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CLINICAL STUDY

Assessment of left ventricular function by tissue Doppler echocardiography in pediatric chronic kidney disease

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Abstract

Background: Cardiovascular (CV) disease remains the most common cause of mortality in chronic kidney disease (CKD). *Methods*: In this cross-sectional study, 43 pediatric patients with CKD were divided into two groups according to their estimated glomerular filtration rate (eGFR): groups 1 and 2 (eGR; 29–75 and 15–29 mL/min/1.73 m^2, respectively). M – mode, conventional pulsed wave Doppler (cPWD) echocardiography and tissue Doppler imaging (TDI) were performed in all patients and 16 healthy controls. Maximal early (*E* wave) and late (*A* wave) diastolic flow velocities were assessed by cPWD. Using TDI, the early (*E′*) and late (*A′*) diastolic filling velocities were recorded. Early and late diastoles were evaluated using *E′* values and *E*/*E′* ratios, respectively. *Results*: Left ventricular hypertrophy (LVH) was determined in 19/43 (44.2%) patients. The *E*/*E′* ratio was significantly higher in group 2 than in group 1 and controls. *E*/*E′* was found to be positively correlated with left ventricular mass (LVM) index, and negatively with hemoglobin (Hb) levels. Low Hb levels were only independent predictor of *E*/*E′* ($p = 0.001$, β: −0.470, 95% CI: −0.764; −0.196). *E′* ratio was significantly lower in both patient groups compared to the controls. *Conclusions*: LVH and diastolic dysfunction are already present in early stages of CKD. Treatment of risk factors, such as anemia, is important to improve the clinical outcome.

Keywords

Child, chronic kidney disease, conventional pulsed wave Doppler echocardiography, left ventricular function, tissue Doppler imaging

History

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Introduction

Cardiovascular (CV) morbidity is the most likely cause of mortality in patients with chronic kidney disease (CKD).[1,2] Left ventricular (LV) hypertrophy, LV systolic and diastolic dysfunction that are the most common CV abnormalities in adult and pediatric patients with end stage renal disease (ESRD) develop during early stages of CKD and progress as renal function deteriorates.[3–5]

Tissue Doppler imaging (TDI) is a relatively new echocardiography technique evaluating systolic and diastolic function of the left ventricle by measuring regional myocardial contraction and relaxation velocities. In previous studies, it has been reported that TDI is less influenced by confounding factors, such as heart rate, volume status, sampling site, left atrial pressure and superior to conventional pulsed-wave Doppler echocardiography (cPWD), in detecting early impaired myocardial function.[6–10]

The aim of this study is to assess the relation between cardiac risk factors and LV structural/functional abnormalities examined by both cPWD and TDI in pediatric patients with CKD.

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Materials and methods

Study population

Forty-three patients with predialysis CKD who were followed at our institution were included and studied cross-sectionally. Inclusion criteria were (i) aged 7–19 years; (ii) eGFR (estimated glomerular filtration rate) 15–75 mL/min/1.73 m^2; (iii) absence of congenital, structural or primary myocardial and vascular disease. Three patients who were receiving corticosteroid due to their primary disease and one with uncontrolled hypertension were excluded. The patients were divided into two groups according to their eGFR: group 1 consisted of patients with mild–moderate renal failure (eGR: 29–75 mL/min/1.73 m^2) and group 2 with severe renal failure (eGR: 15–29 mL/min/1.73 m^2). We reviewed the medical records for age, sex, cause of CKD, duration of renal failure (since diagnosis), antihypertensive and other medications. Weight, height, systolic (SBP) and diastolic blood pressures (DBP) of the patients and the controls on the day of echocardiographic evaluation were enrolled. Blood pressure was measured three times during the same day in the sitting position by the same physician using a mercury

sphygmomanometer and the appropriate-size cuff. The mean of three measurements was calculated. Hypertension was defined as average systolic BP and/or diastolic BP $\geq$ 95th percentile for sex, age and height or as the use of antihypertensive medications.[11] Uncontrolled hypertension was defined as blood pressure that remains above the 95th percentile for age, sex and height despite use of antihypertensive medications.

