Nephrol Dial Transplant (2002) 17: 645–651

Nephrology Dialysis Transplantation

Original Article

Long-term impact of renal transplantation on carotid artery properties and on ventricular hypertrophy in end-stage renal failure patients

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Abstract

Background. The aim of this study was to examine prospectively the impact of renal transplantation on the morphological and functional characteristics of the carotid arteries and heart in a group of end-stage renal failure patients without overt cardiovascular disease, followed up for >3 years.

Methods. Twenty-two patients were evaluated 2–3 weeks after renal transplantation, and again 12 and 40 months post-transplant, using high resolution ultrasound imaging and echocardiography.

Results. Kidney and patient survival were 100% at the end of follow-up without any major cardiovascular events. After 40 ± 1.2 months, carotid morphological parameters were normalized: carotid intima-media thickness fell from 788 ± 24 to 676 ± 32 μm ($P < 0.01$) and the carotid wall/lumen ratio fell from 118 ± 3 to 103 ± 3 μm ($P < 0.01$). Significant reduction of left ventricular (LV) posterior wall thickness (11.5 ± 0.2 to 11.3 ± 0.2 mm, $P < 0.05$) and LV mass index (172 ± 9 to 158 ± 8 g/m^2, $P < 0.01$) was already observed after 12 ± 0.2 months. Further reduction of LV posterior wall thickness (10.4 ± 0.3 mm, $P < 0.01$) and of LV mass index (136 ± 7 g/m^2, $P < 0.01$) also occurred after 40 ± 1.2 months. However, carotid distensibility (19.5 ± 2.1 *vs* 22 ± 2.4, not significant (NS)) and LV compliance (early to atrial flow ratio: 1.2 ± 0.1 *vs* 1.3 ± 0.1, NS) remained abnormal, and normalization of the LV mass was attained by only 25% of the patients with LV hypertrophy on baseline. Multiple stepwise regression analysis showed that the rate of change of reduction of the intima-media thickness was influenced by age (negative association, $P < 0.001$) and was positively related to white race ($P < 0.05$), female sex ($P < 0.01$) and to the parallel reduction of maximum carotid diameter ($P < 0.001$). Reduction of LV mass index over time was negatively related to the duration of dialysis treatment and to the parallel increase observed in body mass index and haematocrit, and was positively related to the simultaneous reduction of diastolic blood pressure ($P < 0.01$ for all variables).

Conclusions. Successful renal transplantation improves but does not cause complete regression of the cardiovascular alterations of end-stage renal disease. Only intima-media thickness was normalized by transplantation, whereas LVMI and carotid and ventricular distensibility remained abnormal. The results suggest that extended duration of dialysis, weight gain, high blood pressure and high haematocrit may adversely affect the rate of change of post-transplant cardiovascular hypertrophy.

Keywords: carotid artery; end-stage renal failure; left ventricle hypertrophy; renal transplantation

Introduction

Cardiovascular disease is a leading cause of mortality in the renal transplant population [1]. It is widely accepted that this phenomenon stems, at least in part, from the persistence of the cardiovascular alterations already present before the operation. For instance, pre-transplant coronary artery disease, cardiomyopathy and diabetes are associated with increased risk of cardiovascular events after the operation [1]. On the other hand, the course of less serious cardiovascular ailments after renal transplant has not been fully investigated. In this regard, left ventricular (LV)

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hypertrophy and hypertrophy of the large arteries may be particularly important since they are observed in the majority of patients on all modalities of renal replacement therapy, including renal transplantation [2,3], and are well known risk factors for the non-uraemic population [4]. It is not clear, however, if these alterations could be completely reversed by successful renal transplantation and, if not, what factors are hindering this process. In a previous study [5] we showed that LV hypertrophy and compromised diastolic function in haemodialysis patients do not regress 12 months after renal transplant. In the present investigation, we extended these observations by examining prospectively the impact of renal transplantation on the morphological and functional characteristics of the carotid arteries and heart in a group of low risk patients without overt cardiac disease, evaluated a few weeks after the operation, and again 12 and 40 months post-transplant, using high resolution ultrasound imaging and echocardiography.

