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Three-Dimensional Speckle Tracking Echocardiography for the Assessment of Cardiac Function in Newborns with Extra- Cardiac Diseases

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ABSTRACT

Neonatal heart could be affected by extracardiac diseases as neonatal sepsis, neonatal pneumonia, hypoxic-ischemic encephalopathy. Cardiac function in neonates can't be accurately assessed using conventional methods. Advanced echocardiographic parameters can be used to evaluate neonatal cardiac function as Tissue Doppler Imaging (TDI) and speckle tracking echocardiography. This study aimed at assessing the role of three-dimensional speckle tracking echocardiography (3D-STE) in detection of subclinical myocardial dysfunction in newborns with common extra-cardiac neonatal diseases. In this work; 100 asymptomatic cardiac newborns with extra-cardiac neonatal diseases were included as a patient group. Fifty healthy newborns of matched age, sex, and weight served as a control group. Laboratory investigations in the form of complete blood count (CBC), liver function test, renal function test, capillary blood gas, serum electrolytes, cardiac troponin I (cTnT-I) and N-terminal Pro-BNP were drawn. Complete echocardiographic evaluation of the left ventricular (LV) function was performed in the form of conventional echo, tissue Doppler imaging (TDI), 2-dimensional speckle tracking echocardiography (2D-STE) and 3-dimensional speckle tracking echocardiography (3D-STE). cTnT-I and N-terminal Pro-BNP levels were significantly higher in the patient group than the control group. Conventional echocardiography showed normal systolic and diastolic function of the LV. Diastolic function (by TDI) was significantly lower in the patient group than control group. 2D-STE and 3D-STE examination showed that there was a significant decrease in all components of strain in the patient group compared to the control group. In conclusion; 3D-STE is a good tool for prediction of silent cardiac dysfunction in newborns with extracardiac neonatal diseases.

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Introduction

Transitional changes of the neonatal heart from fetal to postnatal circulation make them vulnerable. Changes in preload and afterload occur in both left and right ventricles together with physiological lung changes. Common neonatal diseases outside the heart; as neonatal pneumonia, sepsis, hypoxia… etc.; can affect cardiac function [1].

Measurements of left ventricular cavity; such as shortening fraction (SF) and ejection fraction are not sensitive for subclinical functional changes of neonatal heart. They can be influenced by preload and afterload [2]. Recently, neonatal evaluation of cardiac function can be assessed using quantitative echocardiographic methods as Tissue Doppler Imaging (TDI), two- and three-dimension speckle tracking echocardiography (2D, 3D-STE). These methods are more sensitive than usual measures [3-5].

Several biomarkers can signify myocardial injury in neonates, but their efficacy as a diagnostic tool cannot be established in neonates [6]. Natriuretic peptides and cardiac troponins are commonly used. Cardiac troponins indicate cardiomyocyte injury. While natriuretic peptides signify ventricular strain[7].

This study aimed at assessing the role of three-dimensional speckle tracking echocardiography for detection of subclinical myocardial dysfunction in neonates suffering from common non-cardiac diseases.

Patients And Methods

This case-control, prospective study was performed at neonatal intensive care unit, Tanta University Hospital, Tanta, Egypt during the period from February 2017 to January 2019. This study involved 100 neonates with common extra-cardiac diseases as a patient group. 50 healthy selected from those delivered at Obstetrics Unit, Tanta University Hospital with no cardiac or extra-cardiac diseases; matched for gestational age, sex and weight as a control group. Local ethical committee of Faculty of Medicine,

Tanta University approved the study. The parents of all neonates included in the study had signed an informed consent. The study is in accordance with the ethical standards of institutional research committee and with the 1964 Helsinki declaration and its later amendments.

Inclusion criteria: full term neonates with common extra-cardiac diseases as neonatal pneumonia, neonatal sepsis, transient tachypnea of newborn, neonatal jaundice and hemorrhagic disease of the newborn.

Exclusion criteria: newborn with congenital heart diseases, acquired heart diseases (viral myocarditis), dysrhythmias, symptomatic cardiac dysfunction secondary to extra cardiac diseases, significant pulmonary hypertension, systemic hypertension, dysmorphism, first 3 days of life, newborn with renal dysfunction, maternal pre-eclampsia, and maternal medication as tocolysis.