Glomerular filtration rate was estimated by the Schwartz Formula.[12] Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$.

Sixteen age and sex-matched children who were diagnosed primary nocturnal enuresis formed the control group. These children had a normal cardiac and kidney function (eGFR >90 mL/min/1.73 m^2).

Biochemical analysis

Venous blood samples were drawn on the day of echocardiographic evaluation and stored at −80°C for subsequent biochemical analysis. Serum intact parathyroid hormone (PTH) levels were measured using Electrokemiluminesans Immunoassay (ECLIA) method by means of an autoanalyzer (Roche Modular Analytics E170, Mannheim, Germany). Serum 25 OH vitamin D levels were determined using a UV detector by high-performance liquid chromatography method (LC 20AT, Shimadzu, Kyoto, Japan) and immuChrom brand kit (ImmuChrom GmbH, Tiergartenstr 7, Heppenheim, Germany). Serum 1.25 $(OH)_2$ vitamin D levels were measured using enzyme-linked immunosorbent assay (ELISA) method (Cusabio Biotech Co. Ltd., Wuhan, China).

The other serum biochemical analysis including creatinine, cystatin C, blood urea nitrogen, calcium (Ca), phosphorus (P), hemoglobin (Hb), albumin, hs-CRP (high-sensitivity C reactive protein), lipids were performed by using routine methods at the Department of Biochemistry.

Echocardiography

Conventional and TDI studies (Vivid 7 Pro with 3 MHz transducer, GE, Horten, Norway) were performed in all patients and controls by the same pediatric cardiologist, blinded to the medical records of the patients.

Conventional echocardiography; two-dimensional directed M-mode and pulsed-wave Doppler echocardiographic measurements were done according to the American Society of Echocardiography recommendations.[13] Left ventricular mass (LVM) was calculated using the Devereux formula: $LVM = 0.8 \times [1.04 \times (LVEDD + PWT + IVSDT)^3 - (LVEDD)^3 + 0.6$ g, where LVEDD is left ventricular diameter in end diastole, PWT is posterior wall thickness in diastole and IVSDT is interventricular septum thickness in end diastole.[14] LVM index (LVMI) was calculated by dividing LVM by height $(m)^{2.7}$ and expressed in $g/m^{2.7}$.[15] LVH was defined as the LVMI $\geq$38 $g/m^{2.7}$ ($\geq$95th percentile of the pediatric population).[16] The relative wall thickness (RWT) was calculated as an index of the LV geometric pattern: RWT = (IVSDT + PWT)/LVEDD. Concentric LVH was defined as increased LVMI and elevated RWT ($\geq$0.41), eccentric LVH; increased LVMI with normal RWT, and concentric remodelling; normal LVMI but elevated RWT.[17]

LV systolic function was evaluated by the calculation of ejection fraction (EF) and fractional shortening (FS):

EF: (end diastolic diameter − end systolic diameter)/end diastolic diameter) × 100

FS: (end diastolic volume − end systolic volume)/end diastolic volume) × 100

LV diastolic function was assessed by determining maximal early (*E* wave) and late (*A* wave) diastolic flow velocities, and *E*/*A* ratio.

TDI; LV myocardial TDI studies were performed during contraction and relaxation of LV to assess the sample velocity at the lateral margin of mitral annulus. All parameters were measured during three consecutive cardiac cycles, and their mean value was used. The peak systolic velocity (S' wave), the early (E' wave) and late (A' wave) diastolic septal mitral annular peak velocities were recorded. Early diastole was assessed using the index of LV relaxation (E'). Late diastole was evaluated using the index of LV compliance (LV filling pressure, E/E' ratio).

Diastolic dysfunction was described as significantly lower E', E/A, E'/A' and significantly higher E/E' ratios than in the controls. Systolic dysfunction was described as significantly lower EF, FS and S' values compared with the controls.

The study was approved by the local Ethics Committee of Akdeniz University, and informed consent was obtained from the patients and the controls.

