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Evaluation of cardiac output in neonatal sepsis

Angana Bhattacharjee[1], Saugata Chaudhuri[2], Maitreyi Basu[3]

[1]Junior Resident, [2]Assistant Professor, [3]Professor, Department of Paediatric Medicine, Dr. B C Roy Post Graduate Institute of Paediatric Sciences, Kolkata, West Bengal, India

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ABSTRACT

Background: Neonatal sepsis is a clinical syndrome characterized by signs and symptoms of infection with or without accompanying bacteremia in the 1st month of life imposing significant cardiovascular compromise which poses a huge burden of morbidity. The essential objective of functional neonatal echocardiography is to recognize features of cardiovascular compromise earlier and help in timely institution of management. This study provides an overview regarding the variability of cardiac output (CO) in neonates with culture-positive sepsis. **Aims and Objectives:** The aims and objectives of the study are to assess the variability of CO in term neonates with Gram-positive sepsis and Gram-negative sepsis. **Materials and Methods:** The observational cross-sectional study was conducted in the Department of Paediatrics for 18 months in a tertiary care center. 2D echocardiography was performed on all the neonates who came positive for sepsis screen within the first 2 days of institution of antibiotics. CO was calculated from the echocardiographic finding of Aortic Root Diameter (d), Velocity Time Integral, and Heart Rate recorded at the same time. Normal range of left ventricular output has been defined as 150–300 mL/kg/min each. **Results:** In Gram-negative group, the mean CO (Mean ± SD) of patients was 386.4545 ± 34.2284 mL/kg/min while in Gram-positive group, the mean CO (Mean ± SD) of patients was 345.1532 ± 37.6044 mL/kg/min and the variation stands significant at $P < 0.0001$. **Conclusion:** This research confers about hyperdynamic circulatory status of neonatal sepsis as reflected by increased CO beyond the normal limit in septic neonates. On comparison, a strikingly higher CO was observed in Gram-negative sepsis group than Gram-positive group.

Key words: Neonatal sepsis; Functional echocardiography; Cardiac output; Velocity time integral

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INTRODUCTION

Neonatal sepsis causes considerable neonatal morbidity and mortality, and it has become a global health challenge. The overall incidence of neonatal sepsis ranges from 1 to 5/1000 live birth. Estimated incidence rates vary based on the case definitions and the population studied. Globally, neonatal sepsis and other severe infections were responsible for about 430,000 neonatal deaths in 2013, accounting for approximately 15% of all neonatal deaths.[1] In the cohort study - Delhi National Infection study performed on neonates admitted in intensive care unit of three tertiary care hospitals of India, the incidence of neonatal sepsis has been found to be 14.3% with culture positive sepsis being 6.2%.[2]

Cardiovascular vulnerability stems from particular features of the newborn such as incomplete myocardial development, the presence of fetal shunts, changes in systemic and pulmonary vascular resistance, and more generally, the complex hemodynamic changes that take place during the transition to extrauterine life. The hemodynamic status of sick newborn infants is often assessed by clinical variables such as heart rate (HR), blood pressure, and capillary refill time, and the alterations in these clinical parameters however occur with significantly advanced sepsis.[3,4] It has been demonstrated in several studies that real-time objective physiologic data such as cardiac output (CO) and other measurements of central blood flow provide hemodynamic information much earlier and help to differentiate the assumed underlying physiology.[5]

Functional neonatal echocardiography (FnECHO) serves as a non-invasive portable tool for the clinician to assess the hemodynamic condition of sick neonates and is different

Address for Correspondence:
Dr. Angana Bhattacharjee, Junior Resident, Department of Paediatric Medicine, Dr. B C Roy Post Graduate Institute of Paediatric Sciences, Kolkata, West Bengal, India. **Mobile:** +91-9674524340. **E-mail:** doc.angana94@gmail.com

from echocardiography performed by a pediatric cardiologist, where the main focus is to provide a consultative, cross-sectional, high-end opinion regarding structural heart disease and myocardial functional assessment. FnECHO evolved from the requirement of more rigorous, continuous, and longitudinal monitoring of the hemodynamic condition of critical patients. Hence, the clinical point-of-care ultrasound complements rather than replaces the need for consultative ultrasound. The paucity of standardized data on CO among septic neonates in medical literature often restricts early identification of circulatory insufficiency and institution of target-oriented management. FnECHO provides a wealth of hemodynamic information which when paired with clinical assessment bridges this gap of knowledge targeting the prevention of sepsis-related mortality. Hence, this study was taken up to fill the void of knowledge prevailing in medical literature regarding the affection of CO in neonatal sepsis as well as to understand the variability of CO among Gram-negative and Gram-positive groups of organisms.

Aims and objectives

(1) To evaluate the cardiac output in neonatal sepsis in term neonates
(2) To assess the variability of cardiac output in term neonates with gram positive sepsis and gram negative sepsis.