All neonates included were subjected to:

- Full history taking: antenatal steroids, maternal risk factors of infection, perinatal history, mode of delivery, immediate postnatal history, Apgar score, and resuscitative measures.
- Full physical examination: specially, anthropometric measurements including weight, length, head circumference, physical signs, and New Ballard score for estimation of gestational age [8].
- Routine Laboratory investigations: as complete blood count (CBC), liver function tests, kidney function tests, serum electrolytes, capillary blood gas, and C-reactive protein.
- Research laboratory investigations: Cardiac troponin-I and N-terminal Pro-BNP: by enzyme-linked immunesorbent assay (ELISA) and values were reported as pg/mL.
- Echocardiographic examination: complete echocardiographic examination using (Vivid 9, GE Health care, Horten, Norway) with S7 MHz and V4 matrix real-time 3-dimensional probes. Offline analysis of digital loops stored on the hard disk of echocardiography machine was done by an Echo PAC PC workstation (Echo PAC PC,113, GE, Horten, Norway).

Guided by the American Society of Echocardiography; conventional echocardiography study, tissue Doppler imaging (TDI), 2D speckle tracking echocardiography (2D-STE), and 3D-STE were performed [9].

Left ventricular systolic function was evaluated by conventional echocardiography through measuring LV ejection fraction (LV EF).

At mitral valve (MV) septal annulus TDI was obtained. So; systolic function of LV was represented as S' wave at MV. On the other hand, LV diastolic function by TDI evaluated by E'/A' ratio at MV. Then, Tie index (myocardial performance index MPI) was calculated as the sum of iso-volumetric contraction and iso-volumetric relaxation times divided by ejection time. MPI can assess both systolic and diastolic function of LV.

To obtain 2D-STE images a frame rate of more than 50 frames/cycle was adjusted through three cardiac cycles. During the cardiac cycle, endocardial borders were traced at end diastole and then divided into six equal segments. Longitudinal strain LS) was obtained at apical 2 chamber view. While both circumferential and radial strains (CS and RS) were obtained at parasternal short axis view at mitral, papillary and apical levels.

The 2D-STE images were obtained at a frame rate more than 50 frames/cycle during three cardiac cycles. Endocardial borders traced at end-diastole throughout the cardiac cycle were divided into 6 equal segments. Longitudinal strain (LS) was obtained from apical 2-chamber, 3-chamber and 4-chamber views. Circumferential and radial strain (CS and RS) were obtained from parasternal short-axis views at different levels. After obtaining the 2D planes, the software tracking endocardial borders was manually adjusted to improve tracking quality as needed.

Later, LV 3D full volume image was obtained to evaluate 3D-LS, 3D-CS and 3D-RS. The pyramidal scan volume should include the whole LV cavity, including the myocardium and pericardium. The region of interest (ROI); automatically produced at systole; where 3D-STE was started. ROI shape could be manually adjusted and pulled anywhere by placing attractor points. The last step of 4D auto LV quantification was 3D strain analysis. 3D strain ROI used the meshes created from endocardial and epicardial mesh to measure end-systolic volume and LV mass respectively.

From the results of tracking, 3D global strain derives several parameters including longitudinal, circumferential, area and radial strain. Regional thickening or lengthening indicated positive values while negative values resulted from thinning or shortening (Figure 1).

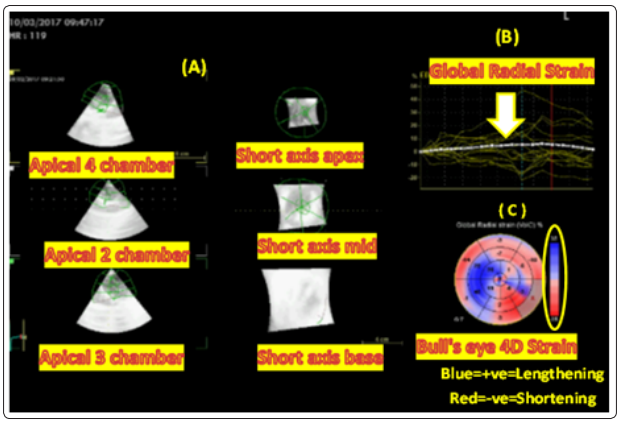

Figure 1: (A) 3D Strain results from a diseased neonate heart from left ventricular (LV) apical 4, 2 and 3 chamber long axis and LV short axis view at apex, mid-muscular and base, showing radial strain, (B) The upper part shows a plot with yellow traces for each of the 17 segments, in addition to a white trace for the global radial strain, (C) The lower part shows a colour coded bull's eye plot with instantaneous strain values. The instantaneous global strain is shown marked with a "G:" to the lower of the bull's eye plot; marked by yellow arrow.
Mid: mid-muscular, 4D: four dimension, +ve: positive, -ve: negative

Global area strain (GAS) was defined as the change percentage in the surface area presented by circumferential and longitudinal strains vectors.

