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Total peripheral vascular resistance in pediatric renal transplant patients

Maria Chiara Matteucci, Ugo Giordano, Armando Calzolari, and Gianfranco Rizzoni

Department of Pediatric Nephrology and Unit of Sports Medicine, Bambino Gesù Children Research Hospital, Rome, Italy

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Background. Abnormal cardiovascular reactivity at rest and during physical exercise may be a risk factor for left ventricular hypertrophy (LVH) in pediatric renal transplanted (Tx) patients. Data on total peripheral vascular resistance (TPR) are not available.

Methods. Eleven renal Tx patients treated with cyclosporine (7 females and 4 males; mean age 14.6 ± 3.3 years; mean time since transplantation 43 ± 35 months) were evaluated for 24-hour blood pressure (BP), TPR and echocardiographic left ventricular mass (LVM). TPR values of patients were compared with data of a group of 11 healthy controls matched for sex and age.

Results. Twenty-four–hour ambulatory blood pressure monitoring showed that all but one patient had normal daytime BP values and six patients showed a reduced or inverse nocturnal dip. LVH was found in 72% of the patients. In comparison with healthy controls, patients showed significantly elevated TPR at rest and during exercise suggesting an increased vascular tone. The degree of LVH in these patients is severe and appears disproportionate to the BP values.

Conclusion. The high incidence of LVH can reflect an augmented cardiovascular reactivity associated with a disturbed circadian pattern. The increase in TPR and the reduction of the nocturnal fall of BP also might contribute to the development of LVH in young renal Tx patients.

In normal individuals a maximal exercise effort is reached when the cardiovascular system has attained its maximum capacity to deliver oxygenated blood to the exercising muscles.

Abnormal cardiovascular reactivity to challenging physically stressful situations may be a risk factor for cardiovascular disease and left ventricular hypertrophy (LVH) in renal transplant (Tx) patients. Measures of cardiovascular reactivity include blood pressure (BP), cardiac output (CO), and total peripheral vascular resistance (TPR).

Knowledge of CO and TPR changes during exercise may be helpful for understanding the effects of renal disease upon exercise performance and possible end-organ effects.

To our knowledge, data on TPR in pediatric renal transplant recipients are not available.

The aim of the study was to evaluate CO and TPR at rest and during exercise and left ventricular mass in children and adolescents with renal transplantation.

Key words: renal vascular resistance, children and transplantation, cardiac hypertrophy, left ventricular hypertrophy, blood pressure.

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METHODS

Patients

Patients were enrolled according to the following criteria: transplantation performed at least six months prior to the beginning of the study and glomerular filtration rate over 40 mL/min/1.73 m^2. Absence of renal artery stenosis on Doppler examination, hyperparathyroidism, or anemia defined as hemoglobin less than 110 g/L was requested.

Controls were identified from a group of young healthy subjects, not trained, who were examined for sport certification.

All patients and/or their families gave informed consent.

Cardiac output

Cardiac output was evaluated by a mass spectrometer using an acetylene re-breathing technique. Although many techniques to measure CO have been described [1], the acetylene technique is well suited for measurement of CO in children at rest and during exercise [2].

This technique is based upon the assumption that inert gases are transported in the blood in purely physical solution. Transportation of most inert gases is blood flow-limited and the gas can be used to estimate cardiac output.

During the acetylene re-breathing maneuver the subject is asked to re-breathe the gas in a bag filled with a mixture of oxygen, acetylene and helium.

The equation for the re-breathing method is based on

the relationships developed by Cander and Foster [3], with modifications by Petrini, Peterson and Hyde [4].

Proper instrumentation such as a mass spectrometer permits the measurement of concentrations of gases rapidly and accurately, and this method has been shown to correlate well with both the invasive Fick method [5] and the Doppler method of CO determination [6].