MATERIALS AND METHODS

The observational cross-sectional study was conducted in the Department of Paediatrics for a period of 18 months. Sepsis screen was performed on all term neonates (assessed by Modified Ballard Score) with suspected sepsis based on clinical signs and symptoms and blood and urine sample was sent for culture and antibiotic sensitivity at the same time. Taking all aseptic precautions, 1 ml of blood drawn from peripheral vein was inoculated into 30 mL BacT/Alert bottle and cultured using Bactec – BacT/Alert 3D 60 (BIOMERIEUX). Similarly, urine sample was taken by suprapubic aspiration and sent for routine pathological, biochemical, and microbiological analysis in addition to culture and antibiotic sensitivity where indicated cerebrospinal fluid (CSF) was analyzed for routine biochemical and pathological examination and sent for culture and antibiotic sensitivity. Afterward, 2D-echocardiography was performed on all the neonates who came positive for sepsis screen within the first 2 days of institution of antibiotics excluding those who required inotrope and ventilatory support immediately after admission. CO was calculated from the echocardiographic finding of Aortic Root Diameter (d) through parasternal long axis view taken at the level of aortic root, Velocity Time Integral (VTI) taken at 5 chamber apical view by pulse wave Doppler across aortic valve, and 60 HR recorded at the same time. An average of three such measurements for each parameter were taken into consideration. Area (A) was calculated from the Aortic Root Diameter by the formula of $\pi d^2/4$. The HR was estimated in the same sitting. The CO was calculated by the following formula: CO = A × VTI × HR. After arrival of culture reports of relevant body fluids following 5–7 days from the collection of samples, only culture-proven septic neonates were included in the study and they were grouped as Gram-positive and Gram-negative cases according to the Gram-staining property of the isolated organisms. The value of CO in case of Gram-positive and Gram-negative sepsis was compared thereafter. Normal range of left ventricular output (LVO) has been defined as 150–300 mL/kg/min each.[6-9] Values above and below the limits of normal range have been categorized as high and low CO, respectively.

Statistical analysis

For statistical analysis, data were entered into a Microsoft Excel spreadsheet and then analyzed by SPSS (version 27.0; SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 5. Data had been summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables. Two-sample t-tests for a difference in mean involved independent samples or unpaired samples. Paired t-tests were a form of blocking and had greater power than unpaired tests.

$P \leq 0.05$ was considered statistically significant.

RESULTS

This study comprised of 100 culture-positive cases of neonatal sepsis in term neonates out of which 31 were Gram-positive and 69 were Gram-negative cases. According to this study, the major contribution among Gram-positive group was attributed to CONS group of organisms followed by *Kocuria* sp. In Gram-negative group, the highest burden was attributed to *Escherichia coli* followed by *Klebsiella* sp. Functional echocardiography was done in all term neonates once the sepsis screen came positive within 2 days of institution of antibiotics. The echocardiographic parameters included in the study were aortic root diameter, left ventricular outflow tract VTI, and HR. CO was calculated from the above parameters. In this study, VTI of flow wave measured across the aortic valve with pulsed wave Doppler showed the mean VTI (Mean±SD) of 7.2101±0.4567 m/stroke in Gram-negative group and mean VTI (Mean±SD) of 6.9258±0.4740 m/stroke in Gram-positive sepsis cases. Distribution of mean VTI with group was statistically significant at P=0.0054 (Table 1).

The mean HR (Mean±SD) of patients with Gram-negative sepsis was 136.0725±8.2003 beats/min. In Gram-positive

group, the mean HR (Mean±SD) of patients was found to be 132.4194±7.6845 beats/min. Comparison of distribution of mean HR with group was statistically significant at P=0.0383 (Table 2).

This study rejected the null hypothesis that there is no significant variability in CO among Gram-positive sepsis and Gram-negative sepsis. The results clearly reflect that the CO is significantly higher in Gram-negative sepsis group than Gram-positive cases and the overall CO is higher than normal values in both groups. In Gram-negative group, the mean CO (Mean±SD) of patients was 386.4545±34.2284 while in Gram-positive group, the mean CO (Mean±SD) of patients was 345.1532±37.6044 and the variation stands significant at P<0.0001 (Table 3).

DISCUSSION

A total of 100 term neonates were included in the study after satisfying the inclusion and exclusion criteria. 69 of them had Gram-negative sepsis as determined by organism isolated from blood, urine, or CSF culture while 31 patients had Gram-positive sepsis.

The organisms isolated in this study were divided into two groups based on Gram staining: Gram positive and Gram negative (Figure 1).

