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Journal of Pediatrics & Neonatal Care

Research Article

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Cardiac functions by tissue doppler and speckle tracking echocardiography in neonatal sepsis and its correlation with sepsis markers and cardiac troponin-T

Abstract

Background: The aim of this study was to assess the right and left ventricle functions and their strain pattern in full term neonates with sepsis and correlate these finding with the laboratory markers of neonatal sepsis.

Methods: The study included 40 full term neonates with sepsis and 40 control apparently healthy neonates subjected to examination with tissue Doppler imaging (TDI) and 2-D speckle tracking echocardiography (STE) and correlated the findings with serum level of C-reactive protein (CRP), serum procalcitonin (PCT) and cardiac troponin-T (cTnT).

Results: The serum levels of CRP, PCT and cTnT were significantly higher in neonates with sepsis than in the controls. There were significant right and left ventricular systolic and diastolic dysfunctions as evidenced by TDI in the neonates with sepsis than in control group. Both RV and LV global longitudinal stain (GLS) and Tei indices were significantly increased in neonates with sepsis than controls. There were significant positive correlation with LV and RV GLS and Tei indices with CRP, PCT and cTnT serum levels.

Conclusion: PCT and CPR are good markers of neonatal sepsis and together with cTnT were correlated with both LV and RV systolic and diastolic dysfunction detected by TDI and STE.

Keywords: neonatal sepsis, procalcitonin; CRP; cardiac troponin T, tissue doppler, speckle tracking echocardiography

Volume 5 Issue 3 - 2016

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Received: July 29, 2016 | **Published:** September 23, 2016

Abbreviations: cTnT, cardiac toponin T; CRP, C-reactive protein; HB, hemoglobin; PCT, procalcitonin; PLT, platelets; TLC, total leucocytic count; IVRT, isovolumetric relaxation tim; GLS, global longitudinal strain; MV, mitral valve; TV, tricuspid valve; FS, fraction shortening; PLSS, peak longitudinal systolic strain

Introduction

Cardiac dysfunction is a well-recognized complication of severe sepsis and septic shock is a major contributor to morbidity and mortality in patients with sepsis.[1] Right ventricular (RV) diastolic dysfunction in neonatal sepsis is reflected by the presence of significant differences in findings obtained by both conventional and tissue Doppler parameters between healthy neonates and those with neonatal sepsis. Due to the special geometric features of the RV such as the tripartite morphology and different myofiber architecture, it sometimes be difficult to evaluate the RV by the standard techniques such as tricuspid annular plane systolic excursion (TAPSE) or RV myocardial performance index (RV MPI).[2] So, the use of modern imaging techniques such as tissue Doppler imaging (TDI) and speckle tracking echocardiography (STE) may be needed to sufficiently assess RV structures and functions. Recently, the new imaging modality speckle tracking echocardiography (STE) was proved to be similar to the cardiac magnetic resonance in reproducibility and accuracy.[3] The aim of the current study was to assess the right and left cardiac function as well as the ventricular strain pattern in full term neonates with sepsis using cardiac TDI and 2-Dimensional STE; and to correlate these finding with the clinical and laboratory markers of neonatal sepsis.

Patients and methods

We conducted this prospective controlled cohort study from January 2014 to June 2015 in the Neonatology and Cardiology Units, Pediatric Department, in a tertiary care hospital. The study included 40 full term neonates with neonatal sepsis who were admitted to Neonatal Intensive Care unit and 40 apparently healthy neonates of similar age and sex as a control group. Inclusion Criteria: Any term-neonate (>37 completed postmenstrual week) presented with clinical signs of neonatal sepsis, and confirmed to have neonatal sepsis by positive blood culture and/or positive sepsis markers. Exclusion criteria include: Infants with congenital malformations, genetic syndromes, congenital heart diseases, premature neonates, infants of diabetic mothers, hypoxic ischemic encephalopathy, and intra-uterine growth retardation. All the enrolled neonates had complete blood count, highly sensitive C-reactive protein, high sensitivity cardiac Tropnin T (cTnT), serum procalcitonin (PCT) level, and blood culture at the time of diagnosis.

