Left Ventricular Mass and Systolic Performance in Pediatric Patients With Chronic Renal Failure

Mark M. Mitsnefes, MD; Thomas R. Kimball, MD; Sandra A. Witt, RDGS; Betty J. Glascock, RDGS; Philip R. Khoury, MS; Stephen R. Daniels, MD, PhD

Background—Children with chronic renal disease have a high prevalence of left ventricular hypertrophy (LVH), which is thought to be adaptive to improve contractility and lower wall stress in the face of increased afterload and preload. The aim of this study was to determine the association between LV mass, LV performance, and LV contractility in children with chronic renal insufficiency (CRI) and children undergoing chronic dialysis.

Methods and Results—Twenty-five children with CRI, 12 undergoing chronic dialysis, and 24 controls had echocardiographic evaluation during rest and peak exercise. LV performance was assessed by calculation of shortening fraction and heart rate–corrected velocity of circumferential fiber shortening (VCF). Contractility (VCF difference) was determined based on the relation between VCF and end-systolic wall stress. Contractile reserve was assessed by the difference between contractility at rest and peak exercise. The dialysis group had higher LVM index than the group with CRI (42.9±10.3 versus 29.9±9.4 g/m², P<0.001). Both groups had higher LVM index compared with controls (22.2±6.1 g/m², P<0.001). At rest, the CRI and dialysis groups had significantly higher VCF (P<0.001) and VCF difference (P<0.05) and significantly lower wall stress (P<0.01) compared with the control group. Dialysis patients had significantly lower contractile reserve compared with the control group (P<0.03).

Conclusions—These results indicate that children with CRI and undergoing chronic dialysis have increased LVM, LV performance, and contractility at rest. However, dialysis patients have diminished contractile reserve during exercise, which might be an indicator for the development of more severe systolic dysfunction over time. (Circulation. 2003;107:864-868.)

Key Words: pediatrics ■ kidney ■ cardiovascular diseases ■ hypertrophy ■ contractility

Cardiac complications are frequent in children with chronic renal disease. Echocardiographic studies show that young patients with chronic renal insufficiency (CRI) and end-stage renal disease have abnormalities of both left ventricular (LV) structure and function.1–5 Children with chronic renal disease have a high prevalence of left ventricular hypertrophy (LVH).1,6–10 In adults with hypertension and chronic renal disease, LVH is thought to be adaptive to improve contractility and lower wall stress in the face of increased afterload and preload.11–13 However, in adults, progression of renal failure frequently leads to systolic dysfunction, which is associated with clinical signs of cardiac failure and decreased survival.3 In contrast, systolic LV function is thought to be preserved in children with chronic renal failure.1,4,5 However, these studies have examined LV systolic performance at rest, and it is possible that evaluation during exercise may unmask more subtle changes in LV function.

The aims of this study were to evaluate cardiac structure, evaluate LV systolic performance at rest and during exercise, and determine the association between LV mass, LV performance, and contractility in children with CRI and undergoing chronic dialysis. We hypothesized that resting LV systolic performance would be normal and related to the presence of LVH. We also hypothesized that children with advanced chronic renal failure and LVH would have decreased LV functional reserve during exercise.

Methods

Subjects

The study population included 25 patients with CRI, 12 children undergoing chronic dialysis, and 24 healthy individuals of comparable age and sex. Inclusion criteria were age 6 to 20 years, measured glomerular filtration rate 20 to 75 mL/min per 1.73 m² for CRI patients, at least 6 weeks of chronic dialysis for dialysis patients, absence of congenital, structural, or primary myocardial disease, and 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. The medical records were reviewed for age, sex, race, type of dialysis modality, cause of chronic renal disease, and duration of
renal failure. All patients had a history and physical examination. Clinical and laboratory data were collected on the day of the echocardiographic evaluation (before dialysis in heart disease patients), including height, weight, heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), serum creatinine, and hemoglobin. The mean of monthly blood pressure measurements for 6 months preceding the echocardiogram was calculated for CRI and dialysis patients. To control for differences in age, 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 SBP, DBP, or both >95th percentile for sex, age, and height or indexed SBP or DBP/H11022. The kidney function for patients with CRI was estimated by measuring glomerular filtration rate (GFR) using a single intravenous injection of Ioversol injection 74% (Optirex 350, Mallinckrodt Inc). Iodine in timed blood samples was measured by x-ray fluorescence analysis (Renalyzer PRX90, Diatron AB Inc), and GFR was calculated from the slope of the iodine disappearance curve.