Subjects and methods

Subjects

We studied all end-stage renal failure patients who had been submitted to a successful renal transplantation in our unit between March 1996 and June 1997. We considered that a patient had a successful renal transplant when discharge occurred within 3 weeks after the operation in the absence of major post-operative complications, with a serum creatinine not higher than 2.5 mg/100 ml and no evidence of rejection. Twenty-two out of 38 individuals fulfilled these criteria and were included in the study. Sixteen patients were excluded because of infection (three cases with CMV and two with sepsis), rejection (seven cases) and renal dysfunction (three cases of cyclosporin toxicity and one of acute tubular necrosis), which could possibly have affected the cardiovascular physiology and therefore confound the analysis of the data. For the same reasons, we did not include data obtained before the operation. Twelve individuals received kidneys from cadaver and 10 from living donors. The mean age was 41.2 ± 7.8 years and the mean dialysis duration was 42.1 ± 7.2 months. There were 10 males, 17 Caucasians and five smokers. The causes of renal failure were chronic glomerulonephritis (4), polycistic kidney disease (4), nephrosclerosis (3), interstitial nephritis (3), diabetes (1), others (4) and not determined (3). Immunosuppressive drug treatment consisted of cyclosporin (3–5 mg/kg/day), azathioprine (1.5–2.0 mg/kg/day) and prednisone (10–20 mg/day). Eighteen patients had a present or past history of hypertension (defined as blood pressure $>140/90$ and/or use of antihypertensive medication). Thirteen patients were receiving antihypertensive medication (11 receiving long-acting calcium channel blockers and two receiving ACE inhibitors) that was administered throughout the investigative period. Left ventricular hypertrophy, as defined by Sokolow index >35 on electro-cardiogram (ECG), was present in half of the patients. Twelve subjects had a patent dialysis fistula that remained functional during the study. All patients were initially studied at the time of discharge, 18 ± 3 days after surgery. The tests were repeated at 12 ± 0.7 and 40 ± 1.2 months after the operation. Before the ultrasonic evaluations, blood was drawn in the fasting state for the determination of haematocrit, and of serum glucose, creatinine and lipids. Body weight and height were determined and the body mass index (kg/height^2) was calculated. Blood pressure was determined using the right or left arm (depending on the presence of a dialysis fistula) with a sphygmomanometer using an automated oscillometric method (Dinamap 1486, Critikon, Inc., Tampa, FL) and cuffs adapted to arm circumference. Mean blood pressure was calculated by dividing pulse pressure by diastolic blood pressure. The Ethics Committee of the Heart Institute approved the protocol and all individuals gave their informed consent to participate in the study.

Follow-up

Patients were followed at the outpatient clinic of the renal transplant unit from the day of discharge until 18–48 months after the final ultrasonic evaluation. All cardiovascular and non-cardiovascular events were recorded.

Carotid artery image acquisition

The technique employed for the carotid image acquisition was described in detail elsewhere [6,7] and will only be summarized here. The tests were conducted in the supine position, in a quiet environment, after a 20 min rest. Blood pressure was determined during image acquisition as described above. Imaging of the cephalic portion of the common carotid artery, 1 cm below the bifurcation, was performed with a real-time high resolution B-mode ultrasound system (Apogee 800 Plus, Advanced Technological Laboratories Inc., Bothel, WA) equipped with a 7.5 transducer, enabling measurements of the arterial diameter and wall thickness. The images and the simultaneously obtained electrocardiographic signal were recorded on a super VHS videotape recorder. Selected images corresponding to the systolic expansion and diastolic relaxation were digitized with a video-frame grabber (Willow Publishers VGA, Willow Peripherals Inc., Bronx, NY) and stored on a computer. Carotid artery diameter and thickness were determined with the aid of a dedicated image workstation and expressed as millimetres using a calibration factor derived from the real-time ultrasound image. At least three measurements of carotid artery diameter and wall thickness were obtained from each patient. The inter- and intra-observer variability coefficient for both indexes was $<2\%$. Carotid distensibility (CD) (10^{-6} N^{-1} m^2) was calculated using the following formula:

