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Original Article

Frequency of Myocardial Dysfunction in Neonatal Sepsis: A Single Center Experience

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Abstract:
Background*:* Myocardial dysfunction is an association of neonatal sepsis that might occur without underlying cardiac structural defect (CSD).
Aims of the work: To study frequency of myocardial dysfunction (MD) in sepsis in full term neonates without CSD.
Subjects and Methods: All the full term neonates with neonatal sepsis admitted to Neonatal Intensive Care Unit, Fayoum University between December 2019 and December 2020 without underlying CSD were included in the study. They underwent conventional echocardiography and tissue Doppler studies.
Results: 103 neonates with neonatal sepsis were included in the study. Of them 30 patients (29.12%) were found to have myocardial dysfunction. Global myocardial dysfunction was encountered in 16 (53.3%), isolated right ventricle dysfunction in 8 (26.6%) cases, isolated left ventricle dysfunction among 6 (20%). The dysfunction was both systolic and diastolic in 2 (6.6%) cases, isolated systolic in 6 (20%), and isolated diastolic in 22 (73.3 %). No noted risk factors were associated with myocardial dysfunction as age (p=0.193), weight (p=0.100), sex (p=0.130) or type of bacterial infection (p=0.125). The outcome among those with myocardial dysfunction and those without was complete resolution in 13 (43.3%) and 43 (59%) patients (p=0.149), cardiogenic shock and death in 17 cases (56.7%) and 30 (41%) (p=0.149) respectively while no cases developed progressive cardiomyopathy.
Conclusions: Full terms with neonatal sepsis can experience significant cardiovascular dysfunction that is either global or limited to right or left ventricle. The dysfunction might be systolic or diastolic or both. Myocardial dysfunction among neonates with sepsis might be self-limiting or culminates increasing the risk of mortality.

Level of Evidence of Study: IV (*1*)**.**
Keywords: echocardiography; myocardial performance index; neonatal sepsis; Tei index. Abbreviations: AO: aortic root; CRP: C-reactive protein; CSD: cardiac structural defect; MD: Myocardial dysfunction; EF: ejection fraction; ET: ejection time; FS: fraction shortening; IVCT: isovolumic contraction time IVRT: isovolumic relaxation time; LAD: left atrial diameter; LV: left ventricle; LVIDD; left ventricular internal diameter end diastole; LVISD; left ventricular end systole; LVPW: LV posterior wall; MV: mitral valve; MPI: myocardial performance index; PAP: pulmonary artery pressure; RV: right ventricle; TAPSE; tricuspid annular plane systolic excursion; TV: tricuspid valve; RBS: random blood sugar; WBCs: white blood cells.

Introduction

The neonatal period is a critical stage in life. Neonatal sepsis is a recognized cause of morbidity and mortality at this age. In developing countries, sepsis is the commonest cause of neonatal mortality and reported to be responsible for about 50% of the total neonatal deaths annually (*2*). Sepsis poses a demanding constraint on the heart (*3*). Cardiovascular complications, myocyte damage, and modification of blood flow of the heart induced by inflammation are consequences of sepsis in neonates (*4*). Clinical manifestations of neonatal sepsis can range from vague nonspecific symptoms to collapse. Early recognition of cardiovascular complications in neonates with sepsis enables the physician to start proper supportive treatment, to monitor response to treatment and to improve outcome (*5*). The use of conventional echocardiography and tissue Doppler has gradually increased in the Neonatal Intensive Care Unit (NICU) to enable proper hemodynamic assessment, and provide immediate prompt intervention (*6*). We aimed to study the frequency of myocardial dysfunction (MD) in

neonatal sepsis- in full term neonates admitted to Fayoum University NICU between December 2019 and December 2020.

Subjects and Methods

This prospective case control study included all 103 newborns with confirmed neonatal sepsis who did not suffer from cardiac structural defects admitted to Fayoum University NICU between December 2019 and December 2020. The study included a control group of 30 healthy sex and age matched full term newborns. The study was approved by the Research Ethics Committee, Faculty of Medicine, Fayoum University, Egypt (IRB: M481). Care takers consented to the trial. The study complied to the Declaration of Helsinki for trials (*7*).

Participants

All full term newborn less than 28 days of life with Score ≥ 2 on Griffin Neonatal Sepsis Score (*8*) were included. Those with history of perinatal asphyxia, those whose mothers were diabetic, those with structural heart defects, preterm newborn and neonates with chromosomal anomalies or dysmorphism were not included in the study.

Methods

The collected data included history (perinatal, natal, and postnatal) including gestational age, APGAR score, Ballard score (*9*), and thorough clinical general and local examination.

