Decreased Maximal Aerobic Capacity in Pediatric Chronic Kidney Disease

Donald J. Weaver, Jr.,* Thomas R. Kimball,† Timothy Knilans,† Wayne Mays,† Sandra K. Knecht,† Yvette M. Gerdes,† Sandy Witt,† Betty J. Glascock,† Janis Kartal,* Philip Khoury,† and Mark M. Mitsnefes*

*Division of Nephrology and Hypertension, and †Division of Cardiology, Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio

ABSTRACT

Adult and pediatric patients with ESRD have impaired maximum oxygen consumption (VO2 max), a reflection of the cardiopulmonary system’s ability to meet increased metabolic demands. We sought to determine factors associated with decreased VO2 max in pediatric patients with different stages of CKD. VO2 max was measured using a standardized exercise testing protocol in patients with stage 2 to 4 chronic kidney disease (CKD) (n = 46), in renal transplant recipients (n = 22), in patients treated with maintenance hemodialysis (n = 12), and in age-matched healthy controls (n = 33). VO2 max was similar between children with stage 2 CKD and controls, whereas lower VO2 max was observed among children with stage 3 to 4 CKD, those treated with hemodialysis, and transplant recipients. In univariate analysis, VO2 max was significantly associated with body mass index, resting heart rate, C-reactive protein, serum triglycerides, serum creatinine, and measures of diastolic function; no significant associations with left ventricular structure or systolic function were identified. In multivariate regression analysis, patient category versus control and the presence of diastolic dysfunction were independent predictors of lower VO2 max. These results suggest that aerobic capacity is decreased in the early stages of CKD in children and that lower VO2 max can be predicted by the presence of diastolic dysfunction, even if systolic function is normal.


Maximal aerobic capacity (VO2 max) represents the cardiovascular system’s ability to take up, distribute, and utilize oxygen to perform work during maximal exercise. Healthy individuals can sustain a three-fold increase in heart rate (HR) and a two-fold increase in stroke volume to generate maximal aerobic capacity. Therefore, VO2 max has been used to assess the capacity of the cardiovascular system to respond to metabolic challenge in numerous disease states including ESRD. Impaired maximal aerobic capacity was observed in adult and adolescent patients with ESRD as well as after renal transplantation. The significance of these findings was underscored by studies suggesting lower survival rates in adults with ESRD and decreased VO2 max. The impaired VO2 max in these patients was associated with several factors, including lower serum albumin, anemia, and chronic heart failure.

Symptomatic heart disease is a rare event in pediatric patients with CKD. However abnormal cardiac structure and function in children with CKD is well recognized. These patients have left ventricular (LV) diastolic dysfunction and increased LV mass even before the onset of ESRD. LV systolic function is generally preserved at rest, but altered contractile reserve was observed during exercise in di-
alyzed children. To address the extent to which these structural and functional LV abnormalities affect cardiovascular reserve, the goals of the current study were to determine VO₂ max in pediatric patients with different stages of CKD and to evaluate the associations of VO₂ max with LV mass, and LV diastolic and systolic function. We hypothesized that altered LV structure and function in children and adolescents with mild to moderate CKD has an early effect on oxygen utilization and decreased cardiopulmonary reserve. We also hypothesized that in this age group impaired maximal aerobic capacity becomes more severe as ESRD is reached.

RESULTS

Patient Characteristics

Patient characteristics are listed in Table 1. The primary cause for kidney disease in all patient groups was congenital anomalies/dysplasia, accounting for 65%, 67%, and 55% in the CKD stage 2 to 4, hemodialysis, and transplant patients, respectively. Glomerular disease was seen in 22%, 25%, and 32% of CKD stage 2 to 4, hemodialysis, and transplant patients, respectively. The remaining diagnoses involved cystic and other disease processes. There was no significant difference in the age, weight, height, or body mass index (BMI) among CKD stage 2 to 4, hemodialysis, and transplant groups. Subjects in the control group were significantly taller and heavier than subjects in other studied groups. There were more males in the control and CKD stage 2 to 4 groups. A higher percentage of black subjects were in the hemodialysis (75%), transplant (21%), and control groups (18%) relative to the CKD stage 2 to 4 group (4%). A higher BP was observed in the hemodialysis and transplant groups compared with the control and CKD stage 2 to 4 groups.

