Nephrol Dial Transplant (1997) 12: 1441–1447

Nephrology
Dialysis
Transplantation

Original Article

Blood pressure independent effects of nitrendipine on cardiac structure in patients after renal transplantation

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Abstract Left ventricular hypertrophy is well established as a blood pressure independent cardiovascular risk factor in patients on renal replacement therapy. The effects of antihypertensive treatment on myocardial structure and function in renal transplant recipients have been so far only rarely investigated. In a double-blind, placebo-controlled study patients were randomized to the calcium channel blocker nitrendipine or placebo if the transplanted kidney had developed a stable phase. Normotensive patients received nitrendipine 2×5 mg daily or placebo, hypertensive patients received 2×10 mg up to 2×20 mg nitrendipine daily or placebo. To achieve adequate blood pressure control, all patients with still elevated blood pressure on study medication received antihypertensive drugs other than calcium channels blockers. Ambulatory blood pressure recording and 2D-guided M-mode echocardiography were performed at baseline and upon completion of the study. In addition, laboratory workup (including serum creatinine and lipids) was done, and serum aldosterone, plasma renin activity, plasma angiotensin II and blood glucose levels were measured in all patients at baseline and after at least 12 months of therapy. Ambulatory blood pressure was almost identical between both groups at study baseline and follow-up. In renal transplant patients on nitrendipine, posterior wall thickness (-0.10 ± 1.77 mm) and septal wall thickness (-0.83 ± 2.23 mm) did not change significantly from baseline. In contrast, posterior wall thickness (0.71 ± 0.92 mm, $P < 0.01$) and septal wall thickness (0.97 ± 2.20 mm, $P < 0.05$) increased in patients on placebo, which differed from the observed changes on nitrendipine (ANOVA: $P = 0.093$ and $P = 0.048$, respectively). Relative wall thickness, a parameter for concentric left ventricular hypertrophy, became numerically smaller on nitrendipine therapy from 0.46 ± 0.07 to 0.44 ± 0.09 (-0.02 ± 0.09, NS) but increased from 0.42 ± 0.08 to 0.48 ± 0.08 in the placebo arm ($+0.04 \pm 0.08$, $P < 0.02$), which was also significant between the two groups (ANOVA: $P = 0.036$). Endocrine parameters, lipids and blood glucose were not different between the two groups.

We conclude from these data that the calcium channel blocker nitrendipine exerted beneficial effects on cardiac structure in patients after renal transplantation independent of blood pressure.

Key words: left ventricular hypertrophy; renal transplantation; calcium channel blocker; blood pressure

Introduction

Left ventricular hypertrophy (LVH) has been identified as a poor prognostic indicator in patients with essential hypertension as well as in patients with secondary hypertension [1,2,3]. Since LVH increases the risk for cardiac complications in hypertensive patients, studies have been undertaken to investigate whether LVH regression during treatment with antihypertensive drugs reduces the risk of cardiac complications in patients with LVH. Indeed, regression of LVH below 200 g was shown to improve overall prognosis in essential hypertensives [4,5]. Similarly, a preliminary report of an ongoing prospective study [6] revealed that regression of LVH improved cardiovascular prognosis.

Calcium channel blockers have been shown to reverse LVH in patients with essential hypertension, although they have been considered to be somewhat less effective than ACE-inhibitors [6,7]. Recently, a randomized study comparing effects of nitrendipine and captopril on left ventricular mass and circadian blood pressure in patients with essential hypertensives, demonstrated a comparable degree of circadian blood pressure reduction and regression of LVH for both drugs [8]. In a recent meta-analysis that included only studies with a double-blind randomized controlled study design, we could not demonstrate a significant difference in reducing left ventricular mass between ACE-inhibitors and calcium channel blockers in primary hypertension [7].

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So far, most studies have dealt with reversal of LVH in essential hypertension. Only a few studies, but not double-blind randomized trials, have focussed on reduction in the left ventricular mass in secondary hypertension or after kidney transplantation. The present study in renal transplant recipients investigated whether the calcium channel blocker, nitrendipine had an influence on left ventricular structure and function. The study design was double-blind and placebo-controlled. Antihypertensive therapy with calcium channel blockers was tested, since calcium channel blockers have been found to reduce acute renal failure of transplanted kidneys [9].

Methods

Study populations

All participants had been previously recruited for the participation in a multicentre randomized double-blind, placebo-controlled study of the German Renal Transplantation Study Group [9]. In addition to this protocol, clinical cardiovascular risk factor evaluation was done in our centre (University Erlangen-Nürnberg). Adult patients receiving a renal transplant were enrolled in the analysis if they fulfilled the following criteria: stable renal function after kidney transplantation (on the average after 6 months), lack of stenosis of the transplant artery (as assessed by duplex sonography or angiograms). Exclusion criteria were history of myocardial infarction in the last 18 months, cerebrovascular stroke, diabetes mellitus, or other serious disorders (including infections). Normotensive patients were randomized to receive nitrendipine 2×5 mg daily or placebo for 2 years, hypertensive patients to receive 2×10 mg to 2×20 mg nitrendipine daily or placebo. If blood pressure was above the diastolic target level of 90 mmHg, antihypertensive drugs other than calcium channel blockers were added. Adequate adjustments were made throughout the whole study period each month.

