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Evaluation of Ventricular Functions in Egyptian Pediatric Patients with End Stage Kidney Disease

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Abstract

Background: In our study, we evaluated the left and right ventricular (LV and RV) functions in children and adolescents with end stage kidney disease (ESKD) by both conventional and two-dimensional (2D) longitudinal speckle-tracking echocardiography (STE) in both patients with ESKD under conservative measures and those ESKD on maintanance hemodialysis (mHD).

Objective of the study: To study ventricular functions in Egyptian Pediatric patients with CRF.

Patients and methods: 49 children with CRF (24 on conservative treatment and 25 on rHD) and thirty healthy controls matched for age and sex were included and subjected to history, clinical, laboratory, two-dimensional (2D) STD and tissue Doppler study to measure different echocardiographic parameters focusing on left and right ventricular functions.

Results: Longitudinal strains of LV and RV were statistically decreased in diseased children than in healthy ones (-11.3 vs. -14.8, p<0.001 for LV and -9.6 vs. -15.3, P<0.001 for RV). In the HD patients, the longitudinal strain of RV was statistically decreased than in the non-HD patients (p=0.02). The longitudinal strain of RV was in a correlation with LV strain and hypertension.

Conclusions: The speckle tracking echocardiography reported early systolic dysfunction of both left and right ventricules in our CRF patients in spite of ordinary ejection fraction (EF) and fractional shortening (FS) by conventional echocardiographic study. Our study raises the importance of echocardiography as the gold standard for diagnosis of myocardial dysfunction in pediatric patients with CRF.

Keywords: Speckle tracking; Ventricular functions; Children; Chronic renal failure

Introduction

Guidelines for American Heart Association (AHA) for reduction of risk of cardiovascular disease (CVD) in children and adolescents categorize children with chronic kidney disease (CKD) as the highest risk group for CVD [1].

Early prediction and management of myocardial functions as cause of morbidity and mortality has become mandatory in management of children and adolescents with CRF [2-4]. However, few studies are available for early recognition of cardiac functions in children and adolescents with CRF [5,6].

To improve general care for pediatric patients with ESRD under maintenance HD, it is necessary to early diagnose children with myocardial systolic or diastolic dysfunction [7-10].

Tissue Doppler imaging (TDI) can early predict cardiac complications in children and adolescents with CRF including left ventricular (LV) hypertrophy (H), LV systolic dysfunction and diastolic heart dysfunction [11,12].

Previously published articles used the conventional echocardiographic study for cardiac function namely ejection fraction EF) and FS but these parameters were inaccurate [2,4,5,7-10,12-14].

Matteucci et al. were the first to discuss left ventricular geometry in children with mild to moderate chronic renal insufficiency [10].

2D STE has been considered as the best echocardiographic approach for early evaluation of subtle myocardial function in children with normal ejection fraction [15] as it can assess deformation, strain and its rate in the circumferential, longitudinal and radial myocardial axes and it can also subtract the whole cardiac tethering and translational motion [14,15].

Objectives

The objective of this study was to evaluate RV and LV myocardial function by 2DSTE in pediatric patients with CRF and to compare results in HD versus non-HD groups of patients.

Subjects and Methods

Sample size and sampling

This study was conducted on 49 pediatric patients with CRF. They were classified into group 1 included 24 patients with CRF under conservative treatment and group 2 included 25 patients with ESRD under rHD. The age of patients ranged from 10-18 years with 13.7 ± 3.9 as mean years. They were 32 males and 17 girls who were selected from the Nephrology Unit of the Pediatric Department of Tanta University Hospital (TUH) during the period from May 2017 till May 2018. Group 3 included 30 apparently healthy controls who were matched for age and sex with normal electrocardiography and transthoracic echocardiography.

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This work was performed after obtaining the acceptance of the research ethical committee of the Faculty of Medicine of Tanta University at Egypt in accordance with the Declaration of Helsinki and after obtaining informed oral or written consents from health care giver of the involved subjects.

Protocol of management of group 1 of patients: Children were on treatment by subcutenous erythropoietin (EPO), the dose was 50 IU/Kg/week, iron dextran intravenously in a dose of 100 mg/Kg/week, folic acid orally in a dose of 1 mg/day, calcium orally in a dose of one gram/day, 1,25$(OH)_2$ vitamin D3 in a dose of 0.01-0.05 µg/Kg/day and antihypertensive medications (iv or oral) for only patients with hypertension. The goal of pharmacologic treatment of hypertension in children is to reduce blood pressure to below the 95th percentile. Therefore, we used the term 'controlled' to indicate blood pressure below the 95th percentile in response to therapy.