The primary outcome was to assess the role of 3D-STE in early detection of subclinical cardiac dysfunction in neonates with extra-cardiac diseases. The secondary outcome was to correlate the findings with laboratory and other echocardiographic parameters.

Statistical Analysis

Data was analyzed using Statistical Package for Social Sciences SPSS V.21 (SPSS Inc.Chicago, IL, USA) software program. Qualitative variables were recorded as number and percentages

and were compared by Chi-square test. Normally distributed quantitative variables were presented as means ± standard deviation (SD) and were compared by Student t- test. Abnormally distributed quantitative variables were presented as median and range were compared by Mann Whitney test. Shapiro-wilk test was used to assess normality of the data. Correlations between different variables were performed using Spearman coefficient. Receiver operating characteristics (ROC) curve was performed to evaluate the predictive value of different variables to diagnose cardiac affection in sepsis patients. P value < 0•05 was significant.

Intra-observer and inter-observer agreements were calculated using the coefficient of variation (i.e., the percentage absolute difference between the measurements divided by their mean value). Measurements were repeated by another operator 48 hours following first examination for 15 randomly selected patients.

Results

We included 100 neonates with common extra-cardiac diseases as the patient group with mean gestational age of (37.94 ± 0.76) weeks, mean postnatal age of (8.99 ± 5.51) days, mean birth weight of (3.31 ± 0.38) kg, and they were 54 males and 46 females. The control group of 50 healthy neonates with mean gestational age of (37.14 ± 1.05) weeks, mean postnatal age of (9.68 ± 4.84) days, mean weight of (3.36 ± 0.23) kg, and they were 25 males and 25 females. There was no statistical difference between patient and control group as regards gestational age, postnatal age, sex, weight, and mode of delivery (P > 0.05). The patient group included 41 cases with neonatal sepsis, 16 cases with hypoxic ischemic encephalopathy (HIE), 15 cases with transient tachypnea of newborn (TTN), 14 cases with neonatal jaundice, 4 cases with hemorrhagic disease of newborn, and 10 cases with post-surgical cases. Apgar score was significantly lower in patients group than control group (Table 1).

Table 1: Characteristics of the studied neonates

Variable	Patient group	Control group	P value
Gestational age (weeks)	37.94 ± 0.76	37.14 ± 1.05	0.235
Postnatal age (days)	8.99 ± 5.51	9.68 ± 4.84	0.185
Sex			
Male	54	25	0.644[a]
Female	46	25	
Birth weight (Kg)	3.31 ± 0.38	3.36 ± 0.23	0.342
Length (cm)	49.17 ± 0.99	49.01 ± 0.95	0.346
BMI	13.62 ± 1.33	14.01 ± 1.16	0.076
Mode of delivery			
Normal vaginal	30	16	0.802
Cesarean section	70	34	
Apgar score	8.29 ± 1.42	9.66 ± 0.48	<0.001*

*: means significant, BMI: body mass index, a: Chi-square test, kg: kilograms, cm: centimeter

Hemoglobin, platelet count, and HCO3 were significantly lower in the patient group than the control group. On the other hand; cardiac Troponin-I and N-terminal Pro-BNP were significantly higher in the patient group than the control group (P < 0.05). Troponin-I had 90% sensitivity and 75% specificity, while N-terminal Pro-BNP had 71% sensitivity and 75% specificity. There was no statistically significant difference between the patient group and the control group as regards WBC, total bilirubin, direct bilirubin, urea, creatinine levels, serum electrolytes (Na, K, Ca), pH, and PCO_2 (P > 0.05) (Table 2).

