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Real Time 3-D Echocardiography for Evaluation of Left Ventricle in Children with Sickle Cell Anemia

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Abstract:

Background: Cardiovascular events and complications are the leading causes of mortality and morbidity in patients with sickle cell anemia (SCA). Early identification of ventricular dysfunction, before the appearance of symptoms, can alter the prognosis by optimizing therapy. This study aimed at clarifying the value of Real Time 3D Echocardiography (RT3DE) in early detection of regional myocardial dysfunction in those patients before the development of overt cardiomyopathy.

Methods: This is an observational cross sectional study that was carried out on 60 children divided into 2 groups; Group 1 included 30 children with SCA, Group 2: 30 children matched for age and sex as a control group. For all children: ethically committee approval and informed consent from the parents or their guardians was obtained. All Children with SCA under the age of 15 who do not show any signs or symptoms of heart failure were included in this study . Any child with present or past history of heart failure or any child with associated congenital or acquired heart diseases was excluded from the study. All children with systemic diseases that may affect cardiac structure and function have been also excluded. All the children were subjected to thorough clinical evaluation for any signs of heart failure, Echocardiography studies , included M mode , Tissue Doppler and 4D echo for assessment of left ventricle.

Results: TDI showed left ventricular systolic and diastolic dysfunction in SCA compared with the control. RT3DE was a sensitive tool to detect an increase in LVEF $\%$ There was no significant LV enlargement through LV LSS and DSI in our cohort. There was no significant relation between hemoglobin level and different echo parameters in the studied groups.

Conclusion: RT3DE with tissue Doppler technique are promising tools for early detection of regional systolic or diastolic dysfunction of left ventricle in children with SCA.

Keywords: High sensitive CRP , Speckle tracking echo, Children

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Introduction

Sickle cell anemia is one of the major types of hemoglobinopathies in Egypt [1]. Cardiac insult secondary to chronic anemia and hemosiderosis remains the major cause of morbidity and mortality in those children with sickle cell anemia [2]. Chronic anemia and the tissue

hypoxia impair free fatty acid oxidation and ATP production in myocardial cells.

Cardiac dysfunction in those patients may be due to myocarditis, and iron overload in the heart, leading to RV diastolic then LV systolic dysfunction, and iron overload in the lungs leading to elevated pulmonary arteriolar resistance, RV dilatation and dysfunction.

However, congestive heart failure develops late in the disease process. Because congestive heart failure is the main cause of death, early recognition of cardiac dysfunction may be useful in modifying therapy [3].

Echocardiography provides noninvasive and fast bedside method to study cardiac function; however, conventional echo-Doppler technique has its limitation in the quantitative assessment of regional myocardial function [4]. Therefore, tissue Doppler imaging (TDI), speckle tracking imaging (STI), and real time 3 dimensional echocardiography (RT3DE) can be applied in the quantitative assessment of regional myocardial function. In children with SCA, wall motion abnormalities may represent an early sign of cardiac disease despite preserved global ventricular function [5, 6]. Based on this concept, this study aimed at clarifying the value of TDI, STI, and RT3DE in early detection of regional myocardial dysfunction before the development of overt cardiomyopathy.

Subjects and Methods

This is an observational cross sectional study that was carried out during the period from December 2012 to November 2013. Cases were selected from hematology department at Tanta University Children Hospital, Tanta, Egypt. This study was conducted on 60 children divided into 2 groups;

Group I: included 30 children diagnosed with sickle cell anemia with their age ranged from 9 months to 12 years. Those children were diagnosed by hemoglobin electrophoresis.

Group II: included 30 healthy children matched for age and sex (as a control group). For all children: ethically committee approval and informed consent from the parents or their guardians was obtained.

Inclusion Criteria: Children with sickle cell anemia under the age of 15 who do not show any sign or symptoms of heart failure.

Exclusion Criteria: Any child with present or past history of heart failure was excluded from the study or any child with associated congenital or acquired heart diseases. All children with

systemic diseases that may affect cardiac structure and function such as systemic arterial hypertension, diabetes mellitus, thyroid disorders, obesity, and renal or hepatic dysfunction have been also excluded from the study.