$$CD = \frac{2\Delta d/d_d}{sbp - dbp}$$

where Δd = the difference between the carotid artery diameter in diastole and systole, d_d = the carotid artery diameter in diastole, sbp = systolic blood pressure, and dbp = diastolic blood pressure. In our laboratory, normal values for intima-media thickness, maximum carotid diameter, wall : lumen ratio and carotid distensibility are 742 ± 23 μm, 6.48 ± 0.13 mm, 114 ± 3 and 26.8 ± 2.0 10^{-6} N^{-1} m^2, respectively, for age- and sex-matched individuals ($n = 62$; 30 males, 32 females; mean age 41 ± 6 years).

Echocardiographic measurements

All subjects underwent uni- and bi-dimensional echocardiography according to the recommendations of the American

Society of Cardiology using an Apogee 800 Plus apparatus equipped with 2 and 4 MHz transducers. End-diastolic ventricular diameter (LVDD), end-systolic ventricular diameter (LVSD), left ventricular posterior wall thickness (LVPW) and interventricular septum (IVS) were measured during five consecutive heart cycles at the peak of the R-wave in the ECG. The tracings were read by two observers unaware of the study hypothesis. In our service, the intra- and inter-observer coefficient of variation is $<5\%$. The following formulas were used to calculate the left ventricular mass (LVM), left ventricular mass index (LVMI), left ventricular relative wall thickness (RWT) and fractional shortening (FS%):

$$\text{LVM (g)} = 1.04 \times [(\text{IVS} + \text{LVDD} + \text{LVPW})^3 - \text{LVD}^3] - 14 \text{ g}$$

$$\text{LVMI (g/m}^2\text{)} = \text{LVM/body surface area}$$

$$\text{RWT (cm)} = 2 \times \text{LVPW/LVDD}$$

$$\text{FS\%} = [(\text{LVDD} - \text{LVSD})/\text{LVDD}] \times 100$$

Upper normal limits for the main echocardiographic variables were defined according to Ganau *et al.* [8] and Hammond *et al.* [9]: LVMI, 134 and 110 g/m^2 for men and women, respectively; and RWT, 0.44 for both sexes. The lower normal limit for the left ventricular FS% was 30%.

Pulsed wave Doppler recordings of the mitral valve flow velocities were obtained from the apical four-chamber view under bi-dimensional guidance. The ratio between peak early (E) and atrial (A) left ventricular filling velocities was used for the assessment of left ventricular compliance. An E : A ratio <1.5 defined altered left ventricular diastolic function [10,11].

Statistics

Values are expressed as means $\pm$ standard error of the mean. The student's t and χ^2 tests were applied to the data when appropriate. Statistical comparisons between the values recorded at the three ultrasonographic evaluations were performed using two-way analysis of variance (ANOVA) for repeated measures. Pearson's correlation was used to test univariate and multivariate associations between study variables. Multiple stepwise regression analysis was used to assess the relevant factors influencing the rates of change of the carotid and left ventricle. All tests were two-tailed. A P value of <0.05 was considered significant.

Results

On the occasion of the first evaluation, the intima-media thickness and the internal carotid diameter were within high–normal range and carotid distensibility was reduced. This was associated with concentric ventricular hypertrophy and compromised ventricular compliance. Left ventricular systolic function and systolic and diastolic blood pressures were within normal limits. Carotid plaques were observed in one patient. Mean serum creatinine and total cholesterol were slightly increased and haematocrit was reduced (Tables 1 and 2, and Figure 1).