Statistical analysis

All statistical analyses were performed using SPSS for Windows 16.0 and the results are expressed as percentage, mean ± standard deviation and median (Interquartile Range, IQR) as appropriate. For comparison of continuous variables among multiple groups, Kruskal–Wallis test or one-way analysis of variance was used. When the difference was significant, Tukey's *post-hoc* test or Mann–Whitney's *U* test with Bonferroni's adjustment was done as appropriate. Categorical parameters were compared using Chi-square test. Serum PTH, 25(OH)D and 1,25$(OH)_2$D levels were log-transformed for normalization of data. Multiple stepwise regression analysis was performed to assess potential independent predictors of LVH, diastolic and systolic dysfunction. Association between two continuous variables was assessed by the Spearman correlation analysis or Pearson correlation coefficient as appropriate. p-Value <0.05 was considered statistically significant.

Results

Clinical characteristics

Forty-three children, 26 boys (60.5%), mean age of 12.3 ± 3.3 years (range: 7.1–19) were included in the study. The underlying renal diseases were urinary tract anomalies in 18 (41.8%) patients, glomerulopathies in three (7%), hereditary/metabolic diseases and renal hypoplasia/dysplasia in five patients (11.6%) each, cystic renal disease, nephrolithiasis and unknown etiology in four patients (9.3%) each. Twenty-four (55.8%) patients were in group 1 and 19 (44.2%) in group 2. Sixteen patients (37.2%) were taking anti-hypertensive

medication. Angiotensin-converting enzyme (ACE) inhibitors were used in eight, angiotensin receptor blockers in four, calcium-channel blockers in three, beta-blockers in one patient. Two patients required two anti-hypertensive medications. Six patients who did not have hypertension were taking ACE inhibitors and/or angiotensin receptor blockers as antiproteinuric therapy. The control group consisted of nine females and seven males, mean age 11.2 ± 3.0 years (range: 7–18.1).

There were no significant differences in age, sex, BMI and casual systolic and diastolic BP between patients and controls (all $p > 0.05$) (Table 1). Both the patient groups had significantly higher median serum total cholesterol, LDL cholesterol, PTH, P, 25(OH)D levels and CaxP product when compared with the controls. In patients with severe renal failure, PTH values were significantly higher and, Hb and 25(OH)D levels were lower than in the patients with mild–moderate renal failure and the controls (Table 2).

Cardiac structure and geometry

Mean LVMI and RWT were significantly elevated in both the CKD groups compared with the controls. LVH was determined in 19/43 (44.2%) patients. Even though the difference did not reach statistical significance, LVH was more frequent in patients with severe CKD than in those with mild–moderate renal failure (group 1; 33.3% and group 2; 57.9%, $p = 0.107$). LVMI was negatively correlated with Hb levels ($p = 0.026$, $r = -0.339$), age ($p = 0.038$, $r = -0.318$) and height ($p = 0.021$, $r = -0.352$), while positively with E/E' ratio ($p = 0.01$, $r = 0.388$). Height was independent predictor of LVH ($p = 0.048$, β: -0.286, 95% CI: -0.379; -0.002). Concentric LVH was the most common abnormal geometric pattern (30.2%).

Systolic function

Ejection fraction, FS and S' values did not differ between the control and patient groups.

Table 1. Clinical characteristics of the patients and control group.

