Left ventricular hypertrophy, treadmill tests, and 24-hour blood pressure in pediatric transplant patients

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Background. Hypertension and left ventricular hypertrophy (LVH) are possible complications in pediatric patients after renal transplantation.

Methods. We performed left ventricular echocardiography, 24-hour ambulatory blood pressure monitoring (24-hr ABPM), and treadmill tests in 28 pediatric renal transplant patients (mean age 16.1 ± 3.7; time since transplantation 36 ± 23 months). Left ventricular mass (LVM) was indexed for height².LVH was found in 82% of the patients. Seven of these patients were normotensive by 24-hour ABPM, but five patients showed a hypertensive systolic BP response during the treadmill test. LVM/height² correlated significantly with the mean 24-hour systolic BP (P = 0.002) and with the maximal exercise systolic BP (P = 0.002).

Results. LVH is frequent in pediatric renal transplant patients. More information is needed with respect to the risk for LVH, including data from 24-hour ABPM and treadmill testing.

During the past few decades, kidney transplantation has significantly improved the life expectancy and quality of life of pediatric renal patients. Kidney transplantation, however, is associated with a number of chronic conditions that are responsible for significant morbidity. After successful renal transplantation, some of these patients remain or become hypertensive [1]. Hypertension (HTN) associated with left ventricular hypertrophy (LVH) has been identified as a major cardiovascular risk factor for adults [2–4]. Therefore, early identification of subjects at risk of developing sustained arterial HTN and/or LVH should be a major goal of a post-transplant rehabilitation program.

Key words: ambulatory blood pressure, pediatric renal transplantation, transplant morbidity, hypertension, cardiac hypertrophy.

METHODS

Admission criteria

Patients were enrolled according to the following criteria: age of more than six years, transplant performed at least six months prior to the beginning of the study, creatinine clearance consistently greater than 40 ml/min/1.73 m², and the absence of clinical and sonographic evidence of renal artery stenosis, hyperparathyroidism, or anemia. Patients with orthopedic limitations or diabetes were excluded from the study.

Because of the development of ambulatory blood pressure-monitoring (ABPM) devices, single blood pressure (BP) measurements do not need to be considered as representative of the average daily BP; ABPM is now accepted as the method of choice for evaluating and monitoring HTN in both adults and pediatric patients [5, 6]. These studies have also established a clear relationship between LVH and HTN when measured by ABPM [7].

In addition, BP measurement during the treadmill exercise test has been shown to be an accurate and noninvasive tool for the early diagnosis of HTN with high predictive value for the development of LVH [8]. In particular, an abnormal BP increase during exercise has been shown in apparently healthy, normotensive men with LVH [9].

Similarly, in a previous study we have observed abnormal hypertensive responses during treadmill testing in normotensive transplanted children and adolescents [10]; however, no data are available on the significance of abnormally increased systolic BP during exercise testing associated with LVH in renal transplanted pediatric and/or adult patients.

The purpose of this study was to evaluate the correlation between systolic BP during a treadmill test, 24-hour ABPM, and changes in left ventricular mass (LVM) in a group of children and adolescents with renal transplantation.

Accepted for publication May 18, 1999
Blood pressure

Blood pressure profiles were evaluated by 24-hour monitoring using the Medilog ABP monitor (Oxford Medical, Oxford, UK) [11]. The apparatus was serviced and calibrated on a monthly basis. BPs were measured every 15 minutes during the daytime and every 30 minutes during the night. Patients were asked to record their periods of activity and sleep during the recording. These diary entries were used to define “daytime” and “nighttime.” Antihypertensive treatment was not modified during the month prior to the study or during the recordings. Recordings containing more than 25% of erroneous measurements were excluded from the analysis. The following parameters were analyzed: mean 24-hour systolic and diastolic BP, mean systolic and diastolic BP during the daytime, the mean systolic and diastolic BP at night, and the day-to-night fall in mean systolic and mean diastolic BP.

Hypertension was defined as any value above the 95th percentile, and borderline HTN was defined as any value between the 90th and 95th percentiles according to previously published normal standards for 24-hour ambulatory BP values in children [12]. HTN was confirmed by repeated 24-hour monitoring.

Echocardiography

Left ventricular echocardiography was performed with a two-dimensional and M-mode echo by a standard technique with subjects in a supine position [13]. Measurements of internal left ventricular end-systolic and end-diastolic diameters, end-diastolic interventricular septal thickness, and end-diastolic posterior wall thickness were made according to the American Society of Echocardiography Criteria [14].

Left ventricular mass was estimated using the equation reported by Devereux et al [15] and was indexed according to the allometric regression equation using height$^{2.7}$ [16, 17].

Treadmill test

All subjects underwent a graded treadmill test until exhaustion according to the protocol established by Cumming et al [18]. BP during exercise was compared with the reference values of a control group of 280 healthy children and adolescents, matched for gender, chronological age, and same stress level [19]. An abnormally high systolic BP response was considered if it was more than 2 sd of the control population and was confirmed by a repeated procedure.