Echocardiography
Each patient had echocardiographic evaluation during rest and exercise. Echocardiograms were performed using standard techniques. LV mass (LVM) was measured by two-dimensional directed M-mode echocardiography at rest according to the American Society of Echocardiography criteria.15 LVM index (mass divided by height or indexed SBP or DBP

<table>
<thead>
<tr>
<th>Table 1. Patients’ Characteristics</th>
<th>Control</th>
<th>CRI</th>
<th>Dialysis</th>
<th>Overall P Value by GLM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y (range)</strong></td>
<td>11.6±2.9 (6–19)</td>
<td>11.1±3.7 (6.3–19.6)</td>
<td>14.7±4.9 (7–19.2)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Weight, kg</strong></td>
<td>41.9±15.3</td>
<td>45.7±29.0</td>
<td>43.8±17.8</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Weight, Z score</strong></td>
<td>0.93±0.26</td>
<td>−1.31±2.9*</td>
<td>−0.60±1.42*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Height, cm</strong></td>
<td>148.4±19.8</td>
<td>141.8±21.4</td>
<td>145.5±18.3</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Height, Z score</strong></td>
<td>0.12±0.05</td>
<td>−1.37±1.46*</td>
<td>−1.56±1.26*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>18.3±3.2</td>
<td>20.9±9.0</td>
<td>21.6±5.5*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Hemoglobin, g/dL</strong></td>
<td>11.8±7.36</td>
<td>11.7±4.1</td>
<td>17.8 NS</td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension, %</strong></td>
<td>0</td>
<td>24</td>
<td>67</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

*P<0.05 vs control."

was assessed by the difference between contractility at rest and peak exercise.

Statistical Analysis
Values are presented as mean±SD. A 2-sample t test was used to compare mean±SD of continuous variables. The general, linear model procedure was used to compare mean±SD among all 3 groups. Categorical variables were compared using the χ² test or Fisher’s exact test. The associations between variables were assessed by Pearson correlation analysis. P<0.05 was considered statistically significant.

Results

Patient Characteristics
The main demographic and clinical characteristics are presented in Table 1. Children with CRI and undergoing dialysis were smaller than control subjects. Nine of 12 dialysis patients were black, whereas 4 (16%) of 25 CRI patients and 4 (17%) of 24 controls were black. There were more boys in the control (62%) and CRI (71%) groups, whereas the dialysis group had more girls (60%). Eight (67%) of 12 dialysis patients and 6 (24%) of 25 CRI patients were hypertensive. In the dialysis group, 3 patients were receiving peritoneal dialysis and 9 patients were receiving hemodialysis. Hemodialysis access was by arteriovenous (a-v) graft (6 patients) or permanent right atrial catheter (3 patients). All 12 dialysis patients were taking antihypertensive medications; 9 patients were taking 1 medication, 2 patients were taking 2 medications, and 1 patient was taking 3 medications. Anti-hypertensive medications prescribed included calcium-channel blockers (10 patients), β-blockers (1 patient), and ACE inhibitors (3 patients). Eight of 25 (32%) children with CRI were taking antihypertensive medications (all patients with CRI were taking only ACE inhibitors). The main causes of chronic renal disease in children with CRI were renal dysplasias/obstructive uropathies (63%) and glomerular and cystic diseases (37%). In dialysis patients, the main cause of end-stage renal disease was glomerular disease (70%), whereas congenital anomalies represented 30%. No difference in the mean hemoglobin level was seen between patients with CRI and those undergoing dialysis (hemoglobin was not measured in control patients). The mean GFR for children with CRI was 39.3±12.5 mL/min per 1.73 m², 7 (28%) patients had mild CRI with GFR 50 to 75 mL/min per 1.73 m².
m², and 18 (72%) patients had moderate CRI with GFR 25 to 49 mL/min per 1.73 m².

Left Ventricular Mass
Both children with CRI (29.3±6.7 g/m²) and children undergoing dialysis (44.9±15.9 g/m²) had elevated LVM index compared with the control group (22.2±6.1 g/m², P<0.001) (Figure). Children undergoing chronic dialysis had significantly higher LVM index compared with patients with CRI (P<0.001). Seven (58%) of 12 dialysis patients and 6 (24%) of 25 children with CRI had LVH. There was no significant difference in LVM index in children with mild or moderate CRI, nor was there a difference between those taking and not taking blood pressure medications in this group of patients.