Total peripheral vascular resistance

The concurrent determination of CO and mean BP allows the derivation of TPR to blood flow [7]. TPR was calculated by the equation, TPR (dyne $\times$ sec $\times$ cm^{-5}) = (MAP/CO) $\times$ 80, where MBP is mean blood pressure (mm Hg) and CO is cardiac output (L/min).

Blood pressure

Blood pressure during the test was measured by auscultation and a mercury sphygmomanometer according to the recommendation of the Task Force on Blood in Children [8] with appropriately sized cuffs. MBP was calculated with the equation: mean arterial pressure MAP = (SBP+ 2 DBP)/3, where MAP is mean arterial pressure, SBP is systolic blood pressure and DBP is diastolic blood pressure.

After completion of the laboratory evaluation the patients underwent ambulatory BP monitoring (Oscillometric Spacelab device) for 24 hours, with a measurement obtained every 15 minutes during the day and every 30 minutes at night. Blood pressure values were compared to normal values for height and sex from the data of Soergel et al [9].

Measures of SBP, DBP and nocturnal dip were calculated as the differences between average daytime minus nighttime readings expressed as a percentage of the daytime average.

A reduced nocturnal dip was defined as <5.5% corresponding to the 5th percentile in healthy children and adolescents [9].

Treadmill test

A symptom-limited exercise test was performed according to the Bruce protocol [10], which involves variable speed and slope. Details of this method are reported elsewhere [11]. The test was stopped when the patients could not continue despite strong verbal encouragement.

Left ventricular mass evaluation

Left ventricular echocardiography was performed with a two-dimensional and M-mode ECHO by a standard technique with subjects in a supine position [12].

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 [13].

Table 1. Twenty-four–hour ambulatory blood pressure monitoring (ABPM), cardiovascular reactivity and echocardiographic results in renal transplant patients

	Mean ± SD	Range
SBP day *mm Hg*	114.3 ± 11.3	94–135
SBP night *mm Hg*	109.2 ± 11	91–125
DBP day *mm Hg*	67.6 ± 8.4	54–80
DBP night *mm Hg*	64 ± 7.5	55–77
24-hour SBP *mm Hg*	112 ± 10.5	96–132
24-hour DBP *mm Hg*	66.9 ± 7.5	56–79
Dip SBP *%*	4.19 ± 7.46	−10.6/13.3
Dip DBP *%*	5.13 ± 8.9	−10.8/19.7
CO at rest *L/min*	4.45 ± 1.08	3.01–6.78
CO during exercise *L/min*	8.54 ± 2.26	13.14–6.27
TPR at rest *dyne* $\times$ *s* $\times$ cm^5	1655 ± 357	1374–925
TPR during exercise *dyne* $\times$ *s* $\times$ cm^5	938 ± 132	1097–690
LVM/$height^{2.7}$ $g/m^{2.7}$	55.4 ± 13.7	75.5–35.52

Abbreviations are: SBP, systolic blood pressure; DBP, diastolic blood pressure; CO, cardiac output; TPR, total peripheral resistance; LVM, left ventricular mass.

Left ventricular mass was estimated using the equation reported by Devereux et al [14] and was indexed according to the allometric regression equation using $height^{2.7}$ [15].

Statistical analysis

Data are expressed as mean ± SD.

Statistical analysis was performed with unpaired *t* tests and the multiple linear regression technique.

RESULTS

The results of the 24-hour ambulatory blood pressure monitoring (ABPM), cardiovascular reactivity, and echocardiographic evaluation are shown in Table 1.