All the children were subjected to (A) through clinical examination for signs of heart failure.

B) Laboratory: all the children were subjected to measurements of hemoglobin levels by Hemogram

C) Echocardiography: Each child underwent a detailed echocardiographic study, including M-mode, two-dimensional, color Doppler, and TDI using a GE Vivid 7 ultrasound machine equipped with an X4 matrix-array transducer. The 3D data set was stored in SunOS format on CD-ROM and transferred to two separate workstations for off-line data analysis. All the measurements were made by only the same pediatric cardiologist.

M-Mode: Echocardiographic evaluation included left ventricle (LV) end-diastolic and end-systolic diameters, septum and LV posterior wall thicknesses in diastole and systole, LV end-diastolic and end-systolic volumes, and LV ejection fraction by Simpson's method. Transmitral flow patterns were obtained by pulsed-wave Doppler echocardiography from apical four chamber views. Mitral peak early (E) and late (A) diastolic velocities, E/A ratio, E wave deceleration time, and isovolumetric relaxation time were measured. These echo parameters were measured from M-mode echo derived from the parasternal long axis view at the mitral chordal level. Left ventricular fractional shortening (LVFS) was calculated. Left ventricular ejection fraction (LVEF) was also calculated from M-mode echo.

Tissue Doppler imaging (TDI): was evaluated at the level of basal segments of anterior, septal, lateral and inferior LV wall and peak myocardial systolic, and early and late diastolic velocities were measured from apical two and four chamber views. All pulsed-wave Doppler and TDI parameters were measured at the end of expiration at a sweep speed of 100 mm/s on

three consecutive heart beats with the average for each taken.

RT3DE: Image analysis – QLAB semi-automated border detection method :

Semi-automated border detection bi-plane LV volume analysis was performed using off-line QLAB version 2.0 (TomTec, Munich, Germany). LV quantification starts by definition of the proper 4-chamber view and adjustment of the LV 4-chamber and orthogonal views to avoid foreshortening. Then it is made sure that the intersection point of the displayed horizontal and vertical lines is in the middle of the LV cavity. Subsequently, the end-diastolic (largest LV volume) and end-systolic (smallest LV volume) frames are identified. On both these end-diastolic and end-systolic frames, 5 identification points are marked: the septal, lateral, anterior, and inferior mitral annulus and the apex. Then the software automatically delineates the LV endocardial border and by sequential analysis the software creates a LV mathematical model or “cast” that represents the LV cavity and LV volumes are calculated. Unsatisfactory delineation of the endocardial border was manually adjusted. LV ejection fraction (LV-EF) is calculated by the software.

Statistical analysis: IBM SPSS statistics (V. 21.0, IBM Corp., USA, 2012) was used for data analysis. Data were expressed as mean \pm SD for quantitative parametric measures. The differences in the variables were compared between the patients and controls using the t-test. Pearson correlation test was used to study the possible association between each two variables among each group for parametric data. Statistical significance was defined as a p value < 0.05 .

Results

The demographic data of the studied groups are represented in Table 1. Female sex predominate in our patients with mean age of 6.7 years. All patients presented with anemia with hemoglobin level of 8.4. Tables 2 shows different echo parameters using conventional echo, tissue doppler and speckle tracking compared to the control. Only tissue Doppler shows significant systolic and diastolic dysfunction in SCA

presented by significant decrease in the S wave as well as E/A ratio respectively. Table 3 reports significant difference in the echo parameters among SCA group by 4D and Dyssonchrony Systolic Index (DSI) while conventional echo failed to show any difference in comparison with the control group. Table 4 shows no significant correlation between different echo parameters by different modes in and hemoglobin level. However there was significant change in LVGLSS with the age of our patients with SCA.