In children with CRI, LVM index was not significantly related to indexed SBP, DBP (measures of afterload), or LVEDD (a measure of preload or volume status). In contrast, in dialysis patients, LVM index was positively correlated with indexed SBP (r=0.74, P=0.01) and DBP (r=0.85, P=0.001) and indexed LVEDD (r=0.72, P=0.02).

Hemodynamic Data at Rest
Patients with CRI had significantly higher heart rate, SF, VCF, and VCF̈, and significantly lower WS compared with controls (Table 2). Dialysis patients had significantly higher heart rate, VCF, VCF̈, indexed SBP, and DBP and significantly lower WS compared with controls. Despite the significantly higher LVM index in patients with CRI compared with those undergoing dialysis, there was no significant difference in WS, VCF, indexed SBP, and VCF̈ for these two groups of patients.

Exercise Echocardiographic Data
All control subjects, 18 of 25 CRI children, and all dialysis patients completed exercise stress echocardiography and were included in the analysis. Children with CRI and undergoing dialysis had significantly less increase in SBP (P<0.001) during exercise compared with controls (Table 3). Children undergoing chronic dialysis had significantly less increase in heart rate than the control group and children with CRI (P<0.001). Children with CRI and those undergoing dialysis had significantly less decrease in WS (P<0.01) compared with controls. Children undergoing chronic dialysis had significantly less increase in VCF (P=0.03) and SF (P=0.02) compared with the control group. Contractile reserve was similar for controls and patients with CRI. Contractile reserve was significantly lower in patients undergoing dialysis compared with the control group (P<0.03). Contractile reserve was also lower in dialysis group compared with CRI patients, but the difference did not reach statistical significance (P=0.11).

Discussion
The important observations of this study are that both children with CRI and children undergoing chronic dialysis have increased LVM, LV performance, and contractility at...
rest. In addition, dialysis patients have diminished contractile reserve during exercise. These findings indicate that important cardiac abnormalities are present in children with CRI and chronic dialysis.

Mechanisms of Increased LVM in Children With Chronic Renal Disease

There are many factors contributing to the development of cardiac hypertrophy in adults with chronic renal failure. Most authors agree that LVH in these patients develops as a response to chronic volume and pressure overload. For example, Levin et al21,22 showed that anemia and hypertension were independent predictors for increased LVM in the predialysis period in adults. In the only pediatric study of patients with CRI, Johnstone et al1 performed a cross-sectional analysis of 32 children (age 1.5 to 16.9 years) and found that 22% had LVH. In their study, serum creatinine level was the only independent predictor of LVM index. In our study, a similar prevalence of LVH (24%) was found in patients with CRI. We found no relationship between LVM index, creatinine concentration (or GFR), and indexed blood pressure in these children. Small sample size might contribute to this process.24,25 This might also explain the increased end-systolic performance.26,27 This could be due to the presence of cardiac hypertrophy in children with CRI undergoing dialysis. These results are not surprising, because most of the dialysis children were hypertensive and were undergoing chronic hemodialysis, with two thirds of them having a-v shunting as a result of their graft. This suggests that, as in adults with end-stage renal disease, the mechanism of LVH in our chronic dialysis patients is most likely attributable to both volume and pressure overload.

Mechanisms of Increased LV Performance in Children With Chronic Renal Disease

Most previous studies have examined LV systolic performance using indexes of performance dependent on loading conditions. This presents a major problem for patients with CRI or undergoing dialysis, because they may have substantial alteration of preload and afterload. Few studies have investigated load-independent contractility at rest or during exercise in children with chronic renal failure. The study by Colan et al4 emphasizes the importance of taking loading conditions into account. They determined that 55% of children and young adults immediately at the onset of dialysis had abnormal ejection phase indexes of LV systolic function at rest. However, this was likely to be attributable to abnormal preload or afterload, because a load-independent measure of contractility was normal in all subjects.