For CKD stage 2 to 4 subjects, the average duration of disease (since diagnosis) was 8.8 ± 5.6 yr. The mean GFR was 45.6 ± 19.9 ml/min per 1.73 m². Of these patients, 12 (26%) were in stage 2, 19 (41%) were in stage 3, and 15 (33%) were in stage 4. There was no significant difference in height (mean z-score: -0.69 ± 1.2, -0.45 ± 1.1, -0.72 ± 1.2; P = 0.78), weight (mean z-score: -0.43 ± 1.7, 0.01 ± 1.4, -0.02 ± 1.5; P = 0.69), or BMI (mean z-score: -0.10 ± 1.6, 0.08 ± 1.5, 0.33 ± 1.3; P = 0.70) among children with CKD stages 2, 3, or 4, respectively.

For dialysis subjects, the average time on dialysis was 1.2 ± 1.3 yr (range, 0.3 to 3.7 yr); two patients had arteriovenous grafts, three patients had fistulas, and seven patients had permanent atrial catheters; mean Kt/V was 1.7 ± 0.7 (range, 1.1 to 2.3).

For transplant recipients, most of the patients (81%) had their first transplant and were treated by maintenance dialysis (68%) before transplant. All subjects were taking triple immunosuppression therapy: steroids (all), calcineurin inhibitors (tacrolimus 77% and cyclosporine 23%), and mycophenolate mofetil (50%) or azathioprine (50%). The mean time post-transplant was 3.9 ± 3.4 (1 to 11.3) years; the mean cumulative duration on dialysis was 1.1 ± 2.3 (0 to 10) years, and the mean duration of renal replacement therapy (dialysis + transplant) was 5.8 ± 3.9 (1.3 to 14.2) years.

Echocardiographic Characteristics

Echocardiographic characteristics are listed in Table 2. Children on maintenance hemodialysis and posttransplant had higher left ventricular mass (LVM) index and prevalence of left ventricular hypertrophy (LVH) than children with CKD stage 2 to 4. Increased contractility (difference between measured and predicted velocity of circumferential fiber shortening [VCFdiff]) was observed in all patient groups. Indices of diastolic function (E/A, E'/A') were significantly lower in hemodialysis patients than in controls and CKD stage 2 to 4 subjects.

Maximal Aerobic Capacity

Patients with CKD stage 2 to 4 on hemodialysis and posttrans-
LV structure on hemodialysis and posttransplant had lower VO₂ max when compared with patients with CKD stage 2 to 4. Figure 1). Transplant and hemodialysis patients had decreased VO₂ max was similar in height/weight-matched controls (37.5 ml/kg per min) and subjects in age-matched control (38.7 ± 5.4 ml/kg per min) and CKD stage 2 (38.6 ± 11.9 ml/kg per min) groups (P = 0.61). As in the analysis utilizing age-matched controls, VO₂ max remained significantly lower in CKD stage 3 and 4, hemodialysis and transplant subjects when compared with height/weight-matched controls (overall P < 0.0001). To adjust for possible differences in body composition, VO₂ max was recalculated using estimated lean body mass (LBM). The differences in VO₂ max among groups remained after adjusting for LBM: controls, 47.4 ± 5.5 ml/kg per min; CKD stage 2 to 4, 42.8 ± 9.9 ml/kg per min; hemodialysis, 33.5 ± 8.1 ml/kg per min; and transplant, 37.5 ± 7.6 ml/kg per min (P < 0.0001).