Echocardiography

Echocardiographic examination was done using (Vingmed Vivid-7, General Electric Vingmed, and Milwaukee, Wisconsin, USA). Data acquisition was performed with a S7 probe at a depth of 16 cm in all the standard echocardiographic views according to the recommendation of the American Society of Echocardiography.[4] All neonates were examined in the right anterior oblique position if possible with breathing room air, or on oxygen supplement or mechanical ventilation according to the individual condition.

Integrated M-mode, two-dimensional (2-D) mode and pulsed and continuous wave Doppler were used to estimate left ventricle (LV) internal dimensions including LV end-diastolic dimension, LV ventricle endsystolic dimension, ventricular septal thickness, posterior wall thickness, fractional shortening, mitral and tricuspid inflow velocities, and systolic pulmonary artery pressure. Tei index, which is a Doppler-derived time interval index that combines both systolic and diastolic cardiac performance, was also calculated as previously described by Tei and colleagues.[5]

Tissue Doppler imaging (TDI) was performed using the same machine and probe at a depth of 16 cm in the parasternal and apical views (standard long-axis and two- and four-chamber images). From the apical four-chamber planes, using pulsed-wave tissue Doppler, the myocardial velocity curves of septal mitral valve annulus, lateral mitral valve annulus, and lateral tricuspid valve annulus were recorded. The electrocardiogram and respiration curve monitoring were connected and traced simultaneously to define the timing of cardiac cycle events and its relation to respiratory events. The beginning of QRS complex was used as a reference point.[6] At least 10 cardiac cycles were recorded at a speed of 100 millimeters/second and the images were stored electronically. The mean values for three heart beats during expiration were used for the analysis. The systolic wave (S) reflects the systolic function of either right or left ventricle. The early/atrial (E'/A') ratio of tricuspid and mitral valve annulus reflects the diastolic function of the right and left ventricle, respectively. Isometric contraction time was defined as the time duration between the beginnings of QRS complex in the electrocardiogram to the beginning of tissue Doppler S wave. The isometric relaxation time was defined as the interval between the end of S wave and the beginning of the early wave. Both isometric contraction time and isometric relaxation time were corrected for heart rate.[7]

For speckle tracking analysis of right ventricular chambers; standard grayscale 2-D images were acquired in the four-chamber view using a 7.5 MHz transducer at a depth of 16 cm with a stable electrocardiography (ECG) recording using acoustic tracking soft -ware (EchoPAC; allowing off -line semi-automated analysis of speckle based strain) to study LV and RV deformation and to measure LV and RV peak global longitudinal systolic strain. LV global peak systolic strain was recorded in 3-standard apical views, and segmental peak systolic strain in basal, mid, and apical segments of anteroseptal, anterior, lateral, posterior, inferior, and septal LV walls. For the STI analysis, we used high frame (65 frames/s) with harmonic two-dimensional images. The RV was divided into six standard segments (at the basal, middle, and apical levels on the septal and RVFW side), and the software generated six corresponding time-strain curves. The peak of the average curve of all the segments was considered as peak global longitudinal strain (PGLS). The peak global longitudinal strain was automatically calculated from the combined deformation of the myocardial segments in each imaging plane and used as a measure of RV function. For myocardial strain, regional thickening or lengthening was expressed as a positive value and thinning or shortening as negative values.[2]

Reproducibility

Intra-observer variability for echocardiographic data was done for patients and controls, where the same sonographer repeated examinations twice at the same day of diagnosis. Intra-observer agreement in interpreting echocardiographic data was determined using Cohen kappa (κ) statistics.

