Temp (°C)			
Mean ± SD	36.7 ± 0.6	37 ± 0.1	< 0.001*
Respiratory rate (c/min)			
Mean ± SD	57 ± 4.2	43 ± 4.9	< 0.001*
Heart rate (b/min)			
Mean ± SD	155.6 ± 17	143.9 ± 6.9	< 0.001*
SBP (mmHg)			
Mean ± SD	61.7 ± 8.5	65.5 ± 5.8	0.011*
DBP (mmHg)			
Mean ± SD	36.8 ± 10.8	42 ± 4.3	0.005*
SPO2/FIO2 ratio			
Mean ± SD	367.9 ± 63.59	470.6 ± 49.9	0.000
Serum lactate (mmol/L)			
Mean ± SD	0.72 ± 0.39	0.44 ± 0.29	0.000

BSA body surface area, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *MBP* mean blood pressure, *SPO2* oxygen saturation, *FIO2* fraction of inspired oxygen, *SD* standard deviation, *p*: *p*-value for comparing between the two studied groups

*Statistically significant at $p \leq 0.05$

Discussion

Many infants with sepsis develop cardiovascular instability; preterm infants are particularly vulnerable due to the unique features of their cardiovascular function and reserve [15].

Characterization of sepsis-related cardiovascular dysfunction has been traditionally based on the clinical patterns identified by bedside physical examination, typically dichotomized as warm and cold shock physiology [16].

The hemodynamic status of sick newborn infants is often assessed by clinical variables such as heart rate, blood pressure, and capillary refill time, which have been demonstrated to be misleading in their accuracy [17].

Early recognition of cardiovascular compromise in sick infants enables the physician to take timely therapeutic decisions and monitor response to treatment more objectively [18].

Bedside echocardiography is an ideal method for monitoring hemodynamic assessment in neonates. It can assess cardiac function, preload, afterload, and cardiac output [19].

Electrical cardiometry (EC) has been proposed as a safe, accurate, and reproducible technique for hemodynamic measurement in children and infants [20].

EC measures alteration in thoracic resistance or impedance using four skin electrodes. EC is able to isolate the changes in impedance created by the circulation, partly caused by the change in orientation of the erythrocytes during the cardiac cycle [21].

In this study, our aims were to assess the early hemodynamic status and cardiac performance in healthy preterm neonates (non-sepsis group) and in the sepsis group by electrical cardiometry in comparison to echocardiography.

In the current study, there was no statistically significant difference between both groups regarding sex, weight, gestational age, postnatal age, mode of delivery, SPO2/FIO2 ratio, and serum lactate level.

Table 2 Comparison between the two studied groups according to echo and EC

		Sepsis ($n = 70$)	Non-sepsis ($n = 70$)	p
SV (ml)	**Echo**			
	Mean ± SD	3.591 ± 0.849	3.107 ± 0.454	< 0.001*
	EC			
	Mean ± SD	3.577 ± 0.882	3.126 ± 0.451	< 0.001*
CO (L/min)	**Echo**			
	Mean ± SD	0.554 ± 0.145	0.441 ± 0.055	< 0.001*
	EC			
	Mean ± SD	0.553 ± 0.151	0.443 ± 0.055	< 0.001*
CI (L/min/m^2)	**Echo**			
	Mean ± SD	3.301 ± 0.891	2.482 ± 0.251	< 0.001*
	EC			
	Mean ± SD	3.297 ± 0.927	2.489 ± 0.252	< 0.001*
SVR (dyn-s/cm$^{5)}$	**Echo**			
	Mean ± SD	6548.7 ± 2289	8547.5 ± 1019.8	< 0.001*
	EC			
	Mean ± SD	6672.9 ± 2577.6	8533.4 ± 1026.3	< 0.001*
SVRI(dyn-s/cm^5)/m^2	**Echo**			
	Mean ± SD	1102.5 ± 370.7	1523.8 ± 232.3	< 0.001*
	EC			
	Mean ± SD	1122.6 ± 433	1519.2 ± 220.2	< 0.001*