To insure that the results were not attributable to inadequate effort, the respiratory quotient (RQ) in each patient group was also examined. All patient groups except for the dialysis patients achieved a mean RQ >1.1 (Figure 3A). The dialysis patients produced RQ = 1.02 ± 0.08, approximating maximal effort. Because HR directly correlates with work intensity, the peak HR for each group were measured (Figure 3B). All groups except for dialysis patients achieved 90% of their mean target HR.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Controlsb (n = 33)</th>
<th>CKD stage 2 to 4 (n = 46)</th>
<th>Hemodialysis (n = 12)</th>
<th>Transplant (n = 22)</th>
<th>Overall P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV structure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVM index, g/m².7</td>
<td>29.1 ± 6.1</td>
<td>33.3 ± 7.5</td>
<td>41.2 ± 13.4</td>
<td>40.5 ± 9.3</td>
<td>0.002</td>
</tr>
<tr>
<td>LVH, n (%)</td>
<td>0</td>
<td>8 (17)</td>
<td>6 (50)</td>
<td>11 (50)</td>
<td>0.2</td>
</tr>
<tr>
<td>LV systolic function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shortening fraction, %</td>
<td>35.7 ± 7.0</td>
<td>40.7 ± 4.0</td>
<td>36.9 ± 6.5</td>
<td>40.2 ± 4.8</td>
<td>NS</td>
</tr>
<tr>
<td>VCF (circumference/s)</td>
<td>1.05 ± 0.17</td>
<td>1.19 ± 0.27</td>
<td>1.17 ± 0.24</td>
<td>1.20 ± 0.19</td>
<td>0.01</td>
</tr>
<tr>
<td>VCF_{diff} (circumference/s)</td>
<td>-0.01 ± 0.16</td>
<td>0.12 ± 0.26</td>
<td>0.09 ± 0.21</td>
<td>0.13 ± 0.17</td>
<td>0.04</td>
</tr>
<tr>
<td>E/A</td>
<td>2.1 ± 0.46</td>
<td>1.9 ± 0.5</td>
<td>1.5 ± 0.5c</td>
<td>1.8 ± 0.5</td>
<td>0.01</td>
</tr>
<tr>
<td>E'/A'</td>
<td>2.3 ± 0.6</td>
<td>2.1 ± 0.7</td>
<td>1.6 ± 0.7c</td>
<td>1.9 ± 0.6</td>
<td>0.04</td>
</tr>
<tr>
<td>E/E'</td>
<td>7.0 ± 1.9</td>
<td>7.7 ± 1.7</td>
<td>8.6 ± 2.5c</td>
<td>9.3 ± 2.3c</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Table 2. Echocardiographic characteristics at rest

*Data presented as mean ± SD. VCF, heart rate corrected velocity of circumferential fiber shortening; VCF_{diff}, difference between measured and predicted VCF.

b Controls represent only age-matched group.

c P < 0.05 versus control.

d P < 0.05 versus CKD stage 2 to 4.

*Comparison among patient groups only.
Univariate Analysis

The results of univariate analysis are listed in Table 3. VO₂ max was negatively correlated with resting HR and BMI but not BP or maximal HR. No significant associations between VO₂ max and BMI remained when BMI z-scores were used in the analysis ($r = 0.09, P = 0.33$). In addition, no association of VO₂ max with absolute BMI values was seen when VO₂ max was adjusted to estimated LBM ($r = 0.06, P = 0.65$). Of the laboratory parameters monitored, an inverse correlation was observed with serum creatinine, triglycerides and C-reactive protein. VO₂ max was not significantly related to hematocrit. No significant correlations were found between VO₂ max and duration of CKD, dialysis, or time after transplantation. Two measures of diastolic function, $E'/A'$ and $E/E'$, were found to be inversely associated with VO₂ max. However, measures of LV performance (VCF), preload LV end-diastolic dimension, afterload (wall stress [WS]), and contractility (VCF$_{\text{adj}}$) were not significantly associated with VO₂ max.