They underwent lab investigations as indicated by the clinical judgment: complete blood count with differential, arterial blood gases, CRP, blood culture, liver function tests, kidney function tests, are relevant chest X-ray.

Echocardiography was performed using GE Vivid 5 echo machine (General Electric, USA) with 5 MHz transducer. A complete echocardiographic examination to exclude the presence of cardiac structural defect (CSD) with great emphasis on right ventricle (RV) dimensions, cardiac function, left ventricle (LV) internal dimensions with assessment of LV ejection fraction. Estimations were made through the standard transthoracic windows, LV end diastolic diameter (LVEDD), LV end systolic diameter (LVESD), LV posterior wall (LVPW), and LV ejection fraction (EF). Transmitral E wave velocity (E) and (A) wave velocity were averaged to generate the mean value. The myocardial performance index (MPI), also called Tei index, was calculated by dividing the sum of IVRT and IVCT by ejection time (ET). It increases in diastolic dysfunction. (LV MPI = (IVCT + IVRT) / LVET). Systolic dysfunction was considered abnormal if EF was less than 55 % and FS was less than 26%, diastolic dysfunction was considered abnormal if MPI/Tei index was higher than normal for age; i.e. in term newborns, the RVMPI value on the first day of life was 0.42 ± 14, dropping to 0.29 ± 0.09 after PDA closure, and finally reaching 0.22 ± 0.09 on the 28th DOL. The LVMPI for term neonates in successive measurements was 0.37 ± 0.10, 0.39 ± 0.07 (*10*).

Statistical Analysis

The collected data were organized, tabulated, and statistically analyzed using SPSS software statistical computer package version 22 (SPSS Inc, USA). For quantitative data, the mean, standard deviation (SD), and range were calculated. Independent t-test was used in comparing between the two groups of the study. Qualitative data were presented as number and percentages, chi square (χ^2) was used as a test of significance. Pearson correlation was run to identify relation between Tei index with other study parameters.

Results

The study included 103 neonates with neonatal sepsis. Of them 30 patients (29.12%) were found to have myocardial dysfunction. Global myocardial dysfunction was encountered in 16 (53.3%), isolated right ventricle dysfunction in 8 (26.6%) cases, isolated left ventricle dysfunction among 6 (20%). The dysfunction was systolic and diastolic in 2 (6.6%) cases, isolated systolic in 6 (20%), and isolated diastolic in 22 (73.3 %). The demographic characteristics and clinical presentations and laboratory findings of the studied groups are presented in Tables 1, 2 and 3. It is notable that among those with myocardial dysfunction 16 cases suffered from hypothermia of 35.63 ± 0.5°C (range= 35.4-37.2 °C), respiratory distress in 22 cases (73.3%) and apnea in 8 cases (26.7%). The clinical features of heart failure were present in 6 neonates (20) % in the form

tachycardia, increased respiratory rate, gallop rhythm, and hepatomegaly were present in 6 cases only (2 cases mild heart failure, 2 cases moderate and 2 cases severe heart failure according to the Ross modified classification (*11*) and all of them progressed to cold shock.

Table 1. Demographic characteristics, vital signs and clinical manifestations of the study groups.

	Group 1 (N=30) Neonates with sepsis and myocardial dysfunction		**Group 2 (N=73) Neonates with sepsis without myocardial dysfunction**		**P value** (between group 1 and 2)	**Control Group (N=30)**		**P value** (among the 3 groups)
	Mean	SD	Mean	SD		Mean	SD	
Age (days)	14.7	8.33	13.5	7	0.38	12.07	7.12	0.193
Gestational age (weeks)	38.87	2.02	37.9	2.1	0.06	38.7	1.58	0.100
Body weight (grams)	2417.5	670.37	2400	584	0.07	2509.1	612.21	0.140
	N	%	N	%		N	%	
Sex								
Males	15	50.0	35	47.9	0.9	15	50.0	0.130
Females	15	50.0	38	52.05	0.9	15	50.0	
Vital signs and capillary refill time								
	N	%	N	%		**N**	%	
Hypothermia	16	53.33	30	41	0.5	0	0	<0.001
Hypotension	20	66.6	37	50.6	0.2	0	0	<0.001
Shock	19	63.3	35	47.9	0.155			<0.001
Bradycardia	2	3.3	3	4.1	0.4	0	0	0.409
Tachycardia	21	70.0	20	27.39	<0.001	0	0	<0.001
	Mean	**SD**	**Mean**	**SD**		**Mean**	**SD**	
Temperature (ºC) (range)	35.63 (35.4-37.2)	1.25	35.9 (35.7-37.5)	1.5	0.59	36.81	0.43	<0.0001
Systolic pressure (mmHg)	67.4(55-85)	19.03	70.2 (60-88)	17.06	0.7	82.93	8.47	<0.0001
Diastolic pressure (mmHg)	35.5(30-55)	15.9	38.9 (35-56)	14.5	0.1	44.77	5.59	<0.0001
Heart rate	160.87	32.12	150	29	0.15	135.4	9.11	0.002
Respiratory rate (in 1min)	48.03	9.99	46	8	0.455	41.4	3.76	0.002
Capillary refill time (in 1sec)	2.55	0.83	2.4	0.5	0.43	1.18	0.33	<0.0001