Many studies support the current standard method of measurement of CO using the non-invasive bedside echocardiography over the invasive procedures of thermodilution. A follow-up systematic review and meta-analysis by Zhang et al., are one such example where meta-analysis and subgroup analysis were used to compare the CO measured using the different types of echocardiography and different sites of Doppler use with thermodilution. No significant differences were found between echocardiography values and that of thermodilution values.[10] Left ventricular outflow tract VTI indicates left ventricular systolic function without confounding factor of area measurements. In this study, VTI of flow wave measured across the aortic valve with pulsed wave Doppler showed the mean VTI (Mean±SD) of 7.2101±0.4567 m/stroke in Gram-negative group and mean VTI (Mean±SD) of 6.9258±0.4740 m/stroke in Gram-positive sepsis cases. Distribution of mean VTI with group was statistically significant at P=0.0054. In the study by Abdalaziz et al., in 2018, it was seen that VTI was compromised at the time of admission with features of septic shock and improved considerably with inotrope use matching the clinical therapeutic target.[11]

In this study, the mean HR (Mean±SD) of patients with Gram-negative sepsis was 136.0725±8.2003 beats/min. In Gram-positive group, the mean HR (Mean±SD) of patients was found to be 132.4194±7.6845 beats/min. Comparison of distribution of mean HR with Group was statistically significant at P=0.0383. In the study by Bohanon, it was concluded that for the initial few hours of sepsis, perfusion is adequately maintained by an increase in HR. The study showed significant variability in HR between septic ELBW neonates and healthy ELBW neonates.[14]

Table 1: Distribution of mean VTI among groups

VTI (cm/stroke)	Number	Mean	SD	Minimum	Maximum	Median	P-value
Gram-Negative	69	7.2101	0.4567	5.7000	8.4000	7.2000	0.0054
Gram-Positive	31	6.9258	0.4740	6.1000	8.1000	6.9000	

VTI: Velocity time integral

Table 2: Distribution of mean HR among groups

HR (beats/min)	Number	Mean	SD	Minimum	Maximum	Median	P-value
Gram negative	69	136.0725	8.2003	118.0000	160.0000	136.0000	0.0383
Gram positive	31	132.4194	7.6845	118.0000	160.0000	130.0000	

HR: Heart rate

Table 3: Distribution of mean CO among groups

CO (mL/kg/min)	Number	Mean	SD	Minimum	Maximum	Median	P-value
Gram negative	69	386.4545	34.2284	301.0000	471.3200	382.9700	<0.0001
Gram positive	31	345.1532	37.6044	253.6600	451.5400	340.6200	

CO: Cardiac output

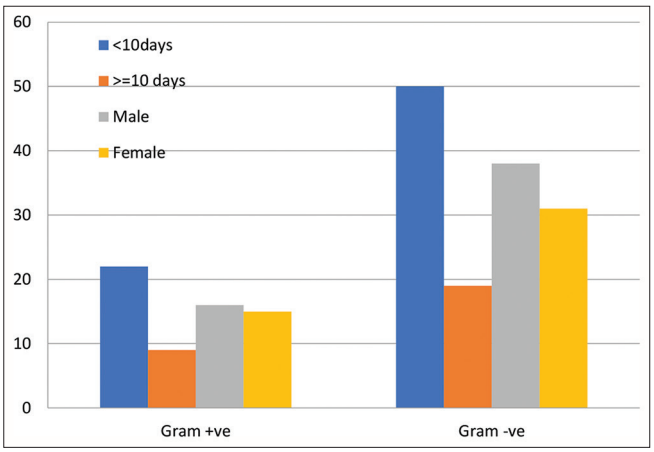

Figure 1: Demography

The hemodynamic status of sick neonates assessed by clinical parameters such as HR, blood pressure, and capillary refill time has been proven to be misleading in their accuracy as they alter much later in the course of the disease. It has been demonstrated in several studies that real-time objective physiologic data such as CO and other measurements of central blood flow provide much more accurate hemodynamic information. Left ventricular CO (LV-CO) is measured as the multiplication of HR, area of aortic root, and VTI of flow wave measured across aortic valve. The normal range for neonatal LV-CO is defined as 150–300 mL/kg/min.[6-9] Saini et al., concluded that the baseline LVO was significantly higher in neonates with septic shock as compared with controls (median 305 mL/kg/min in comparison to 233 mL/kg/min at P<0.001.[12] From the study of Deshpande et al., it was observed that the mean LVO was higher than normal in late-onset sepsis patients. In addition to this, they also concluded that patients with Gram-negative sepsis had higher CO of 378.0 (±138.4) than those with Gram-positive sepsis 240.0 (±86.1).[13] In this study, it has been observed that in Gram-negative group, the mean CO (Mean±SD) of patients was 386.4545±34.2284 while in Gram-positive group, the mean CO (Mean±SD) of patients was 345.1532±37.6044, i.e., the CO was higher in patients with Gram-negative sepsis than those with Gram-positive sepsis. Distribution of mean CO with group came out to be statistically significant (P<0.0001). Since P-value was very small (much less 0.05) and the value of t-statistics indicated that the average CO for Gram negative is significantly higher than the average CO level of Gram-positive cases; our study also seconded the findings by Deshpande et al., who conducted a similar study in western India in 2015 among both term and preterm neonates.[13]

