Evaluation of left atrial functions in children with chronic renal failure

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Abstract

Objective: One-quarter of deaths in children with chronic renal failure is due to cardiovascular complications. Conventional echocardiographic methods are insufficient for evaluating systolic functions in children with chronic renal failure. The aim of the present study was to investigate cardiac functions in children with chronic renal failure by evaluating left atrial volume and functions.

Methods: The present cross-sectional observational study included 44 children undergoing dialysis, 16 children with chronic renal failure but not yet on dialysis, and 20 healthy control subjects. Transthoracic echocardiography was performed for all children. Variables regarding to left ventricle and atrium (left atrial systolic force, left atrial systolic force index, left atrial volume, left ventricular mass index, and relative wall thickness) were measured using two-dimensional and M-mode echocardiography.

Results: Left atrial systolic force index was negatively correlated with systolic blood pressure and left ventricular mass (p=0.01, r=0.266 and p=0.02, r=0.347, respectively). However, it was positively correlated with both early and late diastolic mitral inflow velocity (r=0.518, p=0.001 and r=0.828, p=0.001, respectively). There were no significant difference among the groups in terms of left atrial systolic force index and left atrial volume. However, left atrial systolic force index was higher in children with chronic renal failure but not yet on dialysis.

Conclusion: Left atrial systolic force was negatively correlated with systolic blood pressure and left ventricular mass. These findings suggested that evaluating left atrial systolic force and left atrial volume were useful to determine diastolic dysfunction and the necessity of dialysis in patient with chronic renal failure. *(Anadolu Kardiyol Derg 2014; 14: 280-5)*

Key words: chronic renal failure, left atrial systolic force, dialysis, diastolic dysfunction

Introduction

Frequency of cardiovascular complications in chronic renal failure (CRF) is gradually increasing. The majority of deaths in adults result from cardiac reasons and this rate is 25% in children with CRF (1). Of the hospitalizations in children with CRF, 20% is for rhythm disorders, 10% is for cardiomyopathy, and 3% is for heart attack (2). Today, the importance of cardiovascular complications in CRF is known. However, echocardiographic data on prevention of these complications, detection in early period, and determination of the need for early dialysis are limited. Traditional echocardiographic variables may be inadequate in determining left ventricle (LV) functions (3). Thus, evaluation of size and mechanical functions of left atrium (LA) by non-invasive echocardiographic methods attracts attention (4). In the present study, children that were being followed-up for CRF were divided into two groups as children on dialysis (hemodialysis or peritoneal dialysis) and children not yet on dialysis and it was aimed to evaluate LA functions via various echocardiographic variables and to determine the efficacy of these variables in predicting the need for dialysis in the patients not yet on dialysis.

Methods

Study design

This cross-sectional observational study evaluated the LA volume and functions in children with CRF on dialysis and not yet on dialysis.

Study population

The study comprised 60 children with CRF who were admitted to the Pediatric Cardiology Clinic of Izmir Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital between December 2010 and December 2011 and followed. Children were divided into two subgroups; 44 children (22 girls

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and 22 boys, mean age: 12.7±5.3 years) with CRF on dialysis and 16 patients (6 girls and 10 boys, mean age 9±4.6 years) not yet on dialysis. Age-and gender-matched 20 healthy children (8 girls and 12 boys, mean age 10.6±2.7 years) were included in the study as the control group. Approval of the hospital Ethics Committee was obtained for the study. After informing the parents of all children, consent forms were obtained.

Study variables

Age, gender, weight, and height of the patients, as well as body mass index calculated according to the Haycock formula [0.024265 x $(\text{height-cm})^{0.3964}x(\text{weight-kg})^{0.5378}$], systolic and diastolic blood pressures, mean duration of dialysis, electrocardiography (ECG) findings (heart rate/min, duration of P wave and P-R distance), and two-dimension and M-mode echocardiographic variables for the LA and LV were recorded.

Echocardiographic evaluation

Echocardiographic examination was performed simultaneously with ECG while the patient was resting in lateral decubitus position using GE Vingmed Vivid S6 echocardiography device (General Electric Healthcare, Milwaukee, WI, USA) with 3 MHz transformer and views were obtained through parasternal and apical windows during expirium in at least 5 consecutive cardiac cycles.