Protocol of management of group 2 of patients: Children under regular maintenance HD, HD was initiated when glomerular filtration rate (GFR) was less than fifteen ml/min/1.73 m^3, 3 times/week, the HD session duration was 3-4 hours. Children were hemodialyzed by Fresenius 4008-B HD machine (Made in Germany). The blood flow rate of the machine was 2.5 × weight (kg)+100 ml/min. HD was done using hollow fiber dialyzers of polysulphane type which was fit for the body surface area (BSA) of the children (Fresenius F3 for BSA=0.4 m^2, F4 for BSA=0.7 m^2, F5 for BSA=1.0 m^2 and F6 for BSA=1.2 m^2). The dialysis solution was bicarbonate. All patients were receiving also the same supportive therapy which were mentioned before for group 1.

Inclusion criteria: All children with CRF with LVEF of=or >55%.

Exclusion criteria: Patients of primary cardiac diseases (e.g. congenital or rheumatic heart disease, cardiomyopathy, arrhythmias, severe valvular heart disease, heart failure), those with improper image quality of 2D STE patients with low ejection fraction (EF<55%).

All children were subjected to the following:

1) Full history taking, including demographic data; age, sex, history about primary cause of ESRD (CAKUT, cystic kidney disease, urologic disease, congenital nephrotic syndrome, oxalosis and Alport syndrome; acquired: glomerulonephritis, interstitial nephritis, vasculitis, chronic pyelonephritis, hypertension or others) and duration of dialysis (for group 2 only).

2) Thorough clinical examination including:

- Anthropometric measurements: as nutritional and developmental status assessment methods including weight, height, BM and the mid arm circumference (MAC).
- Vital signs: including arterial blood pressure (ABP) which was evaluated by auscultatory method by using a mercury sphygmomanometric apparatus, in the semi setting position after a period of rest at least ten minutes of rest, in the non fistula arm by using a cuff with an appropriate size and was taken as the mean value of three successive readings in 3 consecutive days.

Hypertension was identified as systolic or diastolic arterial blood pressure more than the 95th percentile for age, height and sex, or intake of antihypertensive drugs [16,17].

3) Routine Laboratory investigation: including complete Blood Count (CBC), serum creatinine and blood urea nitrogen (BUN).

Collection of specimen and its handling

Morning samples of venous blood were withdrawn just before HD sessions. Five ml of them were collected by sterile needles through gentle sterile venipuncture. Two ml was put on 20 uL EDTA solution as anticoagulant for estimation of CBC including differential total leucocytic count (TLC) which was done on Leishman stained peripheral blood smear with evaluation using ERMA PCE-210 N cell-counter from Erma, Inc. Japan.

4) Electrocardiography (ECG).

5) Two-dimensional echocardiogram (2D-echo): Echocardiography was done in Pediatric Nephrology and Cardiology Units of Pediatric Department of TUH using GE vivid 7 (GE Medical System, Horten, Norway with a 3.5 MHz multifrequency transducer). The echocardiography study included two dimensional study including E/A ratio, will be based on the mean of the 6 regional values.

Echocardiographic study was performed in the position of left lateral decubitus, the standard parasternal (short and long axis) and 2-and 4-chamber apical images, additional 4-chamber apical images were done that included the interventricular septum, apex and RV free wall up to tricuspid (T) valve. Images were stored in the cineloop format for off-line digital analysis. Longitudinal strain was evaluated off-line, on the 4-chamber cineloop that included the free wall of RV, using speckle-tracking analysis.

2D Echo, pulse wave Doppler and color Doppler tissue imaging were used for assessment of the following parameters:

- Ejection fraction of left ventricle (EF): for evaluating of systolic function of left ventricle (LVEF >60% was considered as normal).
- End-diastolic diameter (EDD).
- Interventricular Septum (IVS).
- Posterior Wall Thickness (PWT),
- Right Ventricular Diameter (RVID).
- Medial annular E wave (E').
- Lateral annular E wave (E').
- Tricuspid annular E wave (E').

The LV diameters: were measured at the end-systole and end-diastole phases.

- The peak systolic S wave. The early (E') and late (A') diastolic peak velocities of the septal and lateral mitral annuli, and lateral tricuspid annulus, were evaluated by pulse wave Doppler and Doppler tissue imaging.
- Fractional Area Change (FAC): for RV systolic function was assessed using by measuring the difference between RV volume in diastole and systole in A4C view.
- The Pulmonary Artery systolic Pressure (PASP): was measured using tricuspid regurge velocity gradient, and the RA pressure was estimated using inferior vena cava (IVC) diameter and distensibility.
- The E'/A' ratio: evaluated the diastolic function of LV and RV which is defined as ratio of passive filling of the ventricle, the early E wave and active filling due to atrial systole, the atrial A

wave, was also determined, normal ratio ranging from 1 and 2.