Statistical analysis

Results were analyzed by linear and multiple linear regression techniques. The statistical package used was True Epistat (F.L. Gustafson, 5th edition, 1995).

Table 1. Twenty-four hour ambulatory blood pressure monitoring (ABPM), exercise testing and echocardiographic results

<table>
<thead>
<tr>
<th></th>
<th>Mean ± sd</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-Hour SBP mm Hg</td>
<td>119 ± 11</td>
<td>103–143</td>
</tr>
<tr>
<td>24-Hour DBP mm Hg</td>
<td>69.9 ± 10</td>
<td>53–97</td>
</tr>
<tr>
<td>dip SBP %</td>
<td>3.1 ± 6</td>
<td>+14/-14</td>
</tr>
<tr>
<td>dip DBP %</td>
<td>12.3 ± 10</td>
<td>+17/-38</td>
</tr>
<tr>
<td>Exercise SBP mm Hg</td>
<td>147 ± 19</td>
<td>100–190</td>
</tr>
<tr>
<td>LVM/height$^{2.7}$ g/m$^2$</td>
<td>65.6 ± 21</td>
<td>114–312</td>
</tr>
</tbody>
</table>

Abbreviations are: SBP, systolic blood pressure; DBP, diastolic blood pressure; LVM, left ventricular mass.

RESULTS

The results of the 24-hour ABPM, exercise testing, and echocardiographic evaluation are shown in Table 1.

Patients

Twenty-eight renal transplant recipients (15 males and 13 females) fulfilled the inclusion criteria for the study. The mean age was 16.1 years (sd 3.7, range 10 to 24). The average interval since transplantation was 36 months (sd 23, range 7 to 86). The mean creatinine clearance was 76 ml/min/1.73 m$^2$ (sd 31.7, range 40 to 149).

All transplant recipients received immunosuppressive treatment with cyclosporine A, prednisone, and azathioprine. The dosage of cyclosporine was adjusted to maintain trough levels between 250 and 350 ng/ml. Prednisone and azathioprine dosage were 7.5 mg/m$^2$/day and 1.5 mg/kg/day, respectively. Fourteen patients underwent to bilateral nephrectomy before transplantation, and 10 of them were still hypertensive after transplantation. Nineteen patients received calcium channel blockers. No other antihypertensive drugs were used.

Blood pressure profiles

Ten out of 28 patients were diagnosed as hypertensive based on a mean 24-hour systolic BP. Eight had nighttime HTN with daytime BP in the upper quintile, and two had combined daytime and nocturnal HTN. Four patients had borderline HTN. The mean nocturnal dip of systolic and diastolic BP was 3.1% (sd 5.9) and 10.4% (sd 12.3), respectively. Nine of 19 patients receiving calcium blockers were still hypertensive on 24-hour ABPM. Their antihypertensive treatment was modified after HTN was confirmed by a repeated 24-hour ABPM.

Treadmill test

During treadmill testing, 15 out of 28 patients had abnormally high systolic BP (more than 2 sd above the expected mean). Five of these 15 patients with exercise HTN were normotensive by 24-hour ABPM, and their mean nocturnal systolic and diastolic BP dip was 6 and 16%, respectively. Eleven of 15 hypertensive patients at the treadmill were treated with antihypertensive drugs,
Left ventricular hypertrophy

The relationship between LVM indexed for height\(^{2.7}\) (g/m\(^{2.7}\); LVM\(_i\)) and the age is shown in Figure 1. No significant correlation between LVM\(_i\) and age was found. LVH was found in 82% of the patients (23 out of 28). Seven of these patients with LVH were normotensive by 24-hour ABPM. Five showed an exercise-induced systolic BP higher than 2\(\text{sd}\) above the expected mean, and one had a systolic BP during the treadmill test at 2\(\text{sd}\). In all patients, the LVM\(_i\) correlated significantly with a mean 24-hour systolic BP (\(r = 0.55, P = 0.002\); Fig. 2) and with the maximal exercise systolic BP (\(r = 0.55, P = 0.002\); Fig. 3). LVM\(_i\) was not significantly different in the patients who underwent bilateral nephrectomy prior to transplantation. The association between LVM\(_i\), mean 24-hour systolic BP, and exercise systolic BP was also explored by multiple linear regression, but the number of patients examined was insufficient for analysis. No correlation was found between LVM\(_i\) and the mean 24-hour diastolic, nocturnal systolic and diastolic BP dip, glomerular filtration rate, or time since transplantation (data not shown).