Left ventricular and left atrial variables [left ventricle end-diastolic diameter (LVEDD), left ventricle end-systolic diameter (LVESD), left ventricle end-systolic posterior wall thickness (LVSPWT), left ventricle end-diastolic posterior wall thickness (LVDPWT), interventricular septum end-diastolic thickness (IVSDT), interventricular septum end-systolic thickness (IVSST), ejection fraction (EF), fractional fiber shortening (FS), left atrium/aorta ratio (LA/Ao)] were obtained by 2-dimension and M-mode echocardiography in accordance with standard procedure (5).

Percentage of left ventricle ejection was calculated using the biplane Simpson disk method (6), whereas left ventricle mass (LVM) was measured by the Devereux formula (LVM $(g)=1.04x[(LVEDD+IVSDT+LVDPWT)^3-(LVEDD^3]-3.6)$ (7). LVM index ($LVMI=LVM/m^{2.7}$) was calculated to determine left ventricle hypertrophy. All patients were divided into two groups according to LVMI; patients without left ventricle hypertrophy (LVMI <38.6 $g/m^{2.7}$) and patients with left ventricle hypertrophy (LVMI ≥38.6 $g/m^{2.7}$) (8). End-diastolic interventricular septum wall thickness and end-diastolic posterior wall thickness were summed and divided by LVEDD and relative wall thickness (RWT) was calculated (9).

Left ventricle diastolic function was assessed on 4-chamber view by placing the Doppler sample volume between the tips of mitral leaflets and recording pulse wave with a paper speed of 100 mm/sec. The mean of early diastolic wave (E wave), late diastolic wave (A wave), and E/A ratio, which are the mitral valve inflow rates, were calculated from 5 consecutive cardiac cycles.

Evaluation of left atrium

Left atrium systolic force (LASF), which was first defined in 1993 by Manning, was calculated using the equation of "LASF=0.5x(blood mass) x mitral valve area (cm^2) x peak A wave $(cm/sec)^2$); blood mass=1.06 g/cm^3" (unit, kdynes) and this value was proportioned to the body mass index to obtain LASF index ($kdynes/m^2$) (10). Assuming that the shape of mitral orifice was circular on apical 4-chamber view, diameter of annulus during systole and diastole was measured and mitral valve area was calculated using the formula "$\pi.d^2/4$ (d: radius)". The highest volume of the LA was measured during opening and the lowest volume was measured during closure of the mitral valve and LA volume index was obtained by proportioning LA volume to body mass index (11).

Statistical analysis

The Statistical Package for the Social Sciences version 17.0 (SPSS Inc., Chicago, IL, USA) package program was used for statistical analysis. The Kolmogorov-Smirnov (K-S) test was used to verify the normal distribution of variables for the statistical significance between the means of groups. Variance homogeneity was analyzed after the normality test. Chi-square test, which is one of the descriptive statistics, was used for the comparison of categorical variables between the groups. In addition to the descriptive statistical methods (mean±standard deviation) for the evaluation of study data, quantitative data were compared using Scheffe's test, one of the One-way ANOVA Post-hoc tests, for the intergroup comparison of normally distributed data. Linear correlation between numerical variables was analyzed by correlation analysis. Linear correlation between two continuous variables was interpreted using the Pearson correlation coefficient. A two-sided p value lower than 0.05 was considered statistically significant.

Intraobserver and interobserver variability

For the prediction of accuracy of the measurement, 2-dimension and pulse wave Doppler echocardiographic variables were calculated in randomly selected 15 patients and 15 healthy controls. In the present study, intraobserver variability was calculated to be lower than 5% and interobserver variability was calculated to be lower than 7%.