- Diastolic dysfunction was diagnosed in patients presenting with cardiac failure and having a reversal of the E/A ratio.
- The global ventricular longitudinal systolic strain: (Left ventricular strain (LVS), and Right ventricular strain (RVS)) were evaluated via the automated functional imaging method. Three apical views were recorded in each patient (apical long-axis and 4- and 2-chamber views) in gray scale with a frame rate of at least fifty/second. The mitral annulus and the LV apex were defined in each view. Using modified apical 4-chamber view, RV was traced to gain RV global longitudinal systolic strain (LSS). The strain analyses were done on an offline basis [11,14,15].

Statistical analysis

SPSS version 21 was applied for statistical analysis of our study. mean ± SD was used for expression of continuous variables. Unpaired t-test was used to compare between patients and controls and between the two patient groups. Chi-square test was used when appropriate. Pearson's bivariate correlation test was used to correlate between the different Doppler parameters and both RVS and LVS [18].

Results

Table 1 summerized the demographic, clinicolaboratory data of the studied patients and controls. Mean hemodialysis duration was 38 ± 43 months, and the most common duration was ≥3 years (32.7%). There was a statistically significant rise in number (no) of hypertensive patients in HD group if compared to non-HD group (75% vs. 60%, respectively P<0.0001; Table 1), on the opposite side, there was a significant increase in number of anemic patients in non-HD group if compared to HD group (50% vs. 36%, respectively, P=0.002) (Table 1).

The echocardiographic data of the studied children were summarized in Table 2. There was no statistical difference in EF between the studied groups.

The pulmonary artery systolic pressure (PASP) was statistically higher in the patients when compared to the controls. Annular systolic S' velocities were nearly similar in patients when compared to controls while annular early diastolic E' velocities were less in patients if compared to healthy children, as shown in Table 2. Longitudinal RV and LV strains were significantly lower in patients than in controls (RVS: -9.6 vs. -15.8, p<0.001; LVS: -11.3 vs. -14.8, p<0.001). Septum and posterior wall were significantly thicker in HD group when compared to non-HD patients while RV dimensions and RV systolic pressure were comparable between the 2 studied patients groups, as shown in Table 2. Medial mitral annular E' velocity, E'/A' ratio, and lateral tricuspid annular E' wave velocity were significantly lower in HD group II if compared to patients on conservative measures.

Regarding RV systolic function, there was no statistically significant difference between the two studied patients groups in RV systolic excursion velocity (S') (13.2 vs. 11.9, respectively=0.44), or FAC (34.7 vs. 35.2, respectively p=0.1).

Both longitudinal RV and LV strains were significantly lower in group II compared to group I (-8.55 vs. -10.86, for RV respectively p=0.02, and -10.3 vs.-12.6 for LV respectively, p=0.003).

Table 3 summarized correlations of RV and LV strains with different studied parameters, both RV and LV strains were significantly decreased in parallel with the impaired diastolic parameters as identified by pulsed wave tissue Doppler recordings.

Table 4 summarized a multivariate logistic regression analysis of factors which may affect echocardiographic results in the studied groups. They included age, sex, causes of ESRD, dialysis duration, hypertension, anemia. They were hypertension (p=0.001) and anemia (p=0.29).

Discussion

From the current study, we found that RV functions evaluated by 2D STE and tissue - Doppler diastolic velocities were significantly impaired in children with CRF if compared to healthy children despite

		All patient (No=49) 100%	Non-dialysis patients (No=24) 48.98%	Hemodialysis patients (No=25) 51.02%	Controls (No=30) 100%	P1 value	P2 value
Age in years	Mean ± SD	13.7 ± 3.9	13.5 ± 3.9	13.8 ± 3.8	13.6 ± 4	0.4	0.5
1 yr cause of CRF:	CAKUT: No (%)	17 (34.7%)	8 (33.3%)	9 (36%)	-	<0.05	-
No (%)	Acquired causes: No (%)	26 (53.1%)	12 (50%)	14 (56%)	-		
	Unknown: No (%)	6 (12.2%)	4 (16.7%)	2 (8%)	-		
Sex distribution: No (%)	Males: No (%)	32 (65.3%)	17 (70.8%)	15 (60%)	18 (60%)	0.7	0.75
	Females: No (%)	17 (34.7%)	7 (29.2%)	10 (40%)	12 (40%)		
Dialysis duration:	0-6 months: No (%)	10 (20.4%)	-	10 (20.4%)	-	0.001	-
No (%)	6-11 months: No (%)	9 (18.4%)	-	9 (18.4%)	-		
	12-36 months: No (%)	14 (28.6%)	-	14 (28.6%)	-		
	>36 months: No (%)	16 (32.7%)	-	16 (32.7%)	-		
Clinical signs: No (%)	Anemia (Hb<11 gm%): No(%)	21 (42.9 %)	12 (50%)	9 (36%)	-	0.002	-
	Hypertension: (Mean arterial blood pressure over 3 months >95^{th} percentile, or on antihypertensive medication: No(%)	67.3 (62.1%)	15 (60%)	18 (75%)	-	<0.001	-
Laboratory Investigations	Serum creatinine: Mean ± SD	9.1 ± 0.9	8.4 ± 0.3	9.7 ± 1.7	0.93 ± 0.1	0.001	0.001