Multivariate Regression Modeling

To define independent predictors of VO₂ max, multivariate regression modeling using stepwise approach was performed. Variables with $P < 0.15$ from univariate analyses (Table 3) were entered in the regression analysis. Decreased $E'/A'$ ($\beta = 5.23, P < 0.0001$) and patient groups versus control ($\beta = -2.06, P = 0.05$) were found to be independently predictive of lower VO₂ max (model $R^2 = 0.23$).

DISCUSSION

Our study demonstrates new evidence that abnormally low VO₂ max is already present in children and adolescents with CKD stage 3 to 4, suggesting that the cardiovascular system’s response to metabolic challenge is attenuated early in the development of CKD. The results are worrisome because the associations between decreased aerobic capacity and decreased kidney function were found in young patients, a population without preexisting symptomatic cardiac disease and other co-morbid conditions. These data are in parallel with our previous findings, which demonstrated alterations in cardiovascular structure and function early in the course of CKD in children.$^{10–12}$ Importantly, the degree of decrease in VO₂ max in patients with CKD 3 to 4 was similar to that of patients on maintenance hemodialysis. Another concern is the fact that no improvement was seen in our transplant recipients despite having good allograft function. These findings confirm recently reported data by Painter et al.$^7$ who observed low levels of physical fitness and activity in posttransplant children. In contrast, adult studies have shown some improvement in physical activity parameters after renal transplantation.$^{13}$ One reason for this disparity may be the differential effects of CKD on the developing child. However, even in adults, poor cardiovascular fitness is an independent risk factor for mortality.$^6$ Interestingly, Matsumoto et al.$^{14}$ demonstrated that renal transplantation reversed abnormalities in the oxidative metabolism of muscle in children with ESRD, yet disparities in clinical assessment of muscle strength continued after renal transplantation.$^{14,15}$ These results highlight the importance of investigating the role of exercise in improving the cardiovascular risk in patients with CKD.$^{16}$

One important consideration in the analysis was controlling for differences in body size between patients with CKD and controls, because several studies have demonstrated the influence of body composition on VO₂ max.$^{17}$ As expected, patients with CKD were smaller than age-matched controls. Therefore, lower VO₂ max in patients with CKD may simply be the result of growth failure. To address the differences in body size, most studies advocate the adjustment of VO₂ max to LBM instead of body weight. Unfortunately, dual-energy x-ray ab-
sorptiometry (DEXA)-based determination of LBM was not performed in this study. Hence, we used estimated LBM to correct VO₂ max. With this approach, renal patients, including subjects with CKD stage 3 and 4, continued to have lower VO₂ max when compared with controls. It is important to point out that the formula used to estimate LBM was derived from measurements of healthy controls, which limits its applicability to our study population. Another approach to control for body size used in previous studies involved normalization of data with the use of scaling models. However, the ability to use scaling models is dependent on large sample sizes and locally derived exponent values, which vary significantly from study to study. No local exponent values for the control population in this study were available. As a result, a group of historical height- and weight-matched controls were obtained to control for variations in body size observed with age-matched controls. In agreement with previous results, lower VO₂ max was observed in patients with CKD compared with height- and weight-matched controls. Finally, during subgroup analysis, it was noted that patients with CKD stage 2 had higher VO₂ max relative to patients with CKD stages 3 and 4, yet each of these groups of patients had similar height z-scores, weight, and BMI (Figure 2). These results further supported the hypothesis that patients with progressive CKD had decreased aerobic capacity independent of growth failure. It is also important to mention that racial differences in VO₂ max have been observed, with healthy black children having lower VO₂ max relative to white children. It is possible that overrepresentation of black subjects in hemodialysis group might contribute to lower VO₂ max. However, a higher percentage of black subjects in the control population compared with CKD stage 2 to 4 subjects argued that racial disparities were unlikely to account for decreased exercise capacity in patients with CKD.