Results

Clinical and demographic characteristics of the patients

Of the patients receiving dialysis for CRF, 7 (5 girls and 2 boys, mean age 14.5±5.6 years) were receiving hemodialysis and 37 (17 girls and 20 boys, mean age 12.3±5.3 years) were receiving peritoneal dialysis. The mean duration of dialysis was 5.7 years in hemodialysis patients and 3.1 years in peritoneal dialysis patients. Underlying primary disease in dialysis patients were vesicoureteral reflux, nephrotic syndrome, nephronophthisis, renal hypodysplasia, rapidly progressive glomerulonephritis, membranoproliferative glomerulonephritis, neurogenic bladder, Alport syndrome, Bartter syndrome, glomerulocystic disease, and hemolytic uremic syndrome (Table 1).

Comparing clinical characteristics of patient subgroups and the control group, no significant difference was determined in terms of gender, age, body mass index, and heart rate. Hemoglobin level was found to be significantly lower in the both patient subgroups as compared to the control group (p=0.01). Systolic and diastolic blood pressures were found significantly higher in the patient subgroups (p=0.03 and p=0.01, respectively) than those in the control group.

Echocardiographic variables

With regard to 2-dimension pulse wave Doppler and M-mode echocardiographic variables, it was determined that there were no significant differences among the groups in terms of LVEDD and LVESD, interventricular septum end-systolic and end-diastolic thicknesses, end-diastolic posterior wall thickness, relative wall thickness, LA volume, LASF and LASF index. However, end-systolic posterior wall was thicker in both patient groups (p=0.03) than that in the control group. LVMI was also significantly elevated in both patient groups (p=0.01) as compared to the control group; it was the highest in the patient subgroup not yet on dialysis.

It was determined that statistical significance of mitral valve area was low in the patient group (p=0.01) and LA/Ao ratio was significantly higher in both patient groups (p=0.01) being more notable in the patient group not yet on dialysis. Mitral insufficiency that could influence LA systolic force and that might be significant in terms of blood circulation was not detected in the patient subgroups. Diastolic early wave rate and E/A ratio, which are among mitral valve inflow variables, were found to be significantly increased in the patient group with CRF not yet on dialysis (p=0.01 and p=0.01, respectively). P wave duration and P-R distance were significantly longer in the patient group (p=0.01 and p=0.03, respectively) (Table 2).

Table 1. Primary diagnoses of the patients on dialysis

Diagnoses	Number of Patients (n)
Vesicoureteral reflux	24
Nephrotic syndrome	3
Nephronophthisis	3
Renal hypo-dysplasia	3
Rapidly progressive glomerulonephritis	2
Diffuse cystic dysplasia	2
Neurogenic bladder	2
Membranoproliferative glomerulonephritis	1
Alport syndrome	1
Bartter syndrome	1
Glomerulocystic disease	1
Hemolytic uremic syndrome	1

Table 2. Clinical, 2-dimension and pulse wave Doppler echocardiographic and electrocardiographic data of the patient subgroups and the control group

Variables	Patients with chronic renal insufficiency Dialysis (+) (n=44)	Patients with chronic renal insufficiency Dialysis (-) (n=16)	Control group (n=20)	*P
Clinical variables$				
Gender, Girl/Boy#	22/22	6/10	8/12	>0.05
Age, year	12.7±5.3	9.0±4.6	10.6±2.7	>0.05
Body mass index (Haycock), m^2	1.04±0.33	0.98±0.29	1.16±0.26	>0.05
Heart rate, beat/minute	91±19	98±17	86±16	>0.05
Hemoglobin, g/dL	10.7±1.1	10.1±1.3	12.1±1.3	0.01
Systolic blood pressure, mm Hg	110±15	105±15	100±10	0.03
Diastolic blood pressure, mm Hg	70±15	65±10	55±10	0.01
Two-dimension echocardiographic findings$				
LVEDD, cm	3.9±0.7	3.5±0.6	3.8±0.6	>0.05
LVESD, cm	2.5±0.5	2.2±0.5	2.4±0.3	>0.05
IVSDT, cm	0.7±0.1	0.6±0.1	0.7±0.1	>0.05
IVSST, cm	1.1±0.2	1.1±0.1	1.1±0.1	>0.05
LVDPWT, cm	0.7±0.1	0.6±0.1	0.6±0.1	>0.05
LVSPWT, cm	0.9±0.2	0.9±0.1	0.8±0.1	0.03
RWT, cm	0.37±0.07	0.39±0.07	0.37±0.09	>0.05
EF, %	64±6	67±6	67±5	>0.05
FS, %	34±4	35±3	35±3	>0.05
LVM, Devereux	76.7±35.6	62.5±21.4	61.1±20.8	>0.05
LVMI, g/m^2	79.9±19.4	85.4±32.1	61.7±15.7	0.01
LA/Ao ratio	1.13±0.08	1.25±0.16	1.12±0.09	0.01
Mitral valve area, cm^2	4.77±1.70	4.54±1.27	5.84±1.32	0.01
LA volume, mL	18.6±8.2	18.7±7.1	15.4±5.2	>0.05
LA volume index, mL/m^2	17.7±5.04	19.9±8.8	15.8±3.9	>0.05
LASF, kdynes	12.1±5.52	11.7±4.46	11.0±5.69	>0.05
LASF index, kdynes/m^2	12.7±7.53	15.7±10.37	10.3±3.99	>0.05
Pulse wave Doppler findings$				
E wave rate, cm/s	59±19	80±22	60±17	0.01
A wave rate, cm/s	69±15	67±20	61±12	>0.05
E/A ratio	0.87±31	1.22±0.31	1.00±0.31	0.01
Electrocardiographic findings$				
P wave duration, msec	78±7	90±11	72±5	0.01
P-R distance, msec.	141±12	145±22	138±21	0.03