At the second evaluation (12 months), no significant alterations were observed on the carotid variables. However, when patients were again investigated after 40 months, the intima-media thickness was reduced in 14% (788 ± 24 *vs* 676 ± 32 μm, $P<0.01$) and the wall:lumen ratio of the carotid artery in 13% (118 ± 3 *vs* 103 ± 3 μm, $P<0.01$) of cases compared with baseline (Figure 1). The carotid artery distensibility, however, did not change, continuing to be lower than normal (Table 2). Systolic, diastolic, mean and pulse blood pressures also did not change (Table 1). New carotid plaques were not observed.

Table 1. Blood pressure, and epidemiological and laboratory characteristics of the patients

Variables	Exam 1	Exam 2	Exam 3
Systolic blood pressure (mmHg)	138 ± 3	140 ± 3	136 ± 3
Diastolic blood pressure (mmHg)	85 ± 3	82 ± 3	81 ± 3
Mean blood pressure (mmHg)	103 ± 3	101 ± 3	100 ± 3
Pulse pressure (mmHg)	53 ± 2	58 ± 2	55 ± 3
Body mass index (kg/m^2)	23 ± 0.8	25 ± 0.8[a]	26 ± 0.8[b]
Serum creatinine (μmol/l)	132.6 ± 7.9	131.7 ± 6.2	134.4 ± 7.9
Haematocrit (%)	34 ± 0.8	41 ± 1.7[a]	42 ± 1.5[b]
Serum total-cholesterol (mmol/l)	6.20 ± 0.31	6.17 ± 0.39	5.59 ± 0.25
Serum triglycerides (mmol/l)	1.90 ± 0.18	2.26 ± 0.25	2.05 ± 0.15

$P<0.01$; a = Exam 1 × Exam 2; b = Exam 1 × Exam 3.

Table 2. Carotid distensibility, maximum carotid diameter and ventricular systolic and diastolic functions of the patients

Variables	Exam 1	Exam 2	Exam 3	P
Carotid distensibility (10^{-6} N^{-1} m^2)	19.53 ± 2.1	20.55 ± 2.1	22.02 ± 2.4	NS
Maximum carotid diameter (mm)	6.78 ± 0.17	6.90 ± 0.16	6.56 ± 0.20	NS
LV fractional shortening (%)	32.7 ± 0.3	33.1 ± 0.3	33 ± 0.2	NS
E/A	1.22 ± 0.09	1.30 ± 0.09	1.26 ± 0.10	NS

LV, left ventricle; E/A, peak early to atrial filling velocities ratio.

