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Impaired left ventricular diastolic function in children with chronic renal failure

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Background. Diastolic dysfunction is frequent in adults with renal failure. However, in children with mild-to-moderate chronic renal insufficiency (CRI), it has not been evaluated. We compared diastolic function and assessed risk factors associated with diastolic dysfunction in children with CRI with those on dialysis.

Methods. Thirty-three children with CRI, 17 on chronic dialysis, and 33 control patients, had echocardiography performed. Early diastole was assessed using indices of left ventricular (LV) relaxation derived from transmitral and tissue Doppler, and reported as the peak E/A wave ratio, and septal mitral annular velocities (Em). Late diastole was determined using an index of LV compliance (E/Em ratio). Left atrial (LA) dimension was also determined.

Results. Children with CRI had worse diastolic function (lower Em, and higher E/Em ratio than control patients, $P < 0.001$). Dialysis patients had worse diastolic function (lower E/A ratio and Em, and higher E/Em ratio, $P < 0.001$) than CRI children. LA dimension was higher in renal patients when compared with control patients ($P < 0.001$). In children on dialysis, LV relaxation (Em) was significantly related to left ventricular mass (LVM) index ($r = -0.58$, $P = 0.04$), and LV compliance (E/Em) was significantly associated with LA index ($r = 0.67$, $P = 0.01$), LVM index ($r = 0.75$, $P < 0.01$), hemoglobin level ($r = -0.65$, $P = 0.02$), serum phosphorus ($r = 0.56$, $P = 0.05$), and calcium-phosphorus ion product ($r = 0.59$, $P = 0.04$).

Conclusion. Our results indicate that diastolic dysfunction is already present in children with mild-to-moderate CRI. Worse diastolic function in dialysis patients might be related to LV hypertrophy. The results suggest that children with advanced renal failure and diastolic dysfunction may be at risk for ultimate worsening of cardiac function over time.

Key words: chronic renal failure, dialysis, children, cardiovascular disease, diastolic function.

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Both left ventricular (LV) systolic and diastolic dysfunction are frequently found in adults with end-stage renal disease (ESRD). Systolic dysfunction is highly prevalent and indicates early cardiac failure and decreased survival [1] in these patients. Diastolic dysfunction of the left ventricle is even more prevalent in chronically dialyzed adults and usually precedes systolic LV dysfunction [2, 3]. Children with chronic renal failure frequently develop cardiac abnormalities of LV structure and function. Recently we, and others, have shown that children with mild-to-moderate chronic renal insufficiency (CRI) on chronic dialysis have increased left ventricular mass (LVM). However, in contrast to adults, their LV systolic function is preserved at rest [4–7].

Diastolic dysfunction has been described in children on chronic dialysis [5, 6]. However, diastolic function in children with mild-to-moderate CRI has not been evaluated. The aims of this study were: (*1*) to compare LV diastolic function in children with CRI and those undergoing chronic dialysis; and (*2*) to determine the association between LVM and indices of LV diastolic function in these patients. We hypothesized that LV diastolic dysfunction develops early when renal failure is mild or moderate in children, and progresses as renal function deteriorates. We also hypothesized that LV diastolic dysfunction would relate to increased LVM in these children.

METHODS

Subjects

Thirty-three patients with CRI, 17 children on chronic dialysis, and 33 healthy individuals of comparable age and sex were included into the study. Inclusion criteria were: (*1*) age 6 to 20 years; (*2*) measured glomerular filtration rate (GFR) 20 to 75 mL/min/1.73m^2 for CRI patients; (*3*) at least 6 weeks of chronic dialysis for dialysis patients; (*4*) absence of congenital, structural, or primary myocardial disease; and (*5*) good quality echocardiographic images. The Institutional Review Board of Cincinnati Children's Hospital Medical Center approved the study, and informed consent was obtained for each study patient.