Table 2. Clinical presentation and outcome of the studied groups.

	Group 1 (N=30) Neonates with sepsis and myocardial dysfunction		**Group 2 (N=73) Neonates with sepsis without myocardial dysfunction**		**P value**
	N	%	N	%	
Cardiovascular signs					
Tachycardia (>180 beat/min)	21	70.0	20	27.39	<0.001
Heart failure	6	20	0	0	<0.001
Respiratory signs					
Tachypnea	22	73.3	45	61	0.258
Apnea	8	26.7	20	27.39	0.940
Gastrointestinal signs					
Feeding intolerance	21	70.0	50	68.5	0.880
Abdominal distension	9	30.0	23	31.5	0.881
Complications					
Pneumonia	6	20	16	22	0.829
Urinary tract infection	1	3.3	2	2.7	1.000
Meningitis	1	3.3	3	4.1	1.000
Acute Kidney injury	2	6.6	4	5.4	1.000
Hepatitis	2	6.6	3	4.1	1.000
Lethargy	4	13.3	11	15	1.000
Intraventricular hemorrhage	1	3.3	3	4.1	1.000
Seizures	2	6.6	7	9.5	1.000
Shock	19	63.3	35	47.9	0.155
Outcome					
Recovered Completely	13	43.3	43	59	0.149
Progressed to Cardiomyopathy	0	0	0	0	--
Died	17	56.7	30	41	0.149

Table 3. Laboratory investigations of the studied groups.

	Group 1 (N=30) sepsis with myocardial dysfunction		Group 2 (N=73) Neonates with sepsis without myocardial dysfunction		Control (N=30)		P value
	Mean	SD	Mean	SD	Mean	SD	
RBS (g/dl)	129.2	63.49	110	52.5	107.57	21.34	0.086
CRP	59.66	58.4	60	51	4.7	0.53	<0.0001
WBCs count	16.95	17.01	16.2	13	14.61	3.69	0.468
Absolute neutrophil count	8242.2	6957.6	7945.3	5434	4475.4	2371.1	<0.0001
Platelets count	246.5	185.5	254	179.3	369.87	90.59	0.002
Hemoglobin level	10.62	2.77	10.8	2.8	14.65	2.01	<0.0001
ALT (normal: < 45 IU/L).	45	20	39	23	26	12	0.7
AST (normal: < 35 IU/L)	69	30	70	28	66	25	0.8
Total Bilirubin (mg/dL)	11	0.5	10	0.8	10	0.9	0.6
	N	%	N	%			
Positive Blood culture	17	56.7%	43	60			0.834
Klebsiella pneumoniae	7	23.3	15	20.5			0.754
MRSA	4	13.3	6	8.2			0.472
Enterococcus faecalis	3	17.6	2	2.7			0.146
CoNS	1	5.9	11	15			0.173
Pseudomonas aeruginosa	1	5.9	5	6.8			1.000
Escherichia coli	0	0	2	2.7			1.000
Candida Albicans	1	5.9	2	2.7			1.000
Negative blood culture	13	43.3	30	40			0.834

CRP: C-reactive protein; CoNS: Coagulase negative *Staphylococci*; MERSA*:* Methicillin-resistant *Staphylococcus aureus;* RBS: random blood sugar; WBCs: white blood cells

Echocardiographic data of the study groups are summarized in Table 4. Global myocardial dysfunction was encountered in 16 (53.3%), isolated right ventricle dysfunction in 8 (26.6%), and isolated left ventricle dysfunction among 6 patients (20%). The dysfunction was both systolic and diastolic among 2 (6.6%), isolated systolic dysfunction among six (20%) cases, and isolated diastolic among 22 (73.3 %). diastolic among 22 (73.3 %). There was no significant difference between both groups regarding pulmonary artery pressure (p-value 0.090). Pulmonary hypertension was present in 15 (50%) cases of group 1 (3 of them had pneumonia (10%)) with mean ±SD pulmonary pressure of 43±7 mm Hg, 8 of them had RV dysfunction, while in group 2 it was high in 30 cases (41%); (10 (13.7%) had pneumonia) with mean ± SD of 40 ±4 mm Hg.