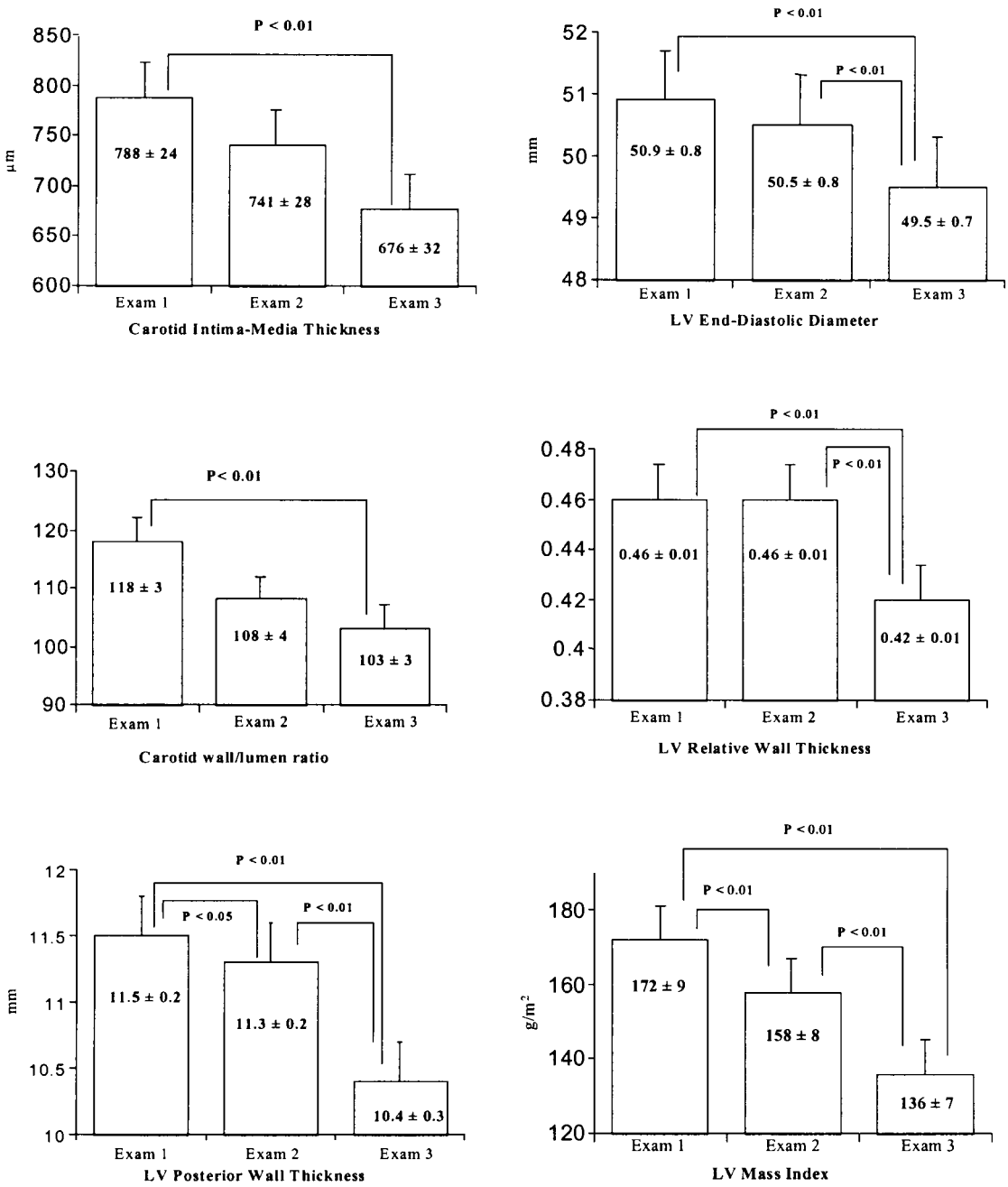

Fig. 1. Statistical comparison of relevant morphological carotid and ventricular variables observed during the three periods of observation.

Echocardiograms (Figure 1) showed a significant reduction in LVMI from 172 ± 9 to 158 ± 8 g/m^2 ($P < 0.001$) at 12 months and to 136 ± 7 g/m^2 ($P < 0.001$) at 40 months. Left posterior wall thickness was also reduced from 11.5 ± 0.2 to 11.3 mm at 12 months ($P < 0.05$) and to 10.4 ± 0.3 mm ($P < 0.01$) at 40 months. Significant reduction of LV end-diastolic diameter was observed in the last period of observation. There was a reversal of concentric hypertrophy, since the RWT fell from 0.46 ± 0.014 to 0.42 ± 0.01 ($P < 0.01$). The magnitude of the reductions of the LV mass at the second and third evaluations was 9 and 21%, respectively. In spite of that, the mean LVMI remained above normal limits. Fifteen individuals out of 20 (75%) with LV hypertrophy at the first evaluation still had increased LV mass at the end of the observation period. At 40 months, only seven out of 22 patients had normal LVMI. On the other hand, mean intima-media thickness was normal at the end of the study, and 18 out of 22 subjects did not present carotid hypertrophy at examination 3. Using a linear regression model, it was possible to calculate the time required to achieve a normal LVMI, assuming that the relationship to all other variables

were unchanged. The resulting equation was: LV mass index at exam 3 = 126.04 + 0.4 × (LVMI at exam 1)– 1.5 × Δt (months). For a patient with an initial LVMI of 180 g/m^2 (approximately the mean LVMI at baseline in this study), it would take ~50 months to achieve a LVMI of 125 g/m^2. Moreover, the diastolic function, as examined by the E:A ratio, remained reduced. Left ventricular fractional shortening remained stable and normal at 12 and 40 months (Table 2). Haematocrit and body mass index increased significantly with time, whereas serum creatinine and lipids did not change.