Parameters	Controls ($n = 16$)	Group 1 ($n = 24$)	Group 2 ($n = 19$)	Total cohort ($n = 43$)	p
Male/female	7/9	16/8	10/9	26/17	0.190
Age (year)	11.2 ± 3.0	12.7 ± 3.5	11.3 ± 3.2	12.3 ± 3.3	0.237
Height (cm)	139.0 ± 16.4	145.6 ± 17.5	135.6 ± 16.4	141.9 ± 16.9	0.960
BMI (kg/m^2)	18.8 ± 2.3	18.7 ± 5.0	18.2 ± 5.7	18.5 ± 5.3	0.283
Casual SBP (mmHg)	102.2 ± 14.4	101.6 ± 10.5	107.3 ± 10.9	104.2 ± 10.9	0.872
Casual DBP (mmHg)	60 ± 12.6	62.5 ± 9.4	63.6 ± 7.6	63.0 ± 8.6	0.949
Hypertension (n, %)	–	7 (29.2)	9 (47.4)	16 (37.2)	0.220
Antihypertensive use (n, %)	–	7 (29.2)	9 (47.4)	16 (37.2)	
Phosphate binders (n, %)	–	12 (50.0)	16 (84.2)	28 (65.1)	
Calcitriol use (n, %)	–	1 (4.2)	5 (26.9)	6 (14)	
Erythropoietin use (n, %)	–	1 (4.2)	5 (26.9)	6 (14)	

Notes: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 2. Biochemical data of the patients and control group.

Parameters	Controls ($n = 16$)	Group 1 ($n = 24$)	Group 2 ($n = 19$)	p
Hemoglobin (g/dL)	12.6 ± 0.9	12.7 ± 1.4	11.2 ± 1.5[a,b]	0.001
Albumin (g/L)	4.5 ± 0.2	4.4 ± 0.5	4.4 ± 0.4	0.655
Hs-CRP (mg/L)	0.03 (0.02–0.04)	0.05 (0.02–0.12)	0.09 (0.02–0.51)	0.149
PTH (pg/mL)	37.5 (28.5–43.7)	58.0 (34.5–80.5)[a]	137 (96–247)[a,b]	<0.001
Serum Ca (mg/dL)	9.5 ± 0.4	9.5 ± 0.5	9.4 ± 0.8	0.888
Serum P (mg/dL)	4.4 ± 0.4	5.2 ± 0.7[a]	5.4 ± 1.0[a]	0.001
CaxP product (mg^2/dL^2)	42.2 ± 4.8	49.9 ± 7.3[a]	51.3 ± 9.4[a]	0.001
Serum 25 (OH)D (pg/mL)	31 (23.2–41.7)	21.5 (16.7–28.0)[a]	15 (7–24)[a,b]	<0.001
Serum 1,25(OH)$_2$D (pg/mL)	10.5 (6.7–15.1)	8.2 (4.9–13)	6.4 (3.6–12.2)	0.644
Triglycerides (mg/dL)	104.4 ± 32.7	141.6 ± 74.9	143.6 ± 61.5	0.118
Total cholesterol (mg/dL)	150.7 ± 11.7	166.9 ± 32.3[a]	189.6 ± 55.9[a]	0.014
LDL cholesterol (mg/dL)	86.4 ± 15.7	91.3 ± 27.6	111.7 ± 44.7[a]	0.045
HDL cholesterol (mg/dL)	45.2 ± 6.7	47.2 ± 13.3	49.2 ± 11.5	0.588
eGFR (mL/min/1.73 m^2)	112 ± 3.2	57.5 ± 14.2	25.0 ± 4.6[a,b]	<0.001

Notes: Hs-CRP, high-sensitivity C reactive protein; PTH, parathyroid hormone; Ca, calcium; P, phosphate; 25 (OH)D, 25 hydroxy vitamin D; 1,25(OH)$_2$D, 1,25 dihydroxy vitamin D; LDL cholesterol, low-density lipoprotein cholesterol; HDL cholesterol, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate.

Data are presented as the mean ± SD or the median (interquartile range, IQR) as appropriate.

p Values are for comparison across all groups obtained from ANOVA or Kruskal–Wallis.

[a]Significant difference with control patients; group 1 and group 2 were compared separately with controls by Tukey's post-hoc test or Mann–Whitney U test.

[b]Significant difference with group 1 patients; group 2 was compared with group 1 by Tukey's post-hoc test or Mann–Whitney U test.

Table 3. Echocardiographic findings of patients and controls.