Statistics

The statistical power of the study was more than 90% (using a computerized program: Power and Precision V3; www.PowerAnalysis.com). Data were presented as mean (± standard deviation) values. The two-way analysis of variance with repeated measures and chi-square test by SPSS V.16 were used to identify statistically significant differences in the different parameters among the groups. For all analyses, a statistical significance of P-value less than 0.05 was used. Wilcoxon's signed-rank test was used to assess the normality of distributions of the data. The Bonferroni correction/adjustment procedure was performed to avoid "significance" due to chance only, in multiple comparisons with echocardiographic parameters. Correlation between sepsis markers and echocardiographic variables was evaluated using Pearson's correlation coefficient.

The Institutional Ethical and Research Review Board of Faculty of Medicine, Tanta University approved the study protocol. All the parents of the included newborns signed a written informed consent before enrolment into the study. We were complied with the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects and/or animals.

Results

The study included 40 term neonates diagnosed with confirmed sepsis and 40 term apparently healthy neonates as a control group. Their demographic, clinical, and laboratory data were shown in Table 1. There was significant increase in the total leucocytes count, and serum levels of CRP, procalcitonin, and cardiac Troponin-T (cTnT) in the neonates with sepsis as compared with the control group. CRP was positive in 85% of cases, the septic group. It was negative in all cases of the control group. Blood culture was positive in 65% of neonates with sepsis (55% were gram positive and 10% were gram negative bacteria).

Table 2 showed the echocardiographic data of the studied groups. The conventional echocardiography showed no significant difference in LV FS (which represent LV systolic function) and both E/A ratios at mitral and tricuspid valves (which represent the diastolic function of LV and RV) between the neonates with sepsis and control group. On the other hand; TDI showed significant reduction of S wave (which represent LV and RV systolic function) and E'/A' wave at mitral and tricuspid valve annuli with significant prolongation of LV IVRT and RV IVRT (which represent LV and RV diastolic function) in the neonates with sepsis than in the control group. These indicated impaired systolic and diastolic functions of both LV and RV in the neonates with sepsis. At the same time, the myocardial performance index (Tei index) was impaired and significantly prolonged for both ventricles in neonates with sepsis than in the control neonates. Speckle tracking echocardiography also showed significantly increased global systolic strain for both right and left ventricles in the patients group than in the control. There was no significant difference in the neonates with gram +ve sepsis compared with those with gram –ve sepsis as regard to the echocardiographic parameters.

Table 3 and 4 showed correlation of echocardiographic data of both LV and RV with body weight and markers of sepsis including TLC, CRP, cTnT and serum PCT. Body weight, showed no significant correlation with any of the echocardiographic data of both LV and RV. At the same time, CRP, cTnT, and serum PCT showed no significant negative correlation with LV FS, E'/A' ratio and S wave of the LV while cTnt showed significant negative correlation with E'/A' ratio and S wave of RV. However, they showed significant positive correlation with Tei Index and GLS of both LV and RV. Only CRP showed significant positive correlation with both LV IVRT and RV IVRT.

Table 1 Demographic, clinical and laboratory data of patient and control groups

		Patient Group (n=40)	Control Group (n=40)	t	P
Postnatal Age (Days)		11.500±5.53	13.8±6.57	1.7	0.09
Gestational Age (Weeks)		38± 0.85	37.95 ±0.83	0.28	0.8
Caesarean Section		22 (55%)	15 (37.5%)	1.1	0.1
Weight at Diagnosis		2.94±0.36	3.06±0.34	1.5	0.1
APGAR Score 1		6.4±2.5	8.3±1.40	-4.2	<0.0001
APGAR Score 5		7.8±1.57	9.4±0.85	-5.66	<0.0001
Sex	Male	21 (52.5%)	22 (55%)	Z = 0.2	0.8
	Female	19 (47.5%)	6 (45%)		
	Total	26 (65%)			
Blood Culture Positivity	Gram +Ve	22 (55%)	0		
	Gram - Ve	4 (10%)			
TLC		17.1± 4.3	7.25±1.3	13.8	<0.0001
CRP (mg/l)		46.9±28.7	3.52 ± 2.4	9.5	<0.0001
PCT (ng/ml)		8.72±5.7	0.8±0.7	8.7	<0.0001
cTnT (mg/L)		0.19±0.08	0.07±0.02	9.2	<0.0001

cTnT, cardiac toponin T; CRP, C-reactive protein; HB, hemoglobin; PCT, procalcitonin; PLT, platelets; TLC, total leucocytic count