Furthermore, in this study, we found out that among Gram-negative organisms, the average CO levels were not significantly different for different organism groups but the variance of CO was significantly different. The maximum CO was observed in neonates with *Acinetobacter baumannii*

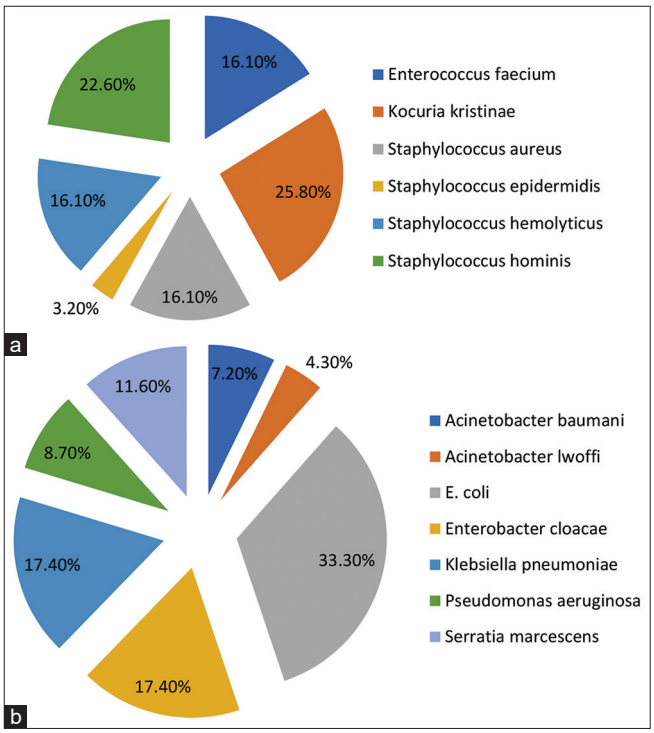

Figure 2: (a) Distribution of organisms among Gram-positive group, (b) Distribution of organisms among Gram-negative group

infection followed by *Enterobacter cloacae*, *Klebsiella pneumoniae,* and *E. coli,* respectively. Maximum variance was observed in *K. pneumoniae* cases. As for Gram-positive group, the average CO and variance of CO both were not significantly the same among the organism groups. Maximum average CO was seen in CONS group overall, *Staphylococcus epidermidis* followed by *Staphylococcus hominis* and *Kocuria kristinae* (Figure 2a and b).

Limitations of the study

Despite a collective wholesome sincere effort this study has some limitations.

1. Due to lack of in-house obstetric department functional echocardiography on the neonates could not be done within first few hours of life and was largely dependant on the period of referral from other zonal district/rural hospitals.
2. Larger sample size would have helped in better validation of result.
3. This study is limited to a single centre however a multi-centric study would have better implication in implementation of the result.
4. Serial measurements of hemodynamic variables instead of single point observation could have provided more real time information as the hemodynamic status is subjected to change.
5. The measurement of cardiac output from the echocardiography parameters are subjected to minimal intra-observer variations.

CONCLUSION

Cardiovascular compromise is one of the primary concerns in neonatal sepsis as it contributes to a notable amount of morbidity and mortality. Timely recognition is often delayed due to excessive reliance on clinical parameters such as heart rate, blood pressure, capillary perfusion which appears late in the course of the disease. Functional Echocardiography is an invaluable tool in neonatal intensive care due to its point of care accessibility which allows bedside evaluation of the hemodynamic status of the patient. This study aims at validating the use of functional echocardiography by early detection of changes in cardiac output in septic neonates. This research confers about hyperdynamic circulatory status of neonatal sepsis as reflected by increased cardiac output beyond the normal limit in septic neonates. On comparison between gram positive sepsis and gram negative sepsis a striking difference of cardiac output was observed as evidenced by high cardiac output in gram negative sepsis group than gram positive group.

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Authors Contribution:
AB- Definition of intellectual content, data collection, tabulation of data, data analysis, manuscript preparation, and writing; **SC-** Statistical analysis, manuscript review; **MB-** Implementation of study protocol, manuscript review.

Work attributed to:
Dr BC Roy Post Graduate Institute of Paediatric Sciences, Kolkata, West Bengal, India.

Orcid ID:
Angana Bhattacharjee - https://orcid.org/0009-0007-1751-463X
Saugata Chaudhuri - https://orcid.org/0000-0003-2565-9250
Maitreyi Basu - https://orcid.org/0009-0002-4425-8962

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