Nineteen (63.3%) of the neonates with sepsis and myocardial dysfunction needed ventilator support and 19 cases (63.3%) were shocked; 17 were in cold shock in spite of IV fluids and received inotropes in the form of noradrenaline and dobutamine.

Seven cases (23.3%) received ampicillin and aminoglycosides, 16 cases (53.3%) received vancomycin and carbapenem, 6 cases (20.0%) received quinolones and only 1 case 3.3% received colistin. Among those with sepsis without myocardial dysfunction; 38 (52%) needed ventilator support, 35 (47.9%) were in septic shock (distributed) and received intravenous fluids and inotropes. Thirty (41%) received ampicillin and aminoglycosides, 40 (54.7%) received vancomycin and carbapenem, and 10 (13.6%) received quinolones.

The outcome of those with myocardial dysfunction and neonatal sepsis was guarded as 17 cases (56.7%) died with septic shock and 6 of them had impaired systolic function and the other 11 patients had diastolic dysfunction (2 of them had no cardiovascular signs), versus 13 cases (43.3%) survived while in patients with sepsis without myocardial dysfunction mortality rate was 41% (73 patients). The cultures of the non-surviving patients were positive in 10 patients; 5 with *Klebsiella* pneumoniae and 1 with each of the following: *Enterococcus* faecalis , *Pseudomonas aeruginosa, Methicillin-resistant Staphylococcus aureus and Candida Albicans*.

The Mean RVTei index for surviving neonates was 0.40±0.02 while for non-surviving patients 0.43±0.02 (p = 0.001). Regarding LVTei index for surviving patients was 0.40±0.032 while for non-surviving patients 0.45±0.031 (p<0.0001). No noted risk factors were associated with myocardial dysfunction like age(p=0.193), weight(p=0.100), gender (p=0.130) or type of bacterial infection (p=0.125). Improvement in cardiac function parameters has been observed in surviving neonates of group 1 (13 cases) and all the discharged patients had normal systolic and diastolic function by echocardiography study repeated 1 week after discharge. Only 43 (59%) patients of group 2 survived.

Table 4. Echocardiography parameters in the studied groups.

	Group 1 (N=30) patients with sepsis and myocardial dysfunction		Group 2 (N=73) Sepsis without myocardial dysfunction		Control (N=30)		P value
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Measurements							
PAP (mmHg)	38.2	9.28	36.5	8.5	34.47	7.38	0.090
AO (cm)	1.01	0.07	1.1	0.06	1.06	0.13	0.114
LAD (cm)	1.15	0.19	1	0.08	1.04	0.09	0.009
LVIDD (cm)	1.67	0.27	1.5	0.23	1.5	0.21	0.01
LVISD (cm)	0.79	0.45	0.8	0.3	0.79	0.25	1.000
TAPSE (cm)	1.7	0.23	1.7	0.2	1.8	0.19	0.091
MAPSE (cm)	1.9	0.33	2	0.1	2	0.23	0.082
EF%	55	14.5	71	2.5	72.23	3.06	<0.0001
FS%	26.5	6.5	34	3	35	2	<0.0001
Right ventricle IVCT	45.97	4.51	41.8	4.9	42.23	5.18	0.004
Right ventricle IVRT	68	5.77	60.6	7.6	61.17	8.69	0.00
Right ventricle CT	271.93	9.37	250	62.2	253.2	60.86	0.106
RV MPI index	0.42	0.03	0.38	0.01	0.37	0.02	<0.0001
Left ventricle IVCT	46.63	6.06	43.4	4.8	43.27	5.17	0.024
Left ventricle IVRT	69.57	6.16	60.1	6.9	59.87	7.39	<0.0001
Left ventricle ET	269.47	10.67	258.05	40.6	257.03	50.23	0.194
LV MPI index	0.43	0.05	0.39	0.05	0.38	0.03	<0.0001
E/A ratio MV	0.91	0.11	1	0.05	1	0.06	<0.0001
E/A ratio TV	0.85	0.09	0.93	0.06	0.94	0.07	<0.0001
	N	%	N	%	N	%	
Dysfunction							
Increased PAP	15	50	30	41	10	33.3	0.423
Increased RV MPI index	24	80	0	0	0	0	<0.001
Increased LV MPI index	22	73.3	0	0	0	0	<0.001
Depressed EF%	8	26.6	0	0	0	0	<0.001
Depressed FS%	8	26.6	0	0	0	0	<0.001

AO: aortic root; E/A: E wave/A wave; EF: ejection fraction; ET: ejection time; FS: fraction shortening; IVCT: isovolumic contraction time; IVRT: isovolumic relaxation time; LAD: left atrial diameter; LVIDD; left ventricular internal diameter end diastole; LVISD; left ventricular end systole; MV: mitral valve; PAP: pulmonary artery pressure; TAPSE; tricuspid annular plane systolic excursion; TV: tricuspid valve.