CAKUT: congenital anomalies of kidney and urinary tract.
BP: blood pressure
Hypertensive: Mean of blood pressure values over 3 months >95^{th} percentile, or on antihypertensive medication.
P1: Statistically significantly different at <0.05 level for dialysis vs. non-dialysis patients.
P2: Statistically significantly different at <0.05 level for patients vs. controls.

Table 1: Demographic, clinical and laboratory data of the studied patients and controls.

comparable findings using systolic excursion velocity. The global LV systolic function was normal in our patients groups; however, the 2 D Echo reported that LV longitudinal strain was significantly decreased in the children under rHD compared to those under conservative treatment (p<0.05) [19].

RV function was studied previously in adult patients with end-stage renal disease (ESRD) using the conventional echocardiographic methods (tricuspid annular plane systolic excursion and right index of myocardial performance). Articles reported that there was decrease in RV function with increase in duration of HD [20].

Impaired mineral bone disease and increases $CaXPo_4$ product had been assumed to be main causes of LV systolic and diastolic dysfunction in dialysis patients [21].

Our results agreed with Hyashi et al. who used the color Doppler velocity imaging for evaluating LV function in their chronic kidney disease patients and Sood et al. who reported that LV diastolic dysfunction was a prognostic factor for their HD patients and added that 2D Echo underestimate LV function [22,23].

Our study was in agreement also with Yan et al., who reported that the 2D-STE contributes to the early identification of impaired LV myocardial function in their CRF patients who have preserved LV ejection [24].

Our results also agreed with Rathod et al. concluded that renal patients have a higher incidence of both systolic and diastolic dysfunctions, and added that diastolic dysfunction occurred earlier than the systolic dysfunction [25].

This work was also in agreement with de Bie et al. who reported diastolic dysfunction by STE as a prevalent event among their uremic patients and also concluded that LV mass and PWV were the only markers of diastolic dysfunction in their CRF patients [26].

Our results disagreed with Chen et al. who found that 3D STE had early detected disturbed myocardial function in their CRF patients

		All patient (No=49) 100%	Non-dialysis patients (No=24) 48.98%	Hemodialysis patients (No=25) 51.02%	Controls (No=30) 100%	P1 value	P2 value
EF	Mean ± SD	0.6 ± 0.1	0.64 ± 0.09	0.60 ± 0.07	0.6 ± 0.1	0.096	0.7
EDD	Mean ± SD	5.2 ± 0.8	5.10 ± 0.88	5.22 ± 0.74	4 ± 0.7	0.612	<0.001
IVS	Mean ± SD	1 ± 0.3	0.99 ± 0.18	1.20 ± 0.32	0.8 ± 0.2	0.007	0.006
PWT	Mean ± SD	1.1 ± 0.2	0.92 ± 0.12	1.10 ± 0.25	0.8 ± 0.1	0.004	0.002
RVID	Mean ± SD	2 ± 0.5	1.90 ± 0.46	1.88 ± 0.31	1.9 ± 0.3	0.825	0.126
FAC	Mean ± SD	34.7 ± 3	-	-	36.9 ± 2.7	-	0.09
PASP	Mean ± SD	35 ± 10	36.8 ± 11	32.6 ± 7.8	25 ± 6	0.14	<0.05
Medial S	Mean ± SD	7.8 ± 2	-	-	9 ± 1.7	-	0.9
Medial annular E' wave	Mean ± SD	7 ± 3	8 ± 3	5.7 ± 1.8	12 ± 3	0.002	<0.001
Medial A'	Mean ± SD	8.4 ± 2	-	-	7.8 ± 2	-	0.4
Medial E'/A'	Mean ± SD	0.9 ± 0.4	1 ± 0.4	0.7 ± 0.2	1.7 ± 0.7	0.004	<0.001
Lateral S	Mean ± SD	8 ± 2	-	-	8 ± 2	-	0.9
Lateral E' wave	Mean ± SD	8 ± 3.2	7.6 ± 2.7	7.5 ± 3.6	11 ± 3.4	0.88	0.004
Lateral A'	Mean ± SD	9.1 ± 3	-	-	8 ± 3.1	-	0.4
Lateral E'/A'	Mean ± SD	1.5 ± 0.6	0.9 ± 0.3	0.9 ± 0.6	0.9 ± 0.5	0.8	0.002
Tricuspid S	Mean ± SD	12.6 ± 2.9	-	-	12.4 ± 2.3	-	0.9
Tricuspid E' wave	Mean ± SD	10 ± 4	10.7 ± 4	8.3 ± 2.9	13 ± 6	0.04	0.03
Tricuspid A'	Mean ± SD	13 ± 6	-	-	13 ± 3	-	0.8
Tricuspid E'/A'	Mean ± SD	1 ± 0.4	0.9 ± 0.6	0.8 ± 0.5	0.8 ± 0.6	0.35	0.2
LVS	Mean ± SD	-10.4	-	-	-14.7	-	<0.001
RVS	Mean ± SD	-8.7	-	-	-15.2	0.02	<0.001