Table 2 Comparison between echocardiographic data between patients and the control group

	Patient Group (n=40)	Control Group (n=40)	t	P
LV FS	39.4±4.4	41.2±5.14	-1.7	0.09
E/A ratio MV	0.87±0.35	1.0±0.3	-1.8	0.08
E'/A' Wave Mitral Annulus	0.50±0.14	1.1±0.17	-17.2	<0.0001
S Wave Mitral Annulus (Cm/s))	3.8±0.9	5.4±0.98	-7.6	<0.0001
LV IVRT	68.0±18.3	61.0±7.2	2.2	0.02
LV TEI Index	0.47±0.051	0.38±0.06	7.2	<0.0001
LVGLS	10±2.35	-18.3±2.7	14.7	<0.0001
Pul Systolic Pressure (mmHg)	38.5±5	30.5±4	7.9	<0.0001
E/A Ratio TV	0.9±0.2	1.0±0.3	1.7	0.08
E'/A' Wave Tricuspid Annulus	0.84±0.05	1.21±0.04	-36.5	<0.0001
S Wave Tricuspid Annulus(cm/sec)	4.3±0.6	7.6±0.4	-28.9	<0.0001
RV IVRT	69.0±15.3	63.0±6.2	2.3	0.02
RV TEI Index	0.44±0.05	0.36±0.06	15.4	<0.0001
RVGLS	7.3±2.35	-18.3±2.7	19.4	<0.0001

FS, fraction shortening; IVRT, isovolumetric relaxation tim; GLS, global longitudinal strain; MV, mitral valve; TV, tricuspid valve

Table 3 Correlations between weight, CRP, HB, PLT, TLC, Procalcitonin, and cTnT with the echocardiographic data of the LV

	LV FS		E'/A'		S		IVRT		Tei Index		GLS	
	R	P	R	P	R	P	R	P	R	P	R	P
wt	0.14	0.55	0.03	0.9	0.14	0.55	0.13	0.6	0.2	0.4	0.01	0.97
TLC	-0.05	0.82	-0.29	0.21	-0.05	0.82	0.31	0.19	-34	0.15	-0.26	0.27
CRP	-0.22	0.36	0.1	0.67	-0.22	0.36	0.52	0.02*	0.67	0.01*	0.533	0.016*
cTnT	-0.43	0.011	0.545-	0.036	-0.43	0.01	0.4	0.047	0.728	0.02	0.85	0.001*
PCT	-0.15	0.85	-0.34	0.15	-0.54	0.01	0.35	0.21	0.66	0.01	0.57	0.03

CRP, C-reactive protein; cTnT, cardiac toponin T; FS, fraction shortening; GLS, global longitudinal strain; HB, hemoglobin; IVRT, isovolumetric relaxation time; PCT, procalcitonin; PLSS, peak longitudinal systolic strain; PLT, platelets; TLC, total leucocytic count

Table 4 Correlations between weight, CRP, HB, PLT, TLC, Procalcitonin, and cTnT with the echocardiographic data of the RV

	E'/A'		S		IVRT		Tei Index		GLS	
	R	P	R	P	R	P	R	P	R	P
wt	0.03	0.9	0.14	0.55	0.13	0.6	0.2	0.4	0.01	0.97
TLC	-0.29	0.21	-0.05	0.82	0.31	0.19	-34	0.15	-0.26	0.27
CRP	-0.1	0.67	-0.22	0.36	0.52	0.02*	0.67	0.01*	0.533	0.016*
cTnT	0.545-	0.036*	-0.43	0.01*	0.396	0.047*	0.43	0.02*	0.357	0.03*
PCT	-0.24	0.25	-0.44	0.01*	0.25	0.31	0.57	0.03*	0.52	0.04*