Table 2: Laboratory findings in the studied neonates

Variable	Patient group	Control group	P value
Hemoglobin	13.91 ± 2.17	15.45 ± 1.48	<0.001*
White blood count	16.49 ± 7.09	18.0 ± 3.99	0.099
Platelet count	293.6 ± 134.2	357.4 ± 102.7	0.002*
Ph	7.40 ± 0.15	7.40 ± 0.05	0.599
PCO2	33.32 ± 10.88	35.48 ± 6.44	0.131
HCO3	19.57 ± 4.21	22.56 ± 2.21	<0.001*
Na	139.8 ± 6.18	139.2 ± 6.21	0.585
K	4.40 ± 0.83	4.40 ± 0.89	0.968
Ionized Ca	1.01 ± 0.19	1.08 ± 0.15	0.062
Total bilirubin	7.53 ± 4.85	6.07 ± 2.51	0.310
Direct bilirubin	1.45 ± 1.79	0.90 ± 0.51	0.144
Blood urea	36.52 ± 12.92	36.13 ± 10.05	0.850
Serum creatinine	0.44 ± 0.30	0.43 ± 0.15	0.858
Cardiac Troponin-I	26.27 ± 41.58	15.29 ± 1.19	<0.001*
N-terminal Pro-BNP	120.4 ± 203.1	42.77 ± 11.75	<0.001*

*: Means significant, BNP: Brain natriuretic peptide, Ca: serum ionized calcium, HCO_3: Bicarbonates, K: serum potassium, Na: serum sodium, PCO_2: Carbon Dioxide Pressure

45% of the patient group had no echocardiographic evidence of cardiac dysfunction and none of the cases had clinical evidence of cardiac dysfunction.

For conventional echocardiography; there was no significant difference between the patient and the control group as regards the LV systolic or diastolic function (P > 0.05). In TDI; there was a significant reduction of LV systolic function presented as systolic tissue Doppler velocity (S') and in diastolic function of left ventricle expressed by MV E′/A′ ratio in the patient group compared to the control group (P< 0.05). On the other hand, LV MPI was significantly higher in the patient group than the control group (P < 0.05) with sensitivity of 73% and specificity 94%. There was a significant reduction in the mean values of LS, RS, CS by 2D-STE in the patient group than the control group (P < 0.05), sensitivity was 80% and specificity 67.44% for 2D global longitudinal strain (2D GLS). There was a significant reduction in the mean values of LS, CS, RS and AS by 3D-STE in the patient group than the control group (P < 0.05); with sensitivity 100% and specificity 100% for 3D GLS (Table 3).

Table 3: Echocardiographic findings in the studied neonates

Variable	Patient group	Control group	P value
SF	33.94 ± 4.68	33.77 ± 4.73	0.831
EF	66.15 ± 6.02	66.04 ± 6.11	0.914
LVIDd	16.73 ± 3.94	16.45 ± 3.92	0.680
MV S'	4.05 ± 0.93	4.40 ± 0.78	0.025*
E'/A' ratio	0.67 ± 0.19	0.73 ± 0.12	0.021*
MPI	0.41 ± 0.08	0.31 ± 0.03	<0.001*
2D LS	-12.69 ± 4.38	-17.74 ± 1.98	<0.001*
2D CS	-11.53 ± 4.58	-17.20 ± 2.15	<0.001*
2D RS	10.23 ± 4.94	22.0 ± 2.46	<0.001*
3D LS	-5.60 ± 3.39	-17.29 ± 3.61	<0.001*
3D CS	-7.81 ± 3.40	-20.05 ± 5.33	<0.001*
3D RS	11.36 ± 4.69	25.11 ± 5.82	<0.001*
3D AS	-14.49 ± 5.43	-35.26 ± 8.06	<0.001*
Cardiac Troponin-I	26.27 ± 41.58	15.29 ± 1.19	<0.001*
N-terminal Pro-BNP	120.4 ± 203.1	42.77 ± 11.75	<0.001*

*: means significant, 2D: 2 dimensional, 3D: 3 dimensional, AS: area strain, CS: circumferential strain, E'/A' ratio: ratio of the early (E') to late (A') ventricular filling velocities, EF: ejection fraction, LV: left ventricle, LVIDd: left ventricle end diastolic diameter, LS: longitudinal strain, MPI: myocardial performance index, MV: mitral valve, S': systolic tissue Doppler velocity, RD: radial strain, SF: shortening fraction

There was a negative correlation between cTnT-I levels and 3D- CS group with no significant correlation with other various echocardiographic parameters. There was no significant correlation between N-terminal Pro-BNP levels and various echocardiographic parameters (Table 4).