Healthy children were recruited from the families of personnel at Children's Hospital. They were selected to match subject group for age and sex. The medical records were reviewed for age, sex, race, type of dialysis modality, cause of chronic renal disease, and duration of renal failure or dialysis. All patients had a history taken and physical examination performed. Clinical and laboratory data were collected on the day of the echocardiographic evaluation [before dialysis in hemodialysis (HD) patients], including height, weight, systolic (SBP) and diastolic (DBP) blood pressure, serum creatinine, blood urea nitrogen (BUN), calcium, phosphorus, and hemoglobin. Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$. To control for differences in age and body size, blood pressures were indexed to the age, sex, and height specific 95th percentile for each subject (calculated mean SBP or DBP was divided by the age-, sex-, and height-specific 95th percentiles for SBP or DBP). Hypertension was defined as indexed SBP or DBP $\geq$1.0. The kidney function for CRI patients was estimated by measuring GFR using a single intravenous injection of Ioversol injection 74% (Optiray 350®; Mallinckrodt, Inc., St. Louis, MO, USA) [8]. Iodine in timed blood samples was measured by x-ray fluorescence analysis (Renalyzer PRX90; Diatron AB, Inc., Svedala, Sweden), and GFR was calculated from the slope of the iodine disappearance curve. Hemodialysis patients received dialysis treatment three times per week for 3 to 4.5 hours in each session. Change in the body weight during dialysis treatment preceding echocardiographic evaluation was calculated. "Dry weight" was defined as the body weight below which hypotension or muscle cramps occur. Children on peritoneal dialysis had daily treatment using continuous cycler-assisted peritoneal dialysis (CCPD) modality. The dialysis adequacy was estimated by most recent Kt/V values.

Echocardiography

To minimize the effect of fluid overload, patients on hemodialysis had echocardiographic evaluation within 24 hours after hemodialysis treatment on Monday or Wednesday, when their weight was close to "dry weight." Echocardiograms were performed using standard techniques. LVM was measured by two-dimensional directed M-mode echocardiography at rest, with measurements made according to the American Society of Echocardiography criteria [9]. LVM index (mass divided by height raised to a power of 2.7 ($g/m^{2.7}$)) was used to evaluate LVH accounting for body size, as described elsewhere [10]. LVH was defined as LVM index greater than the 95th percentile for normal children and adolescents [11]. Relative wall thickness (RWT) was measured to assess the LV geometric pattern [10]. Patients with increased LVM index and elevated RWT (>0.41) had concentric LVH; those with increased LVM index and normal RWT (<0.41) had eccentric LVH. Concentric remodeling was defined as elevated RWT, but with normal LVM index.

Diastolic function was estimated echocardiographically by transmitral and Tissue Doppler, with diastolic relaxation and filling indices calculated. Early diastole was assessed using indices of LV relaxation and reported as the ratio of maximal early (E wave) and late (A wave) diastolic flow velocities (E/A) obtained from pulsed-wave transmitral Doppler [12] and septal mitral annular peak velocities (Em) recorded during Tissue Doppler examination [13]. Late diastole was determined using the index of LV compliance—a ratio of peak transmitral E velocity to early diastolic mitral annular velocity (E/Em) [14, 15]. In addition, left atrial (LA) size was determined and indexed by height to adjust for differences in body size [16].

Statistical analysis

Values are presented as the mean value $\pm$ SD. A two-sample t test was used to compare mean $\pm$ SD of continuous variables. The general linear model (GLM) procedure was used to compare mean $\pm$ SD among all three groups. Categorical variables were compared using the chi-square test or Fisher exact test. The associations between variables were assessed by Spearman correlation analysis. A P value ≤ 0.05 was considered statistically significant.

RESULTS

Patient characteristics

Thirteen (76%) of 17 dialysis patients, 4 (12%) of 33 CRI patients, and 6 (18%) of 33 control patients were black. There were 12 (36%) girls in the control group, 11 (33%) girls in the CRI group, and 8 (47%) girls in the dialysis group. Six (35%) of the dialysis patients and 18 (55%) children with CRI were on antihypertensive medications. Among dialysis patients, two patients were taking one antihypertensive medication, three patients were taking two antihypertensive medications, and one patient was taking three antihypertensive medications. Only one patient was on a beta-blocker, four children were taking a combination of calcium channel blockers and angiotensin-converting enzyme (ACE) inhibitor. Among children with CRI, only one patient required a combination of two medications to control his blood pressure. Other patients were taking ACE inhibitors or angiotensin receptor blockers (four children). Eight (24%) children with CRI and normal blood pressure were taking ACE inhibitor or angiotensin receptor blocker as an anti-proteinuric agent. The main causes of chronic kidney disease in children with CRI were renal dysplasia/obstructive uropathy (67%) and glomerular and cystic disease (33%); in dialysis patients the main cause of ESRD was glomerular