Parameters	Controls ($n = 16$)	Group 1 ($n = 24$)	Group 2 ($n = 19$)	p
LV structure				
LVMI (g/m$^{2.7}$)	33.1 ± 2.8	37.8 ± 6.6[a]	43.0 ± 14.9[a]	0.012
LVH (n, %)	–	8 (33.3)	11 (57.9)	0.107
RWT	0.3 ± 0.04	0.4 ± 0.09[a]	0.4 ± 0.1[a]	0.001
LV geometry (n, %)				
Normal	17 (100)	14 (58.4)	3 (15.8)	
Concentric LVH	–	8 (33.3)	5 (26.3)	
Eccentric LVH	–	–	6 (31.6)	
Concentric remodelling	–	2 (8.3)	5 (26.3)	
LV systolic function				
EF (%)	71.5 ± 5.9	72.0 ± 5.9	73.4 ± 6.4	0.79
FS (%)	40.5 ± 4.8	40.8 ± 5.1	42.0 ± 5.5	0.76
S' (cm/s)	8.93 ± 1.48	8.87 ± 1.94	8.63 ± 2.03	0.88
LV diastolic function				
E/A	2.12 ± 0.48	1.8 ± 0.8	1.7 ± 0.5	0.09
E'/A'	2.70 ± 0.68	2.37 ± 0.83	2.22 ± 0.66	0.18
E' (cm/s)	17.93 ± 1.98	16.04 ± 2.54[a]	14.21 ± 3.22[a]	0.001
E/E'	5.66 ± 0.88	5.65 ± 1.18	7.10 ± 1.81[a,b]	0.001

Notes: LV structure, left ventricular structure; LVMI, left ventricular mass index; RWT, relative wall thickness; LVH, left ventricular hypertrophy; EF, ejection fraction; FS, fractional shortening; S', peak systolic velocity; E, peak of early diastolic flow velocities; A, peak of late diastolic flow velocities; E', early diastolic peak filling velocity; A', late diastolic peak filling velocity.

Data are presented as the mean ± SD or the median (interquartile range, IQR) as appropriate.

p Values are for comparison across all groups obtained from ANOVA or Kruskal–Wallis.

[a]Significant difference with control patients; group 1 and group 2 were compared separately with controls by Tukey's post-hoc test or Mann–Whitney U test.

[b]Significant difference with group 1 patients; group 2 was compared with group 1 by Tukey's post-hoc test or Mann–Whitney U test.

Diastolic function

The E/E' ratio was significantly higher in group 2 than in group 1 and the controls. E/E' was positively correlated with LVMI ($p = 0.01$, $r = 0.388$), and negatively with Hb levels ($p = 0.02$, $r = -0.348$). Low Hb levels were only independent predictor of E/E' ($p = 0.001$, β coefficient: -0.470, 95% CI: -0.764; -0.196). E/A and E'/A' ratios were similar among the groups. E' velocities were significantly higher in both the patient groups compared to the controls. No significant correlation was found between E' and any of the parameters in Tables 1–3. There was no association between E/A, S', E', E/E', E'/A' ratios and age.

Discussion

Herein, we reported a comprehensive study assessing global left ventricular function by conventional and tissue Doppler methods and cardiac risk factors in pediatric predialysis CKD patients.

In the patients with CKD, the abnormalities of diastolic function precede systolic dysfunction.[6–9] Conventional PWD has been widely used to assess LV diastolic function and, in this method, a decrease in the E/A ratio, the index of LV relaxation, indicates diastolic dysfunction. In previous studies, reduced E/A ratios in children on dialysis have often been reported.[7,8,18,19] In addition, Mitsnefes et al.[6] determined low E/A ratios in predialysis pediatric patients as well. Whereas, in another studies in CKD patients, E/A ratios were similar to that in healthy children, in contrast to Mitsnefes et al.[9,10] We also did not find any significant difference in E/A ratios between the patient and control groups. However, cPWD is influenced by several factors, such as preload and left atrial pressure, and this may explain the controversial results related to the E/A ratios in patients with CKD.