Tables 3 and 4 show the multivariate analysis of the factors associated with absolute changes of intima-media thickness of the carotid artery and LVMI. It was observed that the rate of change of reduction of the intima-media thickness of the carotid artery was negatively correlated with age and male sex, and was positively correlated with white race and with the parallel reduction of maximum carotid diameter. Reduction of LVMI over time was negatively correlated with duration of dialysis treatment and with the parallel increase observed in body mass index and haematocrit, and was positively correlated with the simultaneous reduction of diastolic blood pressure. Overall, the model explained 67% of the total observed variation in LVMI. Systolic, mean and pulse pressures, and serum creatinine, total-cholesterol and triglycerides and type of kidney donor, antihypertensive medication, duration of hypertension, presence of dialysis fistula, left ventricular hypertrophy on ECG and smoking status did not influence the carotid or ventricular variables. Changes in carotid intima-media thickness and changes in left ventricle mass were not correlated.

At the end of follow-up, all patients were alive with functioning grafts and no major cardiovascular events were observed.

Table 3. Correlation between rate of change of the intima-media thickness and of other variables (stepwise multiple regression analysis)

Parameters	β	T value	P
Age (years)	−0.001	−3.98	0.001
Sex (male)	−0.019	−3.078	0.007
Race (white)	0.019	2.64	0.02
Δ Maximum carotid diameter (mm)	0.12	30.12	0.0001

β, standard regression coefficient.

Table 4. Correlation between rate of change of the left ventricle mass index and of other variables (stepwise multiple regression analysis)

Parameters	β	T value	P
Δ Body mass index (kg/m^2)	−8.161	−3.28	0.004
Time on dialysis (months)	−0.535	−3.46	0.003
Δ Diastolic blood pressure (mmHg)	1.246	3.55	0.002
Δ Haematocrit (%)	−2.99	−3.84	0.001

β, standard regression coefficient.

Discussion

The main finding of the present investigation was that cardiovascular hypertrophy of end-stage renal failure patients may improve beyond the second post-transplant year. However, this process progressed at slow pace, since left ventricular hypertrophy, compromised LV compliance and reduced common carotid artery distensibility observed a few days after operation persisted for > 3 years after the transplant. Although the intima-media thickness and the LV mass, posterior wall thickness and end-diastolic dimension were significantly reduced, the changes were not sufficient to normalize the LV mass in the majority of patients. This happened despite control of blood pressure, correction of anaemia and stable and adequate renal function in patients with mild-to-moderate degrees of baseline ventricular hypertrophy. Therefore, successful renal transplant in low risk renal failure patients was not sufficient to completely normalize the cardiovascular alterations of chronic uraemia after a prolonged period of observation.

Few studies have investigated the long-term consequences of renal transplant on carotid morphology and function. This is an important aspect, since increased large vessel stiffness is a predictor of mortality in end-stage renal failure patients [12] and persistence of such alteration may conceivably influence their post-transplant course. Our results suggest that carotid hypertrophy may be more promptly and completely reversed compared with LV hypertrophy, but this may be a reflection of the modest degree of baseline intima-media hypertrophy of our cases. On the other hand, several investigators have analysed the impact of renal transplantation on LV hypertrophy in end-stage renal failure patients. The majority of these studies, however, covered relatively short periods of time. In general, they showed a regression of LV mass close to 10% during the first post-transplant year [5,13,14], a figure similar to that recorded in the present work. Recently, Rigatto *et al.* [15] reported their findings in a large cohort of transplanted patients followed up to 4 years. They observed a significant 10% reduction in LV mass that reached a nadir at 2 years but, contrary to our results, remained unchanged during the third and fourth post-transplant years. The more intense and persistent reduction of LV mass in our study is probably related to the fact that our patients showed no evidence of overt cardiac disease, had a good blood pressure control and only one was diabetic. As far as we know, ours is the first work to show that improvement in cardiovascular hypertrophy still seems possible beyond the second post-transplant year.