Table 1 : Demographic data of the studied groups

	Control	SCA
No	30	30
Male Sex (%)	11(55)	13(43.3)
Age (years)	2-10 (6.5 \pm 2.8)	0.75 -12 y (6.7 \pm 2.8)
Hemoglobin (g/dl)	10.5-.8 (12.4 \pm 0.79)	6.6-10 (8.4 \pm 0.99)

Discussion

Sickle cell anemia (SCA) is associated with long-standing severe anemia. Abnormal cardiac findings present in those patients are primarily the result of chronic anemia and the compensatory increased cardiac output.(3) Congestive heart failure, the main cause of death develops late in the disease process. Early detection of cardiac abnormality may be helpful to modify treatment [7,8].

Although one would expect an increase in left ventricular ejection fraction (LV EF) in response to high cardiac output and increased preload secondary to chronic anemia, the absence of this response in the current study might reflect an early marker of systolic alteration. In contrast, RT3DE showed that LVEF was significantly higher in our cohort when compared to controls.

This may be due to the high cardiac output state and increased preload secondary to chronic anemia in these patients. RT3DE is superior to conventional echo in detection of significant increase in the LVEF in SCA compared to control. This may be explained by the accuracy

of RT3DE and by the fact that the accuracy of left ventricular (LV) volumes and ejection fraction (EF) on conventional echocardiography is limited by image position, geometric assumption, and boundary tracing errors [9, 10].

Table 2: Echocardiography parameters in SCA group vs. control group

Variables	SCA (n=30)	Controls (n=30)	p
E/A	1.53±0.17	1.60±0.16	0.2
S(cm/s) (TDI)	6.9±0.40	7.2±0.44	0.012*
É/Á (TDI)	1.48±0.45	1.72±0.24	0.024*
Global LV LSS (%)	-19.62±2.9	-21.5±1.71	<0.3

- Values are expressed as mean ± SD *Significant(p<0.05)
- E:early mitral filling velocity, A:late mitral filling velocity, S: Mitral annulus systolic velocity estimated by tissue Doppler, É:Early mitral annulus diastolic velocity estimated by tissue Doppler, Á: Late (atrial) mitral annulus velocity estimated by tissue Doppler.

Table 3: Comparison between SCA and Control as regards EF-2DE and EF-4DE.

Variables	SCA (n=30)	Controls (n=30)	p
LV EF(2DE)	72.267 ± 6.2131	73.45 ± 4.5708	0.2
LVEF (4DE)(%)	74.167± 5.5029	66.1± 5.098	<0.05*
LV DSI(%)	3.65 ± 1.5507	2.13 ± 0.2296	<0.05*

•Values are expressed as mean ± SD *p < 0.05 is of significance

DSI: Dyssonchrony Systolic Index, EF (4D) :Ejection Fraction measured by Real Time 3 Dimensional Echo, EF (2D) :Ejection Fraction measured by two Dimensional Echo

Table 4 : Relation of echocardiographic parameters in SCA with age and hemoglobin level.

	Age		Hemoglobin	
	r	p	r	p
EF(2D)	-0.241	0.199	-0.227	0.228
E/A	-0.079	0.611	0.052	0.785
S	-0.045	0.814	0.026	0.893
É/Á	0.283	0.13	-0.32	0.085
LVGLSS	-0.376	0.04*	0.226	0.229
EF(4D)	-0.245	0.191	-0.175	0.354
DSI	0.246	0.19	0.092	0.627

*p<0.05 is of significance **E**:mitral inflow early velocity, **A**:mitral inflow late(atrial)velocity. **DSI**:Dyssynchrony Systolic Index, **EF (4D)** :Ejection Fraction measured by Real Time 3 Dimensional Echo, **EF (2D)** :Ejection Fraction measured by two Dimensional Echo,

LV LSS:Left ventricular Longitudinal systolic strain **S**:Mitral annulus systolic velocity estimated by tissue Doppler, **E**:Early mitral annulus diastolic velocity estimated by tissue Doppler, **A'**:Late (atrial) mitral annulus velocity estimated by tissue Doppler

Reduced systolic velocity of mitral annulus displacement (Sm) by Tissue Doppler is considered a sensitive marker of left left ventricular systolic dysfunction in individuals with preserved left ventricular ejection .In current study, there was significant decrease in mitral annulus systolic velocity(S wave) in SCA children when compared to controls. This reflects an impaired contraction and segmental wall motion abnormalities in this group of patients .This is different from that found by other previous studies [11-13].These studies found that LV systolic function was preserved in the majority of SCD patients studied in a resting state. They concluded that when LV dysfunction was present, it had been seen particularly in older patients and those with associated conditions such as hypertension and renal disease .