In contrast to the E/A ratio, early diastolic myocardial peak velocity (E') by TDI is a relatively preload-independent index of LV relaxation and used to assess LV early diastole.[20–22] In our study, we determined significantly lower E' values in both the patient groups when compared to the controls. In accordance with our findings, in other studies, the relatively low E' velocities indicating diastolic dysfunction were shown in predialysis and dialysis patients.[6,8–10]

E/E' ratio by the combination of transmitral flow velocity with annular velocity, another index of diastolic function, evaluates LV myocardial compliance at end-diastole particularly in patients with preserved systolic function. Increased E/E' ratios point out elevated filling pressures, and therefore, impaired diastolic function.[20,23] Mitsnefes et al.[6] found significantly higher E/E' ratio in both predialysis and dialysis patients than in the controls. In their study, they did not find any association between age and E/E'. Simpson et al.[10] determined an age-related increase in E/E' z-scores in predialysis patients, and they thought that this increase may not have major clinical relevance in childhood but might be an early indication of diastolic dysfunction in later life. Lindblad et al.[9] observed significantly higher E/E' ratio in predialysis patients and a young age correlated with an increased E/E'. In our study, E/E' ratios were significantly higher in severe CKD patients, but not associated with age.

In summary, the most sensitive determinants in detecting diastolic dysfunction in our patients were E' velocity and E/E' ratio, as reported previously in both CKD patients and after renal transplantation.[24]

The studies by cPWD show that LV systolic function is usually preserved in patients with CKD.[25] However, in a previous study, it was demonstrated that fractional shortening measured at the midwall levels (mS) was significantly decreased in children with predialysis CKD.[4] In that study, subclinical systolic dysfunction defined as reduced mS was associated with low hemoglobin levels. In another study,[26] although predialysis and dialysis patients had increased LV mass, LV performance and contractility at rest, it was shown that contractile reserve diminished during exercise in the cohort of dialysis. Simpson et al.[10] determined that S' values were reduced compared with normal, and negatively correlated with patient age. In their study, they used age specific z-scores of measurements because raw TDI values were influenced by patient age, whereas, Lindblad et al.[9] observed that S' values were not significantly different between reference and predialysis patients. Similarly, in the present study, EF, FS and S' values of both the patient groups were similar to the controls. However, even if our patients have normal systolic function at rest, it is possible that stress tests may detect subtle changes in LV systolic function.

As above-mentioned, some studies have reported that age may affect indices of systolic and diastolic function measured by TDI,[9,10,27] but not others.[16,28,29] In our study, there was no relationship between age and TDI indices of diastolic and systolic function.

Left ventricular hypertrophy is the most frequent cardiac alteration in CKD and associated with high cardiac morbidity and mortality.[25,30,31] The prevalence of LVH in predialysis pediatric patients has been varied between 7% and 39% in different studies[3,6,9,10] and anemia, hypertension, age, increased cardiac output, elevated PTH levels have been reported as independent predictors of LVH.[3,18,19,32,33] In our study, we determined that LVH was more frequent than those found in previous studies, with a prevalence of 44%, and as expected, tended to be higher in severe CRI. LVMI correlated negatively with Hb level, age, height, while positively with E/E' ratio. In addition, it was found that E/E' ratio was significantly correlated negatively with Hb levels, and positively with LVMI, like in the study of Bakkaloglu et al.[18] Furthermore, low Hb levels were independent predictor of elevated E/E'. Anemia leads to flow/volume overload and increased cardiac output, thereby contributing to the development of CV structural and functional alterations in patients with CKD.[34,35]

Our study has some limitations. First, the study was conducted cross-sectionally. Second, ambulatory blood pressure monitoring could not be performed in our patients.

Conclusion

Our study demonstrated that LV structural and functional abnormalities developed during early stages of CKD and TDI were more sensitive in early detecting LV diastolic dysfunction compared to cPWD in predialysis pediatric patients. Optimal correction of anemia that is a modifiable risk factor in progression of cardiac disease may be essential to improve the clinical outcomes in CKD.

Declaration of interest

The study was supported by a grant from the Scientific Research Fund of Akdeniz University.

The authors have declared that no conflict of interest exists.

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