The reduction of approximately 10% in 12 months and 20% in 40 months in LV mass in the present study should also be compared with that reported in chronic renal failure patients not submitted to renal transplantation. Haemodialysis alone is not usually associated with regression of ventricular hypertrophy [5,16,17]. On the other hand, significant reduction of LV mass (10–20%), without achieving normalization, has been shown to be induced by correction of anaemia by erythropoietin treatment in predialysis [18] and haemodialysis patients [19,20]. However, there is no data concerning observations extending for more than 1 year in this set. As expected, the reduction of ventricular mass observed in erythropoietin-treated patients was mainly due to reduction of ventricular volume, probably related to control of high cardiac output state. Instead, in our patients, decreased posterior wall thickness was more pronounced, as reflected by the reduction of relative wall thickness, and this may be better explained by the control of blood pressure during the follow-up.

The reasons for the slow pace of correction of cardiovascular abnormalities in renal transplant patients are not readily apparent. Some evidence, however, may be provided by considering the factors influencing the changes in ventricular mass and intima-media thickness. We found that longer duration of dialysis treatment, weight gain, increase of haematocrit and failure to reduce diastolic blood pressure concurred to hamper the correction of ventricular hypertrophy in our patients. Blood pressure and body weight are known to correlate positively with LV mass in normal and hypertensive individuals [11]. The inverse correlation between the reduction of ventricular mass and increase of haematocrit merits a more expanded discussion. Anaemia is an important factor leading to eccentric LV hypertrophy in haemodialysis patients [21,22]. However, in individuals with haematocrit within normal limits, higher haematocrit correlates positively with LV mass and with the wall and interventricular septum width caused by higher whole blood viscosity [23]. The lack of correlation between changes of intima-media thickness and LVMI is intriguing and may be related to the modest degree of baseline carotid hypertrophy in the majority of our patients. Also, the fact that the rates of change of carotid and ventricular hypertrophy were not influenced by the same factors suggests that these alterations may develop independently. Finally, the duration of dialysis treatment negatively influenced the reduction of ventricular mass. It is tempting to speculate that this was a consequence of a diffuse interstitial fibrosis, as documented by Mall *et al*. in both animals [24] and humans [25], with renal failure, which tends to increase with the duration of uraemia, is independent of blood pressure and does not regress after transplant. Such alteration could also explain the enduring compromised ventricular and carotid distensibility observed in our study despite the improvement in ventricular and carotid hypertrophy. Capron and Grateau also advanced the possible existence of a specific vascular disease associated with dialysis in recent review [26].

Some limitations of the present study should be discussed, the most important being the small size of our sample. This, however, is in part mitigated by the homogeneity of the study group and by the fact that all subjects completed the investigation. The latter aspect increases considerably the precision and significance of the estimates of the echocardiographic changes. Also, a control group consisting of haemodialysis patients should be desirable, but this would be beyond the purpose of the study and, in any case, the subject has already been explored by other authors [5,16–20]. Finally, we have studied a selected transplant population and, therefore, our conclusions can not be generalized. On the other hand, the inclusion of only patients with the most favourable characteristics and in whom blood pressure was well controlled, demonstrated that even under the most favourable circumstances, total regression of cardiovascular abnormalities is unlikely to occur after renal transplantation.

We conclude that successful renal transplant in low risk patients may not completely normalize the cardiovascular alterations of chronic uraemia, although some improvement may still occur 3 or more years postoperation. Prolonged dialysis duration, weight gain and high blood pressure may adversely affect the rate of change of LV hypertrophy of renal transplant patients.

Acknowledgements. This investigation was supported by the E.J. Zerbini Foundation, São Paulo, Brazil. The authors are indebted to Mrs Creusa Dal Bo for statistical analysis and to Mrs Elettra Greene for editorial assistance.

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Received for publication: 13.3.01
Accepted in revised form: 27.11.01