Patients

Eleven renal transplanted patients (7 females and 4 males, with mean age of 14.6 ± 3.3 years) were enrolled. Mean time on dialysis was 45 ± 38 months and mean time since transplantation was 43 ± 35 months. Eighty percent of the patients had been on peritoneal dialysis and had no arteriovenous fistula, and the remaining 20% had a non-functioning fistula. All patients received prednisone (dosage 7.5 mg/m^2/day) and cyclosporine (mean concentration 300 to 350 ng/mL $\times$ h). Mean cyclosporine concentration was calculated by the mean AUC = 195.8 + (2.4 $\times$ C2) + (7.7 $\times$ C6), where AUC is area under the curve, C2 is the concentration two hours after cyclosporine administration, and C6 is the concentration six hours after cyclosporine administration [16]. Seven patients were on antihypertensive treatment. All patients on antihypertensive treatment were taking a calcium channel blocker, and two of them were taking an angiotensin-converting enzyme inhibitor. Only three of the seven patients on antihypertensive treatment were hyper-

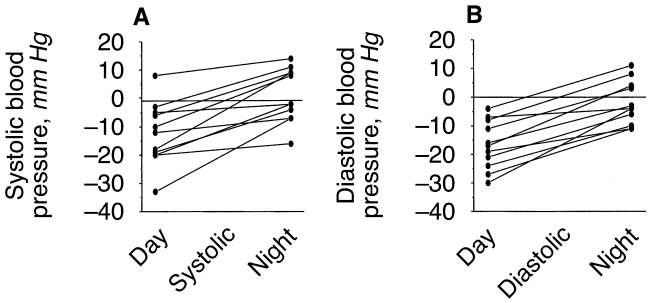

Fig. 1. Daytime and nighttime (*A*) systolic and (*B*) diastolic blood pressure profiles of the pediatric patients. Blood pressure is expressed as the difference in mm Hg to the individual height and gender statistics for the 95th percentiles of ambulatory day- or nighttime blood pressure [5].

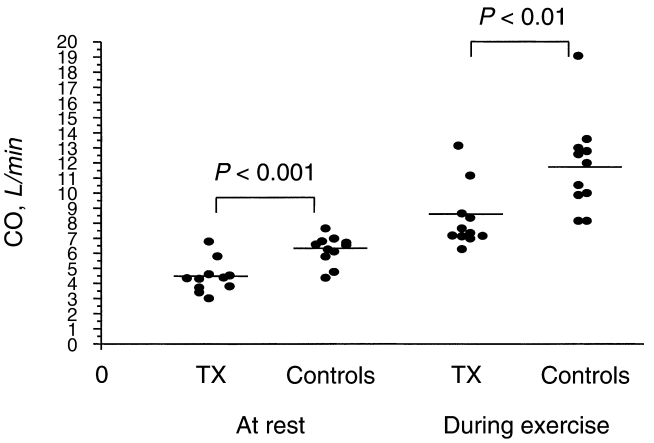

Fig. 2. Cardiac output (CO; L/min) in renal transplanted patients (TX) and controls at rest and during exercise. CO was found to be significantly lower in patients in comparison to control subjects both at rest and during exercise.

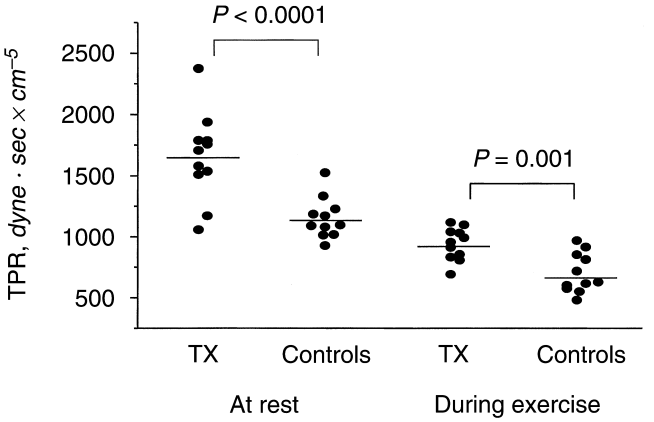

Fig. 3. Total peripheral vascular resistance (TPR) in renal transplanted patients versus controls. In comparison with healthy controls, patients showed resting TPR to significantly elevated at rest and during exercise.

tensive before transplantation. Eleven healthy untrained subjects (7 females and 4 males; mean age 13.1 ± 1.8 years) being evaluated for sports certification were identified as the controls. They were matched for sex and age (mean age of patients vs. mean age of controls, P = NS). Weight and height of patients were similar in patients and healthy controls (51.2 ± 8.3 vs. 52.4 ± 11.2 kg and 150 ± 8.3 vs. 157 ± 12 cm respectively, P = NS).