SV stoke volume, *CO* cardiac output, *CI* cardiac index, *SVR* systemic vascular resistance, *SVRI* systemic vascular resistance index, *SD* standard deviation, p: p-value for comparing between the two studied groups

*Statistically significant at $p \leq 0.05$

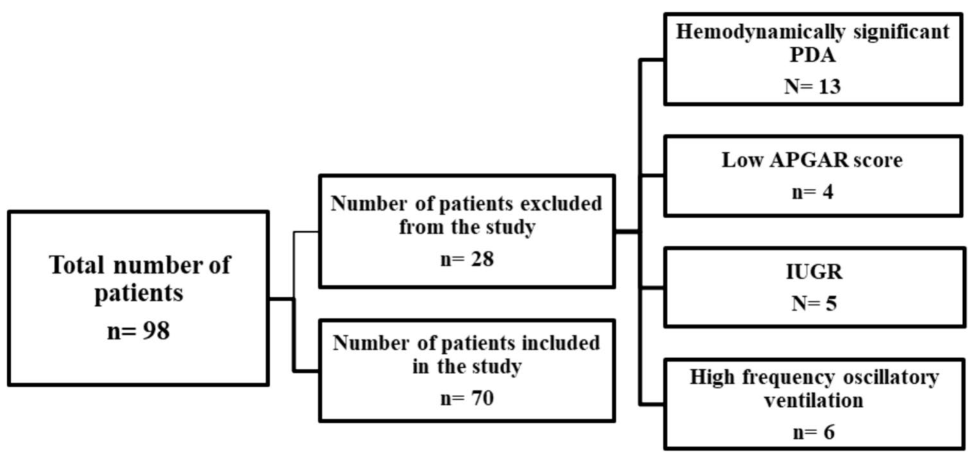

Fig. 1 Correlation between echo and EC parameters in each sepsis group ($n = 70$). SV (ml) correlation (r: 0.935; $p < 0.001$*). SV, stoke volume. r_s: Spearman coefficient; *Statistically significant at $p \leq 0.05$

Mean blood pressure is commonly used in the NICUs as a simple, continuous, bedside measure of adequate perfusion in a neonate. This facilitates monitoring hemodynamics and response to treatment. However, it is limited by the lack of robust normative values in both term and preterm babies [22].

The heart rate was higher in the sepsis group. This could be explained by sympathetic dysfunction, as both overactivation and downregulation have been described in sepsis. Activation of the adrenergic system in sepsis, which is important for a physiological response to infection, if excessive, may result in overproduction of catecholamines that leads to tachycardia [23].

Stroke volume and cardiac output values of the healthy preterm neonates enrolled in this study came in agreement with Boet et al. [24], while the mean values of SV, CO, and CI in the sepsis group (3.6 ± 0.8 ml, 0.6 ± 0.1 L/min, 3.3 ± 0.9 L/min/m^2 respectively measured with FoCUS, and 3.6 ± 0.9 ml, 0.6 ± 0.2 L/min, 3.3 ± 0.9 L/min/m^2 by EC) were significantly higher compared to the same parameters levels obtained from the neonates of the non-sepsis group (3.1 ± 0.5 ml, 0.4 ± 0.1 L/min, 2.5 ± 0.3 L/min/m^2

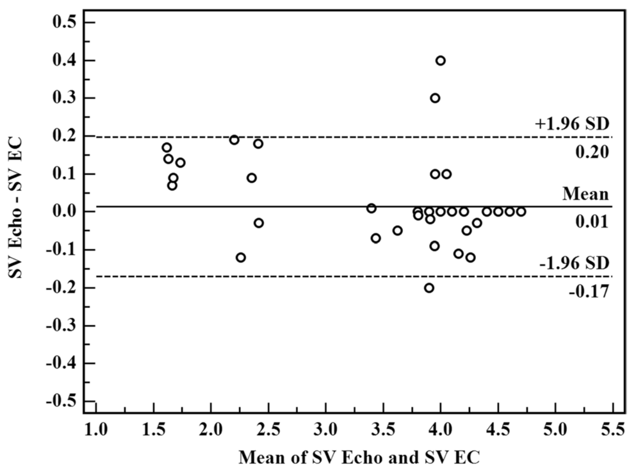

Fig. 2 Correlation between echo and EC parameters in each sepsis group ($n = 70$). CO (L/min) correlation (r: 0.995; $p < 0.001$*). CO, cardiac output. r_s: Spearman coefficient; *Statistically significant at $p \leq 0.05$