$One-way ANOVA test (data are represented as mean±standard deviation)
#χ^2 :Chi-square test *p: Significance of difference test
A - diastolic late wave of mitral filling; E - diastolic early wave of mitral filling; EF - ejection fraction; FS-fractional fiber shortening; IVSDT - interventricular septum end-diastolic thickness; IVSST - interventricular septum end-systolic thickness; LASF - left atrium systolic force; LA - left atrium; LVDPWT - left ventricle end-diastolic posterior wall thickness; LVEDD - left ventricle end-diastolic diameter; LVM - left ventricle mass; LVMI - left ventricle mass index; LVSPWT - left ventricle end-systolic posterior wall thickness; LVESD - left ventricle end-systolic diameter; RWT - relative wall thickness

Table 3. Relation between left atrium systolic force index and E wave, A wave, left ventricle mass index, systolic blood pressure, and mitral valve area

	***P**	****r**
E wave	0.001	+ 0.518
A wave	0.001	+ 0.828
LVMI	0.02	-0.347
Systolic blood pressure	0.01	- 0.266
Mitral valve area	0.17	- 0.154

*One-way ANOVA test
**Pearson correlation analysis
A - diastolic late wave of mitral filling; E - diastolic early wave of mitral filling; LASF - left atrium systolic force; LVMI - left ventricle mass index

It was determined that LASF index was higher in the patient group not yet on dialysis as compared to the both patient group on dialysis and control group but the difference was not significant (Fig. 1). With regard to the variables that could influence the LA systolic force, a strong positive linear correlation was found between LASF index and diastolic early and late wave rates of mitral filling (r=0.518, p=0.001 and r=0.828, p=0.001, respectively). While LASF index was negatively correlated with LVMI and systolic blood pressure (r=0.347, p=0.02 and r=0.266, p=0.01, respectively), no relation was determined with mitral valve area (r=0.154 p=0.17) (Table 3).

Discussion

In CRF, LA dilatation can be encountered secondary to increased preload due to fluid retention; however, there is limited information on mechanical adaptation of the LA in response to this situation. Volume load is the most notable stimulus in ventricular hypertrophy and atrium dilatation. Left atrium function is closely associated with left ventricular function during entire cardiac cycle. In case of decrease in left ventricular compliance and increase in stiffness, LA pressure is gradually increased to protect LV filling in accordance with Frank-Starling mechanism. Contractility, systolic load, and work load are also gradually increased in line with the increase in LA pressure. Thus, it is not surprising that increase in LA size and LASF index appear as the strong predictors of unintended cardiovascular events and these unfavorable effects have been demonstrated in population-based cohort studies conducted in the patients with congestive heart failure (19). In patients on dialysis due to renal failure, increase in LV and end-diastolic pressure and diameter gradually enhance LA preload and afterload and heart failure symptoms become more remarkable as a consequence of high atrial pressure (20,21). In the present study, clinical symptoms of congestive heart failure were not present in the patients on regular hemodialysis or peritoneal dialysis and all were in the New York Heart Association Class 1 and 2.