DISCUSSION

Left ventricular hypertrophy has been recognized as a major risk factor for cardiovascular mortality in adults, but few data are available in renal pediatric transplant patients. Lorig et al reported that 22% of transplanted children had LVH [20], and more recently, Johnstone et al showed a severe increase in LVM above the 95th percentile in 63% of a group of renal transplanted children [20, 21]. In this study, LVH was found in 82% of our renal transplant patients. A possible reason for these differences is the relatively small number of patients examined in the studies. In our study, only 43% (10 out of 23) of the patients with LVH were found hypertensive by 24-hour ABPM. The remaining 56% (13 out of 23) had a normal 24-hour BP pattern, but five showed hypertensive systolic BP response at the treadmill test. The BP response during exercise testing has been reported to be closely associated with LVH in nonrenal patients [22], and high exercise BP levels are strongly associated

Fig. 1. Left ventricular mass (LVM) indexed for height\(^{2.7}\) (g/m\(^{2.7}\)) versus age. No significant correlation was found between LVM/Ht\(^{2.7}\) and age of patients (\(N = 28; P = 0.08; r = 0.332\)). All patients are represented as closed circles.

Fig. 2. Left ventricular mass (LVM) indexed for height\(^{2.7}\) (g/m\(^{2.7}\)) versus mean 24-hour systolic blood pressure (SBP). The regression line is shown. Values are expressed as \(\text{sd}\). Symbols are: (○) normotensive patients; (●) hypertensive patients. The line was drawn for all data points (\(N = 28; P = 0.002; r = 0.55\)).

Fig. 3. Left ventricular mass (LVM) indexed for height\(^{2.7}\) (g/m\(^{2.7}\)) versus exercise systolic blood pressure (SBP). The regression line is shown. Values are expressed as \(\text{sd}\). Symbols are: (○) patients with normal exercise SBP; (●) patients with a hypertensive exercise response. The line was drawn for all data points (\(N = 28; P = 0.002; r = 0.55\)).
with important coronary risk factors [23]. The reasons for this association are poorly understood. In nonrenal patients, overactivity of the sympathetic nervous system has been demonstrated in adults [24]. These authors postulate that normotensive subjects with exaggerated BP response to exercise may have undiagnosed transient BP increases during normal activities with resulting LVH development. Our data suggest that in renal transplant patients, HTN may not be sufficient for the development of LVH. Most of the associations that we have made cannot be determined to be causal because the measures were not performed prior to transplantation in a systematic fashion. No data are available on LVM before transplantation from patients reported by either Soergel et al [5] and Johnstone et al [21]. We cannot exclude a preexisting LVH in our patients because previous echocardiographic data were not available, and chronic HTN cannot be considered because not all patients had been studied by ABPM. Our severely hypertensive patients underwent bilateral native kidney nephrectomy pretransplantation. In our analysis, we did not find a difference in LVMi when nephrectomy was performed, suggesting that severe HTN prior to transplantation does not necessarily affect the development of LVH. LVH, however, is found most frequently after renal transplantation [21], suggesting that chronic uremia may not be the only cause for the development of LVH after transplantation. Johnstone et al reported a significant difference (P < 0.01) in the incidence of LVH in children with chronic renal failure (22%) and children treated by chronic dialysis (30%) [21]. In renal transplant patients, other factors such as medications may contribute to the development of cardiac hypertrophy. We considered the effect of medications on LVH development in our patients. All of our patients were receiving the same low-dose prednisone therapy when the study was performed. We cannot exclude a permissive or additive effect of steroids in our patients because we did not have a steroid-free control group, but a clear relationship between steroids and LVH is still lacking (abstract; Arch Dis Child 709:F25, 1994). Johnstone et al did not find a correlation between LVM and steroid administration [21]. Cyclosporine administration, on the other hand, has been associated with increased sympathetic nerve activity secondary to the inhibition of the phosphatase activity of calcineurin resulting in endothelin-mediated renal arteriolar vasospasm [25]. More recently, cyclosporine and Tacrolimus have been reported to up-regulate endothelial nitric oxide synthase expression with consequent hemodynamic changes associated with HTN [26]. In a previous report, we hypothesized that this cyclosporine-related effect might play a role in normotensive renal transplant children and adolescents who demonstrate an abnormal hypertensive response to exercise testing [10]. Finally, data by Hollander et al suggest that conversion from cyclosporine to azathioprine in kidney transplant patients results in improved patient survival by lowering cardiovascular mortality [27]. In conclusion, our data show that LVH is a frequent complication of renal transplantation in pediatric patients. LVH is not always associated with HTN even when evaluated by 24-hour ABPM, suggesting that other factors may contribute to cardiac hypertrophy.

More information is needed with respect to risk factors for LVH, including the data that can be gathered from ambulatory BP and treadmill testing, as well as all of the factors discussed earlier in this article. Prospective long-term follow-up studies are required to determine the significance of increased LVM in pediatric patients who progress from chronic renal failure to transplantation.

ACKNOWLEDGMENTS

The authors thank Dr. V. Di Ciovino and Dr. G. Di Liso of Epidemiology Unit for their assistance.

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