Discussion

Neonatal myocardial dysfunction is known to be primary associated with inborn errors of metabolism, mitochondrial disorders or neuromuscular disorders or secondary to other conditions as sepsis. Our study revealed that a third of full term babies with neonatal sepsis suffered from myocardial dysfunction despite not having an underlying cardiac structural defects. It is not clear if this dysfunction is part of the neonatal sepsis systemic inflammatory response (SIRS) associated with infection, or related to the neonatal immaturity of the immune system that is overwhelmed by infection. Or due to down-regulation of ß-adrenergic receptors at the cardiomyocyte level that is mediated by many substances and toxins secreted by bacteria called the myocardial depressant factors (*12*). We did not study the immune response or immune profile among our studied neonates. We cannot rule out the possibility that those with myocardial dysfunction had underlying inborn errors of metabolism, mitochondrial disorders or neuromuscular disorders, as they did not undergo neonatal screening for metabolic or genetic diseases (*13*). We cannot rule out drug/toxemia induced mitochondrial fluidity membrane damage as well. The high frequency of myocardial dysfunction (29.12%), among full term babies in our study might not reflect the true frequency of myocardial dysfunction in neonatal sepsis, as cases are referred from all over the government to our tertiary care center.

Myocardial dysfunction among full term neonates with sepsis was associated with higher mortality than those without myocardial dysfunction (56% versus 41%), yet this difference did not mount to statistical significance. It is a serious complication or association of neonatal sepsis

that should be promptly diagnosed and managed (*14–16*). Hence, it seems necessary to search for the underlying cause of this dysfunction among high risk neonates with sepsis. We command the neonatal screening program for metabolic diseases among high risk neonates admitted to neonatal intensive care units established in Egypt since 2021 (*17*).

The myocardial dysfunction in our studied cohort was not typical, it was global myocardial dysfunction, isolated right ventricle dysfunction, or isolated left ventricle dysfunction. The dysfunction was both systolic and diastolic, isolated systolic or isolated diastolic. The lack of uniformity suggests a multifactorial etiology, type of bacteria, or immune response. It is important to highlight that 13(43.3%) of those with myocardial dysfunction had culture negative sepsis, hence SIRS might be a possibility, or mitochondrial depletion (*18–21*). In neonates with sepsis, the discharge of cytokines, acidosis and hypoxia may result in the advancement of pulmonary hypertension and in this way right ventricular dysfunction, whereas right-heart dysfunction will impair left-heart function (*22*). In our study, however, pulmonary artery pressure was slightly elevated in cases than control group but did not mount to statistical significance. It suggests that myocardial dysfunction in sepsis was multifactorial and can be due to direct respiratory failure, hypoxemia, hypercapnia, acidosis and mechanical ventilation induced.

It is surprising however, that cardiogenic shock developed in both groups, and myocardial dysfunction was not an essential predictive step for cardiogenic shock.

Early recognition by echocardiography and proper supportive therapy of myocardial dysfunction in patients with sepsis was essential to initiate prompt management (*12*, *23*). Moreover we did not come across cases that progressed to cardiomyopathy, which is congruent to previous reports (*24*). A dramatic improvement in systolic and diastolic cardiac function parameters was observed by comparing the echocardiographic parameters during and after resolution of sepsis 1 week after resolution of sepsis.

Conclusion

Full terms with neonatal sepsis can experience significant cardiovascular dysfunction despite lack of structural defects. The myocardial dysfunction is either global or limited to right or left ventricle. The dysfunction might be systolic or diastolic or both. Myocardial dysfunction among neonates with sepsis might be self-limiting or progressive increasing risk of morbidity and mortality. Echocardiography is an important diagnostic tool in Neonatal Intensive Care Unit. Neonatal Screening for inborn errors of metabolism is necessary to exclude underlying cause.

Author Contributions:

All authors contributed to the study conception and design. All read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest in connection with the reported study. Authors declare veracity of information.

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