Table 4: Correlation between troponin I and N-terminal Pro-BNP and echocardiographic variables

Variable	Cardiac Troponin-I		N-terminal Pro-BNP	
	R	P value	R	P value
MPI	0.002	0.988	0.055	0.592
2DLSS	-0.251	0.013	-0.109	0.287
2DCSS	-0.227	0.033*	-0.064	0.552
2DRSS	0.132	0.219	0.126	0.243
3DL	-0.052	0.658	0.112	0.337
3DC	-0.065	0.583	-0.049	0.676
3DR	-0.005	0.963	-0.107	0.363
3DA	0.045	0.708	0.175	0.138

*: means significant, 2DCSS: 2 dimension circumferential, 2DLSS: 2 dimension longitudinal systolic strain, systolic strain, 2DRSS: 2 dimension radial systolic strain, 3DA: 3 dimension area strain, 3DC: 3 dimension circumferential strain, 3DL: 3 dimension longitudinal strain, 3DR: 3 dimension radial strain, MPI: myocardial performance index, r: Spearman coefficient.

Inter-observer reliability was excellent for all the 3D-strains: ICCs were 0.9 for LS, 0.88 for CS, 0.93 for RS, and 0.91 for AS. 3 minutes and 5 minutes average were needed for complete acquisition and analysis of data by 3D-STE and 2D-STE respectively.

Discussion

The neonatal cardiac function can be affected by extra-cardiac diseases such as TTN, neonatal pneumonia, perinatal asphyxia, neonatal sepsis and others.1To the best of our knowledge, this study is the first to evaluate the role of 3D-STE in comparison to cTnT I and N-terminal Pro-BNP for early detection of subclinical cardiac dysfunction in newborn with extra-cardiac neonatal disease.

In our study, serum levels of cTnT- I and N-terminal Pro-BNP were significantly higher in the newborns with extra-cardiac neonatal diseases than the healthy control group that presented an indicator of myocardial injury caused by the disease. Similar results were obtained by other investigators [10, 11].

We found no significant correlation between N-terminal Pro-BNP levels and various echocardiographic parameters. However, there was a significant negative correlation between cTnT-I levels and 2D CSS in the patients group.

Our study showed that conventional echocardiography could not detect any systolic or diastolic LV dysfunction. This can be explained by low sensitivity of conventional echocardiography to detect minor structural changes occurred in neonatal heart. LV systolic and diastolic dysfunctions were detected only by TDI especially LV MPI which was significantly higher in patients group than control group. This was in agreement with Alzahrani, 2017 who had conducted a prospective cohort study that included 30 full-term neonates with neonatal sepsis [12].

In this work there was a significant decrease in all 2D strain including LSS, CSS and RSS in patient group than control group. Similar to our results; Awny et al, 2016; reported an impaired LV GLS by speckle tracking echocardiography in neonate sepsis group than control group [13].

Moreover, in absence of clinical symptoms of myocardial dysfunction, LV systolic dysfunction in the form decreased all 3D cardiac strains were detected. Choosing a sufficient frame rate, optimizing the gain, reducing the depth to include the entire LV cavity in the image sector could increase feasibility and accuracy of 3D-STE that depend mainly on the quality of the images obtained as well as the choice of a well-trained operator [14].

In our work there was a significant decrease in 3D LS, CS, AS and RS in the patient group than the control group. There was no available data about 3D-strain values in newborns with extra-cardiac diseases to compare with.

From our results, myocardial strain was found to be a sensitive means in detection subclinical LV systolic dysfunction. Strain is better compared to tissue velocity measurement that can be influenced by tethering [15]. Also, TDI is an angle-dependent method for strain measurement [16]. The use of 2D-STE to quantify LV deformation has been demonstrated, it is limited by foreshortened views, geometric modeling, and speckles motion out of plane. 3D-STE was recently developed to avoid these limitations and provides rapid image acquisition with a shorter scan time independent of operator skills by simultaneous data analysis of different strain [17]. Disadvantages of 3D-STE are mainly its dependanse on the images quality, the patients' cooperation for breath holding, and the regularity of the heart rate [14].

Limitation of the study: 3D-ST needs regular heart rate, so newborns with irregular heart rate are not suitable for analysis. Further studies are required to detect the effect of common extra-cardiac neonatal diseases on cardiac function using 3D-STE.

Conclusion

The use of 3D-STE as a novel tool and Area strain as a new parameter was successful in prediction of early cardiac dysfunction in newborn with extra-cardiac neonatal diseases.

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Conflict of Interest

There was no conflict of interest.

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