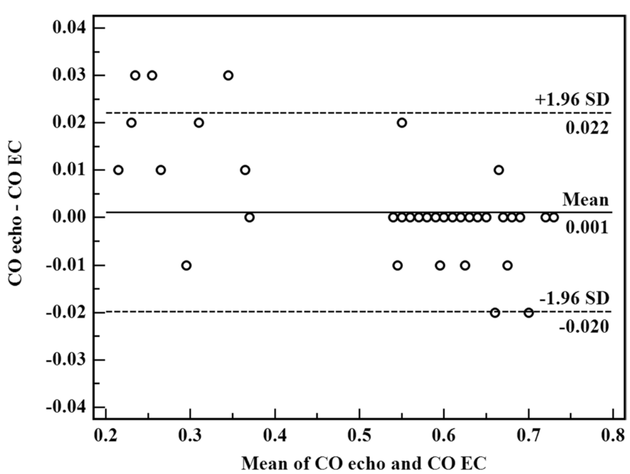

Fig. 3 Correlation between echo and EC parameters in each sepsis group ($n = 70$). CI (L/min/m.^{2}) correlation (r: 0.994; $p < 0.001$*). CI, cardiac index. r_s: Spearman coefficient; *Statistically significant at $p \leq 0.05$

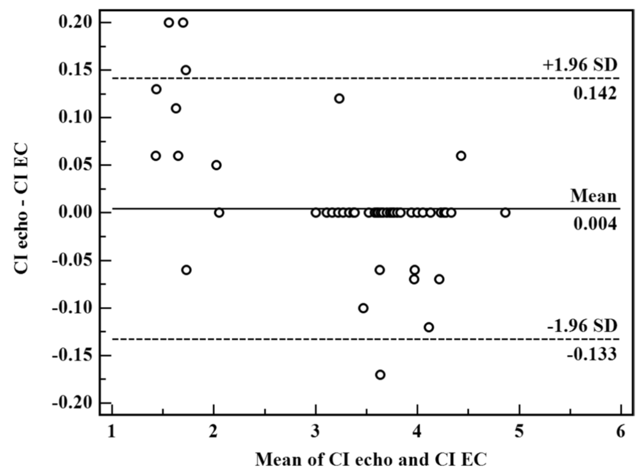

Fig. 4 Correlation between echo and EC parameters in each sepsis group ($n = 70$). SVR (dyn-s/cm.^{5}) correlation (r: 0.979; $p < 0.001$*). SVR, systemic vascular resistance. r_s: Spearman coefficient; *Statistically significant at $p \leq 0.05$

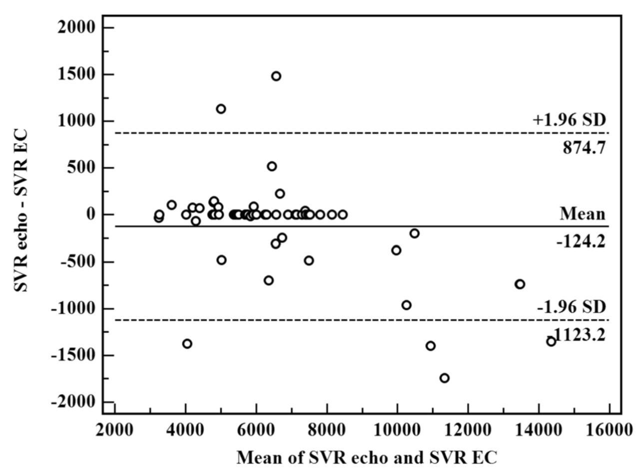

Fig. 5 Correlation between echo and EC parameters in each sepsis group ($n = 70$). SVRI (dyn-s/cm^5)/m.^{2} correlation (r: 0.986; $p < 0.001$*). SVRI, systemic vascular resistance index. r_s: Spearman coefficient; *Statistically significant at $p \leq 0.05$

respectively measured with echo and 3.1 ± 0.5 ml, 0.4 ± 0.1 L/min, 2.5 ± 0.3 L/min/m^2 by EC).