Another novel and potentially important finding of our study is that decreased diastolic function was an independent predictor of worse VO₂ max. Previous investigations have demonstrated the presence of diastolic dysfunction in this patient population with the use of tissue Doppler imaging (TDI). TDI is superior to traditional Doppler measurements of diastolic function in that TDI is relatively independent of loading conditions. In addition, transmitral flow is influenced by changes in HR and LV compliance. Because of these confounding factors, traditional flow Doppler measurements have had poor correlation with exercise capacity in previous investigations. Studies using TDI to investigate adult patients with subclinical diastolic dysfunction as a result of atherosclerotic cardiac disease have suggested that elevated LV filling pressures were the primary mechanism for decreased exercise capacity. Similar findings in hypertensive adults suggested that impaired LV filling may reduce oxygen delivery and cause exercise fatigue. Our CKD patient population has several reasons for impaired LV filling: e.g., patients on hemodialysis are likely to have volume overload and increased LV volume. In addition, these patients are often hypertensive with evidence of pressure overload, thereby impacting LV filling. The cross-sectional nature of our study prevented elucidation of the mechanisms of association between diastolic dysfunction and impaired VO₂ max in patients with CKD.

In this study, significant associations were also found between lower VO₂ max and elevated BMI in correlation analysis. Generally, a high BMI is associated with increased absolute VO₂ max secondary to higher stroke volume in obese patients. However, recent studies have argued that, when comparing individuals of different body size, VO₂ max should be adjusted for fat-free mass, fat mass, and body weight. As a result, there is no difference between adjusted VO₂ max in obese and normal-weight patients. In agreement with these studies, when VO₂ max was corrected for estimated LBM or BMI z-scores were used in the analysis, BMI was no longer a significant independent predictor.

In a univariate analysis, we noted that laboratory measures of inflammation (C-reactive protein) were inversely associated with VO₂ max. It is well-recognized that CKD is associated with elevated levels of inflammatory mediators including TNF-α and IL-6. These cytokines have been shown to induce muscle atrophy through enhanced catabolism, which may impact oxygen utilization in these patients. Castaneda et al. demonstrated that resistance training may reverse the malnutrition-inflammation complex associated with poor prognosis in individuals with CKD, and recent reviews have highlighted the antiinflammatory role of exercise in other disease states. In our study, no cytokine measurements were performed. In addition, the cross-sectional nature of our study precludes determination of a direct cause and effect relationship between exercise and inflammation.

Together, the results of our study suggest that cardiovascular adaptations early in the progression of CKD may result in irreversible functional constraints in pediatric patients contributing to accelerated progression of cardiovascular disease. Longitudinal studies are now required to assess the progression of these changes over time and to determine if physical activity programs would improve the cardiovascular outcomes of these patients.

**CONCISE METHODS**

**Subjects**

Forty-six patients with CKD stage 2 to 4, 12 patients on maintenance hemodialysis, 22 patients with renal transplants, and 33 healthy age-matched controls were included and studied cross-sectionally. Inclusion criteria were age 6 to 20 yr; measured GFR 16 to 89 ml/min per 1.73 m² for CRI patients; at least 6 wk of maintenance 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.

Healthy children were recruited from the families of personnel at...
Cincinnati Children’s Hospital Medical Center. A separate group of height- and weight-matched historical controls were also obtained (n = 78). The medical records were reviewed for age, sex, race, cause of CKD, and duration of renal failure or dialysis. Length of time post-transplant was also recorded. All patients had a history and physical examination performed. Clinical and laboratory data were collected on the day of the echocardiographic evaluation and exercise testing, including height, weight, systolic (SBP) and diastolic (DBP) blood pressure, serum creatinine, calcium, phosphorus, hemoglobin, serum lipids, and high-sensitivity C-reactive protein. BP values were indexed to the age-, sex-, and height-specific 95th percentiles for SBP or DBP >1.0. The kidney function for CKD stage 2 to 4 and renal transplant patients was estimated by measuring GFR using a single intravenous injection of ioversol injection 75% (Optiray 350; Mallinckrodt, Inc., St. Louis, MO). 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 h in each session. “Dry weight” was defined as the body weight below which hypotension or muscle cramps occur.