CRP, C-reactive protein; cTnT, cardiac toponin T; FS, fraction shortening; GLS, global longitudinal strain; HB, hemoglobin; IVRT, isovolumetric relaxation time; PCT, procalcitonin; PLT, platelets; TLC, total leucocytic count

Citation: Awny MM, Abd-Rab-Alrasol OT, Al Biltagi MA, et al. Cardiac functions by tissue doppler and speckle tracking echocardiography in neonatal sepsis and its correlation with sepsis markers and cardiac troponin-T. *J Pediatr Neonatal Care*. 2016;5(3):11–12. DOI: 10.15406/jpnc.2016.05.00184

Discussion

Neonatal sepsis is a frequent cause of admission to neonatal intensive care unit with significant morbidity and mortality; partly related to the concomitant severe cardiac dysfunction and the associated perfusion insufficiency especially in overwhelming sepsis.[8] Many laboratory markers are used to detect and to monitor neonatal sepsis. CRP and PCT are both proteins released in response to infection and/or inflammation. CRP is a good but non-specific marker for diagnosis of neonatal sepsis. However, it does not rise significantly until almost 14-48 hr after the onset of infection.[9] In our study, CRP and PCT were significantly higher in the neonates with sepsis than the control group and CRP was positive in 85% of the sepsis group. Combination of both CRP and PCT may increase the sensitivity to early detect neonatal sepsis and can be used to rule out sepsis rather than to rule it in. However, in spite that PCT and CRP are broadly used, they have limited capabilities to differentiate sepsis from other inflammatory conditions and to predict outcome. Other new biomarkers like soluble triggering receptor expressed on myeloid cells-1 (sTREM-1), soluble urokinase-type plasminogen receptor (suPAR), proadrenomedullin (ProADM), and presepsin may have a role in the near future.[10]

In the current study, cTnT was significantly higher in neonates with sepsis than in control neonates. Possible reasons for elevation of cTnT in neonates with sepsis is reduction of myocardial perfusion the associated arterial hypotension, microscopic tissue damage secondary to microvascular thrombosis, and due to the enhanced apoptosis in response to release of pro-inflammatory cytokines.[11,12]

TDI and STE are relatively new echocardiographic techniques, which measure the myocardial tissue functions and myocardial strain pattern; and are superior to conventional echocardiography in terms of early assessment of global systolic and diastolic functions. Data about echocardiographic changes in heart of neonates with sepsis are still needed especially regarding RV performance. This is especially important as the cardiac effects of sepsis in not limited to the left side of the heart but mostly include the RV as well.[13]

In our study, there was significant LV and RV systolic and diastolic dysfunction detected by TDI (reduced S wave and E'/A' ratio and prolonged IVRT of both LV and RV). There were also increased Tei indices in both ventricles, which denotes presence of global right and left ventricular dysfunction. However, conventional echocardiography failed to document presence of systolic or diastolic dysfunction of both ventricles with normal LV FS and normal E/A ratio of mitral and tricuspid valves. This agreed partially with the work of Tomerak et al.[14] who found LV global ventricular dysfunction by the significantly higher LV Tei index in the non-survivor neonates with sepsis than in the survivors. However, they detected also LV diastolic dysfunction by the reduced E/A ratio in the septic premature and full-term neonates, compared to the controlled non-septic newborns. This difference between their study and our study may be due to the different stage of sepsis during the performance of echocardiographic examination as we examined our patient once admitted to NICU. At the same time, they studied the left ventricular function only and they did not extend their work to involve the right ventricle.[14] However, Abdel-Hady et al.[15] found that TDI was more sensitive than conventional echocardiography in detecting ventricular dysfunction in the septic neonates which agreed with our results. They detected significantly higher RV and LV Tei indices and significantly lower mitral and tricuspid peak annular S wave in septic neonates compared to non-septic neonates.[15] Presence of preserved LV FS in our cases with sepsis despite occurrence of cardiac dysfunction may be related to other factors rather than affection of the muscular pump as it is affected by the "hemodynamic" as well. Meanwhile, the hemodynamics of sepsis are often much different from a stage to stage with shifting from low cardiac output states to high cardiac output states.[16]