In contrast, the mean values of SVR and SVRI were significantly lower in the sepsis group (6548.7 ± 2289 dyne-s/cm^5 and 1102.5 ± 370.7 (dyne-s/cm^5)/m^2 by FoCUS and 6651.6 ± 2590.3 dyne-s/cm^5 and 1122.6 ± 433 (dyne-s/cm^5)/m^2 by EC) than those measured in the non-sepsis group (8547.5 ± 1019.8 dyne-s/cm^5 and 1523.8 ± 232.3 (dyne-s/cm^5)/m^2 by FoCUS and 8533.4 ± 1026.3 dyne-s/cm^5 and 1519.2 ± 220.2 (dyne-s/cm^5)/m^2 by EC).

These findings can be explained by the different anatomical structure of the premature heart. The immature heart has a lower mass, fewer and less organized myofibrils, fewer mitochondria, fewer L-type calcium channels, and shallower T-tubules, resulting in decreased the ability to facilitate the release of calcium from sarcoplasmic reticulum, higher overall collagen content as well as a higher ratio of collagen rigidity-increasing type I to elasticity-increasing type, and less adrenergic innervation and adrenoreceptor density [25].

Functionally, these anatomic differences are translated into lower functional reserve in response to altered loading conditions and stresses, lower diastolic performance, less ability to increase stroke volume in response to increases in preload, and a greater tendency for systolic dysfunction and lower stroke volume in face of acute increases in afterload [15, 26].

While individual variations may occur, the predominant physiological response to sepsis in the vascular system also appears to be developmentally regulated. In adult patients, predominant physiology is known to be that of warm shock, whereas in children, sepsis tends to produce primarily cold shock physiology. Physiological studies in preterm infants, similar to adults, have demonstrated warm shock physiology to be the predominant phenotype. This is postulated to be due to an impaired ability to regulate vascular tone during shock, in part driven by an inherent imbalance of the autonomic nervous system characterized by a relatively higher parasympathetic drive. Relative adrenal insufficiency, by decreasing SVR, may also be a contributing factor in preterm infants [15].

The Pearson coefficient test was used to evaluate the correlation between the EC measurements and the echocardiogram measurements. SV, CO, CI, SVR, and SVRI measurements by EC showed significant positive correlation with FoCUS measurements among sepsis group cases.

Bland–Altman plots were made to evaluate the agreement of SV, CO, and CI readings by echo and EC. Bias was defined as the mean difference between the EC and echo measurements. In sepsis group, the mean bias of SV reading was 0.02 ± 0.098 (limits of agreement − 0.17–0.21). The mean bias of CO reading was 0.000 ± 0.004 with (limit of agreement of − 0.008–0.008). The mean bias of CI reading was 0.000 ± 0.024 with (limit of agreement of − 0.048–0.047). These differences show an accepted degree of agreement between EC and echocardiogram that are nearly equivalent in evaluation of the beforementioned hemodynamic measurement in preterm neonates diagnosed with sepsis owing to the tiny bias and narrow limits.

The current study had some limitations; it was a single-center study, sample size was relatively small, preterm neonates with septic shock were excluded from the study as many neonates could be presented with different types of septic shock with variable hemodynamics which require a separate study. Furthermore, cases on HFOV were not included as many authors have suggested reduced EC accuracy under HFOV, lack of studies about the reproducibility of the EC in neonates, the time points of evaluation can be variable within first 24 h of age and on the 3rd day, and neonates with different respiratory disorders like RDS were not included.

Conclusions

Neonatal sepsis is a unique hemodynamic state, and neonates with sepsis showed high cardiac output as demonstrated by echocardiography and electrical cardiometry. There was a strong correlation between cardiac output measurements obtained by electrical cardiometry and FoCUS. Electrical cardiometry can be recommended as a useful tool for continuous hemodynamics assessment in the preterm neonates with sepsis. Both FoCUS and EC can be used for hemodynamics assessment in NICUs.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

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