**Echocardiography**

Echocardiograms were obtained using standard techniques. LVM was measured with two-dimensional directed M-mode echocardiography with measurements made according to the American Society of Echocardiography criteria. LVM index (mass divided by height raised to a power of 2.7 [g/m^2.7]) was used to evaluate LVH. LVH was defined as LVM index >95th percentile for normal children and adolescents. Diastolic function was estimated echocardiographically using both transmitral flow velocities and tissue Doppler indices. Early diastole was assessed using indices of LV relaxation and reported as the ratio of maximal early (E wave) and late (A’ wave) diastolic septal mitral annular peak velocity (E/A’). Late diastole was determined using the index of LV compliance, a ratio of peak transmural E velocity to early diastolic mitral annular velocity (E’. E’). To assess systolic function, LV performance was measured by calculating the shortening fraction and HR-corrected VCF. A load-independent index of contractility was determined on the basis of the relationship between VGF and end-systolic WS by calculating the VCFdif for the calculated WS. Left ventricular end-diastolic dimension indexed by body surface area raised to the 0.5 power was used as an estimate of LV preload. End-systolic WS and indexed SBP and DBP were used to estimate LV afterload.

**Exercise Testing**

Subjects underwent recumbent ergometer (KHL Model 8450; Lode, Groningen, Holland) maximal exercise test using the James protocol. HR and a 6-lead rhythm strip were recorded at rest, during each minute of exercise, immediately after exercise, and 1, 3, 5, 10, and 15 min after exercise. BP were obtained at rest 2 min into each workload, immediately after exercise, and 1, 3, 5, 10, and 15 min after exercise using the auscultation method and a manual sphygomanometer with a cuff appropriately sized for the patient. Echocardiographic parameters were assessed immediately before and after exercise. Oxygen consumption (VO2 max) was measured at rest and during each stage of exercise using a metabolic cart (Parvomedics Model TrueMax 2400, Sandy, UT). VO2 max is expressed in milliliters of oxygen consumed per kilogram of body weight per minute. VO2 max was also corrected for estimated LBM using the following equations: Male: LBM = 1.10 × weight – [128 × (weight^2/height^3)]; Female: LBM = 1.07 × weight – [148 × (weight^2/height^3)]18,19,39

The RQ was also determined at peak exercise. RQ, the ratio of carbon dioxide excreted relative to uptake of oxygen, is useful in assessing effort. At peak exercise, values approximate 1.2, demonstrating that the patient is excreting higher amounts of carbon dioxide, which corresponds with the clearance of this gas from the lungs as a result of muscle metabolism. A ratio ≥ 1.1 may indicate a submaximal effort. All studies on hemodialysis patients were obtained within 24 h postdialysis. Because HR directly correlates with work intensity, the peak HR for each group was also measured.

**Statistical Analysis**

Values are presented as mean ± SD. A two-sample t test or Mann-Whitney Rank Sum Test was used to compare means ± SD of continuous variables. The general linear model procedure was used to compare means ± SD among all four groups. Categorical variables were compared using the χ^2 or Fisher exact test. The associations between variables were assessed by Pearson correlation analysis. Stepwise multivariate regression analysis was used to analyze variables that correlated (P < 0.15) with VO2 max in univariate analysis. P ≤ 0.05 was considered statistically significant. The SAS 9.1 (SAS Institute, Cary, NC) statistical package was used in the analysis.

**ACKNOWLEDGMENTS**

This study was initially presented in abstract form at the Society for Pediatric Research in May 2007. The research was supported by grants 2K12HD28827 and K23 HL69296–01 from the National Institutes of Health (M.M.).

**DISCLOSURES**

None.

**REFERENCES**