In our study, there was impaired both LV and RV GLS by STE. It provides an angle-independent assessment of regional myocardial deformation and does not rely on geometrical assumptions with the ability to measure the motion in any direction within the image plane, unlike the tissue Doppler ability, which is limited to the velocity component toward or away from the probe.[17] Peak longitudinal strain measurement is independent from global cardiac motion and allows quantifying regional myocardial deformation in the different LV or RV segments. Progressive deterioration of LV or RV longitudinal strain has been found in patients with stable FS, suggesting that myocardial strain could be a more sensitive parameter for detecting early ventricular dysfunction.[18] Our work agreed with the work of Haileselassie et al.,[19] who found abnormal peak systolic longitudinal strain for age and low normal peak systolic circumferential strain in infants and children with sepsis compared to the control group while fractional shortening was normal indicating the better sensitivity of strain echocardiography in assisting diagnosis and grading of pediatric sepsis.[19] The cardio depressant effects of sepsis may be due to many interacting factors such as presence of interstitial myocarditis, necrotizing vasculitis with necrosis of cardiac fibers and interstitial edema, myocardial abscesses, direct effects of bacterial endotoxins on myocardium or direct effects of bacteria with bacterial colonization in the myocardium augmented with autonomic dysregulation and impaired calcium flux.[12]

In our study, there was positive correlation between cTnT and many of echocardiographic parameters (LV and RV Tei Index and GLS) and negative correlation with other parameters such as S wave and E'/A' ratio that indicate global cardiac dysfunction. This finding agreed with the work of Mehta et al.,[20] who found significant correlation between the serum level of cTnI and the reduction in EF.[20] In a previous study done by Kristien et al.,[21] high plasma concentrations of cTnT were found in 36% and cTnT was absolutely related to LV dysfunction in multiple regression analysis.[21] Landesberg et al.,[22] showed also that patients with sepsis who have systolic, diastolic or combined dysfunction had significantly higher serum levels of high-sensitivity cTnT than those without cardiac dysfunction.[22] High serum cTnT levels are associated with increased mortality rate and may be suitable to be used as a prognostic marker of myocardial ischemia in patients with sepsis under various therapeutic schedules.[23]

In our study, there was significant positive correlation between CRP level and IVRT, Tei Index, and GLS of both RV and LV, which denotes the significant correlation of CRP level and degree of cardiac dysfunction. CRP itself is doubtful to have a direct role in cardiovascular damage. Conversion of plasma CRP to monomeric CRP is mediated by activated platelets, which are associated with cardiovascular risks and can explain the correlation of CRP with the cardiac dysfunction observed in our study.[24] In our study, PCT was significantly positively correlated with Tei indices of both RV and LV and negatively correlated with S wave at tricuspid valve annulus. Noori et al.,[25] found that PCT had strong and significant correlation with the most echocardiographic parameters in patients with dialed cardiomyopathy.[25] However, the increase of procalcitonin in our patients compared to controls would be related to the systemic inflammatory process associated with the sepsis.

Limitation of the study

We did not perform another echocardiographic examination to correlate the findings with the progression of the sepsis condition. We did not also calculate the cut off point for cTnT, PCT and CPR that could expect presence of cardiac dysfunction because of the different parameters that could expect presence of cardiac dysfunction.

Conclusion

Echocardiographic examination with TDI and STE are able to early detect cardiac dysfunction in neonatal sepsis. PCT, CRP, and cTnT were significantly correlated to the cardiac dysfunction.

Acknowledgments

None.

Conflicts of interest

Authors declare that there is no conflict of interest.

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