Forty percent of deaths in children with CRF and end-stage renal disease occur due to cardiovascular complications. As compared to healthy children of the same age group, the risk of heart-related deaths is 700 times increased in this patient group (12). Again, in a 656-case series, the prevalence of cardiac complications has been reported to be 24% (17% LV hypertrophy, 8% congestive heart failure, 2 cardiomyopathy) in children with end-stage renal disease (13). Thus, it is important to perform close echocardiographic monitoring for the children with CRF, either on or not yet on dialysis, in terms of cardiac complications.

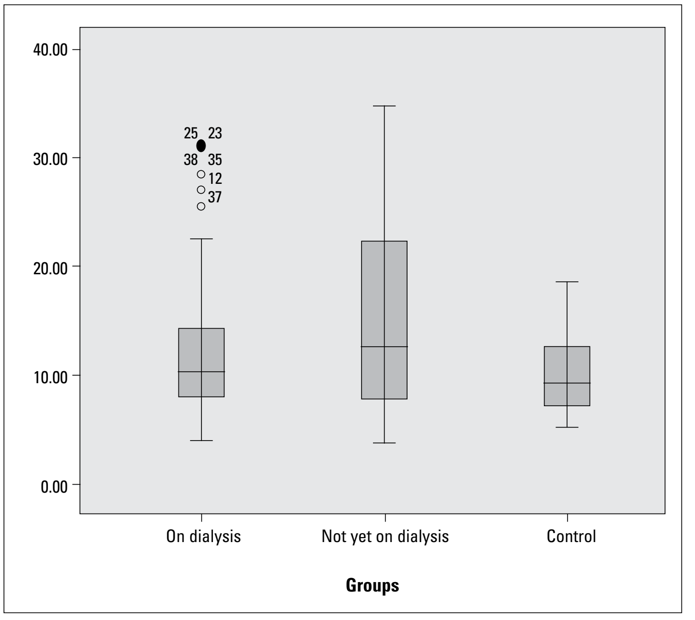

Figure 1. LASF indexes averages between groups

It is thought that LV hypertrophy and increased LVMI in CRF is due to arterial wall stiffness that resulted from endothelial function disorder, which occurs due to arterial calcification. It is known that LV hypertrophy has occurred in 40%-75% of children with CRF (14), concentric hypertrophy has developed in stage 2 patients as well as even in the early-stage CRF patients (15), and high blood pressure has occurred in 50%-60% of patients on dialysis (16). In the present study, particularly diastolic blood pressure levels were at the upper limits in 22% of the patients on dialysis (n=10/44) and in 25% of the patients not yet on dialysis (n=4/16). In a study evaluating 63 pediatric patients on regular dialysis, an increase has been demonstrated in LVMI due to systolic and diastolic cardiac functions and this situation has been associated with hypertensive cardiomyopathy (17). A national study from Turkey, which evaluated cardiovascular risk in children on regular peritoneal dialysis, demonstrated that LVMI and relative wall thickness were significantly increased as compared to the control group (9). In the present study, systolic and diastolic blood pressures and end-systolic posterior wall thickness were higher in both patient subgroups as compared to the control group and LASF index was gradually decreased in the patients with high systolic blood pressure and LVMI. Although, approximately 50% increase has been reported in LV mass in patients on dialysis as compared to healthy controls (18), the present study found LVM to be increased by 25% as compared to the control group. Comparing the groups in terms of LV hypertrophy based on the LVMI, LV hypertrophy was observed in 54% (n=24/44) of the patients on dialysis and in 75% of the patients not yet on dialysis.