Blood pressure profiles

Daytime and nighttime SBP and DBP profiles of patients are reported in Figure 1. BP was expressed as the difference in mm Hg from the individual's values as predicted from the height and sex 95th percentile of normal ambulatory daytime or nighttime BP values [9]. All but one patient had normal daytime values.

One patient had a reduced and five patients had an inverse nocturnal dip, that is, nocturnal hypertension.

The mean nocturnal dip of SBP and DBP in patients was 4.19% (SD 7.46) and 5.13% (SD 8.9), respectively.

Cardiovascular reactivity

The adaptive change in our patients in TPR and CO during exercise was preserved and the performance was not significantly different in comparison with controls (duration 9.45 ± 2.06 in patients vs. 11.13 ± 2.52 min in controls, P = NS). Figure 2 shows data on CO for both patients and controls at rest and during exercise. CO was significantly lower in patients in comparison with controls both at rest (4.45 ± 1.08 vs. 6.25 ± 0.95 L/min, $P < 0.001$) and during exercise (8.54 ± 2.26 vs. 11.75 ± 3.03 L/min, $P < 0.01$).

In comparison with healthy controls, the patients showed a resting TPR that was significantly elevated (1655 ± 357 vs. 1144 ± 159 dyne × sec × cm^5, $P < 0.0001$).

This difference between the two groups remained during the exercise, suggesting a generalized, consistent increased in vascular tone (938 ± 132 vs. 693 ± 166 dyne × sec × cm^5, $P < 0.001$; Fig. 3).

Left ventricular mass

The distribution of LVM index (LVMi) is shown in Figure 4. LVMi was compared to normal values published by de Simone et al [15]. LVMi values of controls have not been reported because healthy subjects examined for sports certification are not requested for echocardiographic evaluation. LVMi was above the normal range in 82% of patients. The possible determinants of LVH in patients (weight, height, sex, age, duration of dialysis, TPR, BP, drugs) also were explored by a multivariate regression model analysis, but the data did not converge after 20 iterations due to the insufficient sample size [17].

DISCUSSION

Left ventricular hypertrophy is found frequently after renal transplantation in pediatric patients [18]. The de-

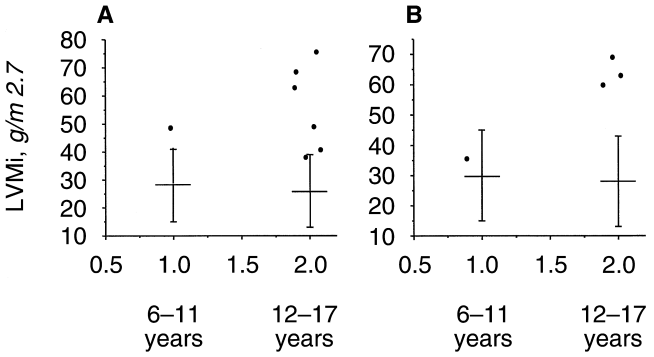

Fig. 4. Left ventricular mass (LVM) indexed for height$^{2.7}$ (g/m$^{2.7}$) in renal transplanted patients in reference to de Simone normal values for age and gender (horizontal line; *A*, females; *B*, males). The whiskers denote the range of the 95th confidence interval [10].

gree of hypertrophy is often severe after renal transplantation [19] as confirmed by our previous [20] and present data. Mitsfenes et al, who studied changes in the LVMi after renal transplantation, recently reported that LVH persists in children and adolescents after renal transplantation [21]. This was not dependent on the type of dialysis, donor source, cause of renal failure, steroid dose or cyclosporine.