Table 1. Patient characteristics

Variable	Control ($N = 33$)	CRI ($N = 33$)	Dialysis ($N = 17$)	P value
Age *years*	13.5 ± 4.0 (5.8–21.3)	13.7 ± 3.9 (6.4–20.0)	14.8 ± 4.0 (6.8–19.6)	NS
Weight *kg*	51.5 ± 21.7	46.2 ± 22.0	49.2 ± 16.5	NS
Height *m*	1.59 ± 0.24	1.48 ± 0.19	1.50 ± 0.18	NS
BMI kg/m^2	20.7 ± 4.5	20.1 ± 6.9	21.3 ± 5.1	NS
Heart rate/min	73.2 ± 10.3	76.9 ± 11.9	91.2 ± 17.6[a,b]	<0.001
Indexed SBP	0.90 ± 0.08	0.95 ± 0.09[a]	0.98 ± 0.12[a]	<0.001
Indexed DBP	0.78 ± 0.10	0.81 ± 0.15	0.89 ± 0.19[a]	0.039
Hypertension %	0	10 (30)[a]	10 (59)[a]	<0.05

CRI, chronic renal insufficiency.
[a]Significant difference with control patients.
[b]Significant difference with CRI patients.

Table 2. Comparison of laboratory characteristics between patients with CRI and patients on dialysis

Variable	CRI ($N = 33$)	Dialysis ($N = 17$)	P value
Serum calcium *mg/dL*	9.2 ± 0.4	8.9 ± 0.9	NS
Serum phosphorus *mg/dL*	4.7 ± 0.9	6.9 ± 2.8	<0.0001
Serum calcium-phosphorus ion product mg^2/dL^2	42.8 ± 8.6	62.8 ± 24.9	<0.0001
Serum PTH *pg/mL*	127.7 ± 159.4	357.6 ± 362.8	0.005
Hemoglobin *mg/dL*	12.5 ± 1.66	11.4 ± 1.8	NS
BUN *mg/dL*	31.7 ± 13.0	49.6 ± 10.9	<0.0001

CRI, chronic renal insufficiency. Data are presented as mean ± SD.

disease (70%), while congenital anomalies represented 30%. The average time on dialysis was 1.16 ± 1.32 years (range, 0.3–3.7 years). Among dialyzed patients, 13 children were on hemodialysis (seven patients with arteriovenous graft, two patients with fistula, and four patients with permanent right atrial catheter), and four children were on chronic continuous peritoneal dialysis. The mean Kt/V for 13 hemodialysis patients was 1.7 ± 0.7 (range, 1.05–2.4) and for four peritoneal dialysis patients was 3.5 ± 0.8 (range, 1.9–4.4). Intradialytic body weight change for hemodialyzed children was 3.2%, ranging from 0.2% to 6.8%. The mean GFR for children with CRI was 39.3 ± 12.5 mL/min/1.73m^2; 12 (36%) patients had mild CRI with GFR 50 to 75 mL/min/1.73m^2, and 21 (64%) patients had moderate CRI with GFR 25 to 49 mL/min/1.73m^2.

There was no significant difference in age, weight, height, and BMI among groups (Table 1). Dialyzed children had higher heart rate, systolic and diastolic blood pressures than healthy control patients, and also had a higher prevalence of hypertension when compared with children with CRI (59% vs. 30%, respectively, $P < 0.05$). Children on chronic dialysis had a significantly higher BUN, serum phosphorus, calcium-phosphorus ion product, and parathyroid hormone (PTH) levels compared with children with CRI (Table 2).

Cardiac geometry

Echocardiographic measures of LV structure and function are presented in Table 3. LVM index was elevated

Table 3. Echocardiographic characteristics

Variable	Controls ($N = 33$)	CRI ($N = 33$)	Dialysis ($N = 17$)	P value
LV structure				
LVM index $g/m^{2.7}$	31.7 ± 5.4	35.4 ± 10.6[a]	39.8 ± 14.9[a]	<0.0001
LVH, *N* (%)	0	7 (21)[a]	7 (41)[a]	<0.05
LV geometry, *N* (%)				
Normal	33 (100)	21 (64)	9 (53)	
Concentric LVH	0	4 (12)	2 (12)	
Eccentric LVH	0	3 (9)	5 (29)	
Concentric remodeling	0	5 (15)	1 (6)	
LV systolic function				
Shortening fraction %	36.6 ± 0.6	39.4 ± 0.7[a]	36.7 ± 1.1	<0.001
LV diastolic function				
LV relaxation				
E/A	2.1 ± 0.46 (1.3–3.1)	2.0 ± 0.4[a] (1.1–3.0)	1.5 ± 0.4[a] (1.0–2.4)	<0.001
Em, cm/sec	13.3 ± 2.3 (9.3–19.0)	11.9 ± 2.2[a] (7.8–15.8)	9.1 ± 3.2[a] (4.8–15.2)	<0.0001
LV compliance				
E/Em	7.0 ± 1.9 (3.8–11.9)	7.7 ± 2.1 (4.7–11.3)	9.1 ± 3.7[a] (5.3–17.8)	<0.0001
Left atrium				
Left atrial dimension *cm*	2.5 ± 0.4	2.5 ± 0.5	2.8 ± 0.5[a]	0.05
Indexed left atrial size *cm/h*	1.5 ± 0.5	1.7 ± 0.2[a]	1.9 ± 0.3[a]	<0.0001