It is known that anemia plays a role in the eccentric and concentric remodeling of the left ventricle in the patients with CRF (22). Anemia has a quite important rate as 96.7% among cardiovascular risk factors in the patients with stage 5 CRF not yet on dialysis (23). Observational studies have determined that deaths due to cardiovascular reasons and complications are lower with keeping hemoglobin level over 12 g/dL. In addition, it is known that high hemoglobin values decrease LV hypertrophy (24). Togetherness of anemia, heart failure, and CRF appears as a cardiorenal anemia syndrome and keeping hemoglobin levels over 11 g/dL is recommended in patients on dialysis (25). In the present study, hemoglobin levels were higher in the patients on dialysis as compared to the patients not yet on dialysis. These hemoglobin levels might have contributed to the higher LVMI, LV hypertrophy, LA volume index, and LASFI in the patients not yet on dialysis as compared to the patients on dialysis.

Systolic functions are usually preserved in children with CRF. Systolic functions can be easily assessed by endocardial fractional shortening and LV contractibility. Subclinical systolic function impairment has been demonstrated in 40% of children on hemodialysis (26). In the present study as well, fractional shortening and ejection percentage were found normal in the both patient subgroups. In such children, subclinical systolic function impairment may be detected earlier by assessing midwall fractional shortening (mwFS).

Neurosecretory factors are important in the regulation of heart beat, blood pressure, cardiac output, and regional blood flow. Some unfavorable cardiovascular outcomes can be encountered in case of continuous activation of this system. Increase in atrial natriuretic peptide, cerebral natriuretic peptide, angiotensin II, and aldosterone levels in the event of increased volume load is the most important factor that influences remodeling of the LA (27). Increase in LA active emptying volume and shortening in LA systole are also important in enhancing the left ventricle ejection volume and cardiac output (28). The present study determined that LA volume, LA/Ao ratio, and LASFI, which are the signs that would support the mechanical functions of LA, were higher in the patient group, with highest values in the patient subgroup not yet on dialysis. These findings suggested that impairment in LA mechanical functions were gradually improved, LA volume reduced, and LA width was decreased when volume load was controlled with dialysis. Moreover, it was determined that both types of dialysis did not alter LASFI and similar results were obtained in both patient groups in terms of volume load control. Impairment in the LA systolic functions in line with increase in renal insufficiency stage (29) was demonstrated also in the present study and our results were consistent with the literature. Decrease in LA volume, SA/Ao ratio, and LASFI may be suggested as the predictors of LA remodeling (30).

It has been demonstrated that LA systolic force is enhanced due to enhanced impairment in left ventricle diastolic function with aging in adults and that there is a positive correlation between E/A ratio, which is one of the mitral valve inflow variables, and LASF (31). In children as well, increase in LASFI and alterations in E and A wave durations are seen due to ventricular diastolic alterations with age (32). The present study demonstrated a positive correlation between LASFI and early and late wave of mitral diastolic filling. A positive correlation between early diastolic wave rate and LASFI can be explained by increase in systolic force due to increase in LA filling pressure and diastolic blood pressure even in the early phase of diastolic function impairment.

It is known that LASFI, which predicts that diastolic function is impaired in the patients with CRF, is associated with RCG data that indicate LA enlargement (33). In the present study, P wave and P-R distance on ECG were significantly longer in both patient groups as compared to the control group and it was found significantly longer in the patient subgroup not yet on dialysis. Length of these durations can be explained by higher LA volume and LA/Ao ratio in the patient subgroup not yet on dialysis.

Study limitations

Although the study was conducted in a tertiary health care center, the number of patients in the subgroups on dialysis and not yet on dialysis was inadequate. The results cannot be generalized to the whole country because the study was a single-center study. It should be kept in mind that LASFI did not completely reflect overall atrial pump functions and temporary pulmonary vein backflow might influence atrial contractions. Moreover, in addition to volumetric measurements used to assess LA functions, tissue Doppler-based tension or 2-dimension tension, which is evaluated by punctate trace, and 3-dimension echocardiography as well can be used to assess LA volume. Multicenter, large-scale studies including these variables and methods are needed to make definite judgment on this subject.

Conclusion

In conclusion, detailed evaluation of LA systolic and mechanical functions while performing echocardiographic assessments during clinical follow-up of children diagnosed with CRF not yet on dialysis indicated that diastolic function impairment and need for dialysis in such patient group could be determined in earlier stages independent from other risk factors.

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