For LV diastolic function, there was no significant difference between SCA and control as regards E/A parameters by conventional Doppler. This may be explained by our younger age group and our exclusion criteria that accept only asymptomatic hemodynamically stable children. Again, conventional doppler technique has some limitations in detection an early mild cardiac diastolic dysfunction in these young aged children. Therefore tissue Doppler was sensitive that it detects significant diastolic dysfunction in our patients compared with controls as regards E'/A' ratio. Similar finding had been reported by other studies [11,14].These findings may be due to the fact that, Overtime, progressive dilation leads to increased wall stress and mass with subsequent impaired LV filling due to a combination of compensatory hypertrophy secondary to anemia and LV dilation along with

a systemic vasculopathy affecting afterload. Direct myocardial damage from micro-vascular disease and iron deposition have also been postulated as etiologies for the cardiac abnormalities [15,16].

With its capability to quickly capture the 3D dynamics of the entire left ventricle, including the timing of regional wall motion independent of its direction, RT3DE imaging has emerged as an alternative approach for the quantification of LV systolic dyssynchrony index (LV DSI) [17]. Most RT3DE dyssynchrony index studies have used the Standard Deviation (SD) of the regional ejection times (interval between the R wave and minimum systolic LV volume) as an index of dyssynchrony. Recent attempts to compare this index against TDI have resulted in fair results that ranged from fair inter technique correlation to poor agreement, which was explained by the angle dependency of TDI and by the fact that these 2 techniques measure different parameters. [18]. RT3DE assessment of LV dyssynchrony has the potential advantage of measuring the timing of the longitudinal, radial, and circumferential motion as opposed to the longitudinal motion only, which is measured by TDI [19].

In current study, SCA children had significant increase in DSI when compared to healthy group (DSI was $4.55 \pm 2.1\%$). This is similar to previous study that showed increased DSI with worsening LV systolic function regardless of QRS duration [19]. Our study showed that there is no significant relation between hemoglobin level and echocardiographic parameters in SCA even with the presence of the effect of the hyperdynamic state as a result of chronic anemia that may affected some echocardiographic

parameters noticed in increased EF in 4D echocardiography . This is different to that reported by other studies [2,20]. They found that there was LV dilation, and its degree is related to the degree of anemia .This may be explained by our younger age group and our exclusion criteria that accepted only asymptomatic hemodynamically stable children. Also, patients with SCD are maintained with a mild chronic anemia (characteristically averaging 9 g/dl) and had a high cardiac output.

In conclusion, the current study points to the pattern of early changes in left ventricular function and volumes indicate that children with SCA who have no overt heart failure may show early regional systolic & diastolic dysfunction. RT3DE with tissue Doppler technique are promising tools for quantitative assessment of myocardial function and early detection of regional systolic or diastolic dysfunction of left ventricle. Hemoglobin levels determination is very important in chronic anemia when they are assisted by echocardiography, as decreased hemoglobin level may cause a hyperdynamic state that may affect the systolic, diastolic function and chamber volume as detected by EFs, S, LVLSS & DSI of 4D echo. We recommend routine follow up echo using the recent echocardiographic modalities as TDI and RT4DE in evaluation of children with SCD as a diagnostic and follow up tools for early detection of impaired cardiac function to allow intervention before the development of overt cardiac insult. Larger multicenter studies in this field may clarify the possibility of application of these new techniques as a routine work in daily practice in various systemic diseases.

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