CRI, chronic renal insufficiency.
[a]Significant difference vs. control.

in both groups with renal disease compared with control patients. Twenty-one percent of CRI patients, and 41% of dialysis patients had LVH. Concentric LVH and concentric remodeling were more common in children with CRI, while eccentric LVH was the most common abnormal geometric pattern in dialysis patients. The left atrial dimension was significantly higher in patients with renal disease compared with control patients. The left atrial dimension was above 95th upper confidence limit for normal children [17] in 10 (59%) of dialysis patients and in 12 (37%) of CRI patients. There was no significant difference in LVM index and left atrial dimension between children with mild or moderate CRI. We did not find significant difference in these variables between hemodialysis and peritoneal dialysis patients.

Diastolic function

Both children with CRI and on chronic dialysis had diastolic abnormalities that were evident by significantly lower Em ($P < 0.001$), and significantly higher E/Em ratio than control patients ($P < 0.0001$) (Table 3). Dialysis patients had worse diastolic function [lower E/A ratio and Em ($P < 0.001$) and higher E/Em ratio ($P < 0.001$) than children with CRI]. There were no children with E/A ratios below 1.0. Eight (47%) of 17 dialysis patients, and six (18%) of 33 CRI patients had Em below the minimal Em value from control patients. Five (29%) children on chronic dialysis had E/Em above the maximal value of E/Em from control patients. No significant difference in the indices of diastolic function was found between children on hemodialysis and peritoneal dialysis.

In children with CRI, no significant relationship was found between indices of LV diastolic function (E/A, Em, or E/Em) and LVM index. The LA index was significantly correlated with LVM index ($r = 0.67$, $P < 0.0001$) in children with CRI. There was no significant correlation between Kt/V and intradialytic body weight change with LVM index, LA index, or indices of LV function in dialyzed patients. In children on dialysis, the index of LV relaxation (Em) was significantly related to LVM index ($r = -0.58$, $P = 0.04$). The index of LV compliance (E/Em) was significantly associated with LA index ($r = 0.67$, $P = 0.01$), LVM index ($r = 0.75$, $P < 0.01$), hemoglobin level ($r = -0.65$, $P = 0.02$), serum phosphorus ($r = 0.56$, $P = 0.05$), and calcium-phosphorus ion product ($r = 0.59$, $P = 0.04$). The LA index was significantly correlated with LVM index ($r = 0.57$, $P = 0.02$) in children on dialysis.

DISCUSSION

The important observation of this study is that not only children receiving chronic dialysis, but also children with mild or moderate CRI had abnormal diastolic function of the left ventricle. These findings indicate that abnormalities of LV function may develop during initial stages of renal impairment in children with kidney disease.

Very few studies have assessed LV diastolic function in pediatric patients with chronic renal failure. Doppler examination of mitral inflow velocity has been the most widely used method to determine LV diastolic function. Using this method, Goren et al [5] showed that LV relaxation (E/A ratio) was impaired in dialyzed children when compared to control patients. Johnstone et al [6] also found a reduction in the E/A ratio in children on chronic peritoneal dialysis and with preterminal renal failure, although none of these patients had E/A ratio <1.0, which is considered to be abnormal. In their study, no association was demonstrated between E/A ratio and LVM.

Unfortunately, the transmitral Doppler velocities, and therefore the E/A ratio, are affected by several factors, including left atrial pressure and preload. This is particularly important for patients with advanced chronic renal failure, because many of them have abnormal volume status.