EF: Ejection Fraction; EDD: End-diastolic diameter FAC: Fractional Area Change; IVS: Interventricular Septum; PASP: Pulmonary Artery Systolic Pressure; PWT: Posterior Wall Thickness; RVID: Right Ventricular Diameter; S: Systolic; LAS; Lateral Mitral Annular Systolic Velocity; LV: Left Ventricular; P1: Statistically significantly different at <0.05 level for dialysis vs. non-dialysis patients. P2: Statistically significantly different at <0.05 level for patients vs. controls.

Table 2: Comparison between echocardiographic and tissue Doppler parameters of the studied patients and control groups.

Characterstisitic		RVS	LVS
MAE	r	0.48	0.5
	p	0.001	0.001
Medial E'/A'	r	0.47	0.52
	p	0.001	<0.001
LAE	r	0.51	0.36
	p	<0.001	0.02
Lateral E'/A'	r	0.54	0.41
	p	<0.001	0.003
TAE	r	0.4	0.4
	p	0.005	0.005
Tricuspid E'/A'	r	0.29	0.38
	p	0.05	0.007

LVS: Left Ventricular Strain; RVS: Right Ventricular Strain; MAE: Mitral Annular E wave; LAE: Lateral Annular E wave; TAE: Tricuspid Annular E wave.

Table 3: Correlation between right ventricular strain (RVS) and left ventricular strain (LVS) and different tissue Doppler parameters.

Characteristic		Adjusted Odds ratio	95% Confidence limit	P
Age		0.98	0.93-1.03	0.4
Sex	Males	0.98	0.7-1.8	0.4
	Females	1.21	0.81-1.83	0.36
Duration of onset of CKD	0-6 months	1.6	0.79-3.29	0.19
	6-11 months	1.18	0.59-2.37	0.64
	12-36 months	0.73	0.4-1.38	0.34
	>36 months:	1.61	0.95-3.46	0.07
Primary cause of ESRD	CAKUT	0.8	0.5-1.3	0.3
	Acquired	0.79	0.49-1.27	0.33
		1.22	0.65-1.27	0.54
Hypertension		2.53	1.57-4.1	0.0002
Anemia		1.6	1.05-2.43	0.0289
Hypertensive: Mean of arterial blood pressure values over 3 months >95th percentile, or on antihypertensive medication. CAKUT: Congenital Anomalies of Kidney and Urinary Tract.				

Table 4: A multivariate regression analysis of factors which may affect echocardiographic results in the studied groups.

who had normal LVEF. They also reported that the global three-dimensional strain and the regional longitudinal strain appear to be higher in their rHD patients when compared with their non-HD patients. The discrepancy in results could be attributed to the difference in the demography of the studied patients [27].

Limitation of the study

The small sample size is a limitation of this study.

Conclusions

Both LV and RV myocardial functions may be impaired in children and adolescents with CRF in spite of preserved ejection fraction and systolic excursion velocity. Finding a lower ventricular function in the pediatric patients on rHD than recently diagnosed non-HD children confirmed that rHD could not protect against the deleterious myocardial effects of waste products; in such patients, another renal replacement therapeutic modality such as peritoneal dialysis, continuous HD or kidney transplantation may be a better therapeutic choice.

Recommendations

Early detection of impaired cardiac strain and dysfunction can be easily achieved using STE as new imaging modalities.

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