A number of factors have been advocated as possible causes of LVH, such as hypertension [22], steroid therapy [23], cyclosporine use [24], and sympathetic overactivity [25]. We cannot exclude a permissive or additive effect of steroids on LVH development, but a clear relationship between steroids and cardiac hypertrophy is still lacking [26]. Our patients received a low dose of prednisone therapy at the time of the study. They had a normal daytime BP pattern and an attenuated or inverse nocturnal dipping. The degree of LVH in these patients appears disproportionate if compared with the blood pressure values. Left ventricular mass increase can only be partly explained by blood pressure anomalies. Galiatsou et al observed in a group of adults with renal transplantation that the increase in LVM index per SD of BP was greater than that reported in general population in the Framingham heart study [27, 28]. Since LVH may develop despite apparent control of BP [20], it is possible that other mechanisms may be involved in the development of LVH in these patients. Thus, the high incidence of LVH can reflect, at least in part, a disturbed BP circadian pattern. The exact mechanism influencing the control of nighttime BP is not known. Cyclosporine has been reported to affect blood pressure regulatory systems, but the exact mechanism by which it might influence the nighttime blood pressure pattern is not known. One possible mechanism may be an augmented sympathetic activity, which would normally be reduced or absent during overnight sleep. This was reported in cyclosporine-treated heart transplant recipients [29]. An increased vascular tone that can be evaluated by the mean of TPR at rest and during acute laboratory stress has been associated with increased LVM [30]. To our knowledge, there are no reports assessing TPR in pediatric renal transplanted patients at rest and during exercise. In adult cardiac transplant recipients an increase in TPR has been described in association with an attenuation of the nocturnal fall in blood pressure [31]. The present study examined the hemodynamic status of a group of young patients with a renal transplant after a relatively long period of transplantation. Hemodynamic evaluations in our small cohort show that CO is significantly lower and TPR are significantly higher in patients in comparison with controls both at rest and during exercise. Normally CO increases with increasing exercise intensity. According to the Frank Starling law, the primary factor in controlling stroke volume and, consequently, CO is the extent to which the ventricle stretches. When the ventricle stretches more it will contract with more force. Another factor that can contribute to an increase in stroke volume at rest and during exercise is TPR. During exercise, increasing vasodilation allows the left ventricle to contract against less resistance, facilitating emptying of the blood from this chamber. This mechanism in our patients seems to be impaired with a consequent augmented workload for the heart at rest and during exercise.

Cyclosporine administration has been implicated as a possible cause for increased TPR with consequent left ventricular hypertrophy. A recent cross-sectional study showed that the use of cyclosporine following transplantation is accompanied by higher rates of LVH in comparison with azathioprine treatment [27]. They found an inadequately controlled arterial hypertension and higher rates for carotid plaque and increased intima-media thickness in the cyclosporine group. Cyclosporine has been indicated to induce an increase in systemic vascular resistance, but the underlying mechanism is not clear. Several mechanisms have been proposed, such as changes in renal circulation [32], increased sympathetic nerve activity [33], increased endothelin-1 mediated vasoconstriction [34], and a decrease in the endothelial nitric oxide-dependent vasodilation [35]. Nitric oxide produced in the endothelium of arterioles is a potent vasodilator through its action on smooth muscle cell relaxation. Its role during exercise in humans has not been clearly established, but is likely to be important. This study was not designed to investigate on these factors.

In conclusion, despite the limitations of a relatively small number of patients, our results show that children and adolescents with a renal transplant have significantly increased TPR at rest and during exercise. The increase in TPR with the possible reduction of the nocturnal fall of BP might contribute to the development of LVH in these young renal transplanted patients.

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Reprint requests to Maria Chiara Matteucci, M.D., Division of Nephrology and Dialysis, Bambino Gesù Children's Hospital and Research Institute, Piazza S. Onofrio 4, 00165 Rome, Italy.
E-mail: matteucc@opbg.net

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