In the present study, we used Tissue Doppler Imaging (TDI) to assess diastolic function of the left ventricle. Early diastolic myocardial peak velocities (Em) recorded during TDI are relatively independent of loading conditions and, thus, superior to conventional Doppler echocardiography indices (E/A) of LV relaxation [13, 18, 19]. In addition, Nagueh et al [13] showed that the effect of preload can be corrected by using the combination of TDI of the mitral annuls and mitral inflow velocity from conventional Doppler (E/Em ratio). These authors and others also suggested that E/Em ratio can be used as an index of LV filling pressures, and therefore, to estimate LV myocardial compliance at end-diastole, especially in those patients with preserved systolic function [13, 15]. Recently, Ie et al [20] studied LV diastolic function in adult patients pre- and postdialysis treatment using TDI. They found a significant difference in Em before and after dialysis and argued that an assessment of LV diastolic function should not be performed shortly before hemodialysis. In our study, to minimize the effect of fluid overload, children had echocardiographic evaluation within the first 24 hours after completing their hemodialysis treatment. Using TDI, we determined that both children with CRI and children receiving chronic dialysis had abnormal diastolic function of the left ventricle.

Some studies suggest that age and heart rate might affect indices of diastolic function measured by TDI [21]. In the present study, there was no significant difference in the age among groups. In addition, we found no associations between age and Em or E/Em in correlation analysis in either group of patients (results are not shown). Our results are also concordant with other pediatric studies showing no relationship between age and TDI indices of diastolic function [22, 23]. Children on dialysis had higher heart rates than other children in our study. However, the difference in diastolic function among groups is unlikely to be attributed to their difference in heart rate. This conclusion is supported by the results of the study by Nagueh et al [24], who validated the use of TDI indices in patients with sinus tachycardia, as well as our data showing no relationship between heart rate and Em or E/Em in healthy control patients (results are not shown).

Another important observation of this study is that both children with preterminal renal failure and ESRD had larger LA dimension than control patients. During ventricular diastole, the LA is directly exposed to LV filling pressures through the open mitral valve. Therefore, increased LA size may result from LV diastolic function [25, 26]. The indices of diastolic function measured by Doppler echocardiography may change in response to a variety of factors. On the other hand, LA size is a more stable measure, which may reflect the duration and severity of diastolic dysfunction [27]. Studies in adults have shown that enlarged LA dimension is associated with atrial fibrillation, stroke, acute myocardial infarction, and congestive heart failure [28–30]. These findings are important because they suggest that children with advanced renal failure and diastolic dysfunction may ultimately be at risk for ventricular systolic dysfunction and future congestive heart failure. Longitudinal studies are necessary to evaluate the progression of cardiac dysfunction in these children.

The diastolic dysfunction and enlarged LA in these patients may in part be attributed to an increased LVM index. However, while both groups with renal disease had

patients with LVH, it is noteworthy that children with CRI were more likely to have concentric hypertrophy, while patients on dialysis were more likely to have eccentric ventricular hypertrophy. This suggests the possibility that diastolic dysfunction may be developing through different mechanisms in the two groups with renal disease. Concentric hypertrophy is thought to result in a stiffer left ventricle, which is more difficult to fill during diastole. On the other hand, eccentric hypertrophy is more likely to result from increased circulatory blood volume. This volume overload may lead to increased atrial and left ventricular dimensions, and less efficient filling of the left ventricle. It is possible that pressure overload may be important in the patients with CRI, while volume overload is more important in the development of diastolic dysfunction in patients on dialysis.

We also showed that children on chronic dialysis had significantly worse diastolic function than children with mild-to moderate CRI. Worse diastolic function in patients on dialysis was associated with decreased hemoglobin level, increased serum phosphorus, and calcium-phosphorus ion product. In patients with ESRD, anemia leads to a chronic increase in cardiac output and contributes to increase in LV end-diastolic volume and the development of LVH [31, 32]. Similarly, the negative effect of hyperphosphatemia and increased calcium-phosphorus ion product on LV compliance most likely relate to LVH because these variables have been shown to be associated with increased LVM in chronically dialyzed patients [33–36].

There are limitations of this study. First, it is possible that some children on hemodialysis continued to have significant fluid overload even after hemodialysis treatment. Second, we could not compare patients on hemodialysis and peritoneal dialysis, because there were only four children on peritoneal dialysis. Third, because of the multifactorial causes of diastolic dysfunction, it is possible that we did not fully control for all confounding variables.

CONCLUSION

Despite these limitations, the results of our study provide support to the concept that LV diastolic dysfunction develops early when renal failure is mild or moderate in children, and progresses as ESRD approaches. This suggests that children on chronic dialysis and LVH might be at higher risk for ultimate worsening of cardiac function over time.

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