Increased systolic performance at rest in our patients with CRI is most likely attributable to a low LV afterload, as demonstrated by a low LV end-systolic WS and elevated contractility, as exhibited by increased VCF difference. It is likely that low end-systolic WS is attributable to increased LVM in patients with CRI. The reason for increased LV contractility in these children is not clear. It is possible that in the state of developing renal failure, elevated contractility is an adaptive mechanism needed to increase cardiac output and improve renal perfusion because of higher metabolic demands. Increased sympathetic activity is thought to contribute to this process.24,25 This might also explain the increased resting heart rate in our patients. Because the indices used to measure function were either independent of heart rate or corrected for heart rate (eg, VCFc), we believe that the difference noted between groups was unlikely attributable to heart rate difference.

One potential mechanism for the hyperdynamic circulation in dialysis patients is increased cardiac workload secondary to the effect of anemia, a-v shunt, and poorly controlled hypervolemia. However, after controlling for loading conditions (preload and afterload), these children continued to demonstrate increased VCF difference, suggesting that the increase in LV performance is attributable to increased contractility.

Despite the fact that dialysis patients had significantly higher LVM index than patients with CRI, both renal groups had similar LV performance and contractility at rest. However, there was a different response to exercise in these patients. Children with CRI had cardiac reserve similar to healthy controls, as demonstrated by the difference in LV contractility between rest and peak exercise data during stress echocardiography. These results suggest that children with mild to moderate renal failure have a physiological response to exercise, which is associated with increased in LV performance attributable to increased contractility and decreased pressure overload.

### Table 3. Hemodynamic Data During Stress Echocardiography

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n=24)</th>
<th>CRI (n=18)</th>
<th>Dialysis (n=12)</th>
<th>Overall P Value by GLM</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔHeart rate/minute</td>
<td>121±20</td>
<td>95±18</td>
<td>68±19*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ΔShortening fraction</td>
<td>14.2±11.9</td>
<td>17.4±4.0</td>
<td>9.5±11.2</td>
<td>NS</td>
</tr>
<tr>
<td>ΔWall stress, g/cm²</td>
<td>-23.9±16.3</td>
<td>-9.8±20.9*</td>
<td>-9.3±13.2*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ΔVCF, circumference/s</td>
<td>0.65±0.46</td>
<td>0.63±0.51</td>
<td>0.32±0.42*</td>
<td>NS</td>
</tr>
<tr>
<td>ΔSBP</td>
<td>65.5±20.9</td>
<td>38.2±14.3*</td>
<td>26.2±18.9*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ΔVCFc, circumference/s</td>
<td>0.58±0.43</td>
<td>0.61±0.48</td>
<td>0.28±0.39*</td>
<td>NS</td>
</tr>
</tbody>
</table>

Δ indicates difference between pick exercise and rest data.

*P<0.05 vs control.
afterload. In contrast, we found that in patients undergoing dialysis, contractile reserve was blunted compared with control and CRI patients. Thus, patients undergoing dialysis may rely on increased LVM to produce normal LV performance at rest. However, this comes at the expense of a blunted response to exercise. These results are concordant with adult studies. For example, Fontanet et al. showed that hypertensive adults with LVM had limited myocardial contractile reserve during dobutamine stress echocardiography. These results may explain why many subjects undergoing chronic dialysis in our study developed exercise fatigue during early stages of the test. Our findings suggest that children undergoing chronic dialysis with increased LVM may not have normal cardiac function and might be at risk of future development of systolic dysfunction and heart failure.

One of the potential mechanisms affecting LV function is the use of ACE inhibitors, because these medications are known to be beneficial to cardiac function and structure. In our study, there was no significant difference in the use of ACE inhibitors in children with CRI (32%) or dialysis patients (25%), making it unlikely that ACE inhibitors accounted for the difference in LVM or LV contractile reserve between the two renal groups. These results should be interpreted with caution because of the small sample size in our study. Larger prospective studies are necessary to evaluate the effect of ACE inhibitors on cardiac structure and function in children with chronic renal failure.

In summary, we demonstrated that children and adolescents with chronic renal failure develop LVH and increased LV performance, which may be an adaptive process in response to increased blood pressure and higher metabolic demands seen in these patients. However, when the cardiovascular system is stressed by exercise, this compensation may be insufficient in children undergoing chronic dialysis. Thus, diminished contractile reserve in these children might reflect the early development of a maladaptive stage of LVH with risk of ultimate worsening of cardiac function and development of congestive heart failure over time.

Acknowledgments

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References

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