At study entry, the diuretic, furosemide, was received by four patients in the placebo group and four patients in the nitrendipine group. Also, in both groups at the beginning of the study, betablockade had already been given to five patients in the placebo group and in the nitrendipine group. Due to the study goal to control arterial hypertension, antihypertensive therapy was intensified in both groups. At follow-up, 12 patients received the diuretic furosemide in the placebo and 15 subjects in the nitrendipine group, respectively. Also, betablockers were administered in the placebo group in nine subjects and in the nitrendipine group in 10 subjects. According to the study protocol, none of the patients received calcium channel blockers throughout the study period. Most important, none of the patients was on an ACE-inhibitor, either before or at study entry or throughout the follow-up of 1 year. The centrally sympatholytic agent clonidin was given in the placebo group in two patients at study entry and in another one throughout the follow-up period. In the nitrendipine group clonidin had been given in three patients at study entry, but could be discontinued in two patients after adding the study medication (later on shown to be nitrendipine).

Blood pressure was measured according to the WHO guidelines four times on two occasions by trained qualified personnel. Blood pressure below 140 mmHg systolic and 90 mmHg diastolic was considered normotensive. If either systolic or diastolic pressure exceeded 140 or 90 mmHg, respectively, patients were considered hypertensive. All patients received triple drug immunosuppressive therapy (cyclosporin A, azathioprine and methylprednison) and antihypertensive medication as indicated based on clinical BP measurements. The study was approved by the Institutional Committee on Human Subjects and informed consent was obtained. All patients randomized into the study underwent extensive laboratory work-up, 24-h ambulatory blood pressure monitoring, and 2D-guided M-mode echocardiography as described below at baseline and follow-up after 18 months.

Laboratory workup

All renal transplant recipients underwent regular laboratory work-up at least every 4 weeks, which included urine analyses, serum creatinine, serum urea, serum uric acid, serum electrolytes and complete blood cell count. In addition, blood glucose level as well as serum lipids (including triglycerides and cholesterol) were determined regularly. Endocrine parameters including plasma renin activity were analysed in all patients by radioimmunassay [10,11]. Unfortunately, some samples for plasma angiotensin II and serum aldosterone at follow-up became defrozen by accident ($n = 5$).

Ambulatory blood pressure monitoring

Ambulatory blood pressure was recorded over 24-h non-invasively (Spacelab 90207) on a routine working-day (for details see [12,13]). In brief, mean arterial pressure as used in this study is the point of maximum cuff oscillations as determined by the monitor. Blood pressure readings taken by the monitor were compared with readings obtained simultaneously with a binaural stethoscope and a standard mercury sphygmomanometer connected to the monitor cuff with a Y-piece. The cuff was repositioned on the contralateral extremity unless differences were less than 10 mmHg systolic and 5 mmHg diastolic. This requirement was achieved in all the study patients. Recordings were made every 15 min from 6:01 a.m. to 10:00 p.m. and every 30 min from 10:01 p.m. to 6:00 a.m. When subjects returned to be monitored they were asked at what time they fell asleep and when they woke up [12]. In addition, tension time index was calculated as the most valid non-invasive parameter for afterload imposed on the left ventricle that can be measured by ambulatory blood pressure monitoring [13]. A built-in error-correction was used (excluding 1% of readings successfully completed) and profiles were added manually (excluding an additional 0.5% of readings successfully completed) to exclude erroneous readings.

Echocardiography

2D-guided M-mode echocardiograms were performed at baseline and follow-up after 12 months of treatment with nitrendipine versus placebo [14]. All echocardiograms were recorded on the third or fourth left interspace with the patient in a half-sided position. All traced echocardiograms were read by two physicians, who were unaware of the 24-h blood pressure data. Septal and posterior wall thicknesses and end-diastolic diameter were measured according to the standard measurement convention of the American Society of Echocardiography [15]. Relative wall thickness, a parameter for concentric LVH, was determined by dividing posterior wall thickness by half the end-diastolic diameter

[16]. Left ventricular mass was calculated according to the formula of Devereux and Reicheck that corrects for a systematic overestimation of the calculated left ventricular mass, based on American Society of Echocardiography measurements [15]. In addition, Doppler sonography was used to evaluate diastolic function [14]. The ratio of maximal velocity of the active to passive filling of the left ventricle (A/E ratio) and contribution of the atrial filling to the total filling (given in %) were used as parameters.

Statistics

All statistical analyses were made on an IBM 486 computer by using SPSS-PC programs [17]. Chi-square analysis, paired and unpaired *T*-tests as well as analysis of covariance were used where indicated (two-tailed *P*-values were given). All data are expressed as mean $\pm$ standard deviation (SD).

Results

The renal transplant recipients receiving nitrendipine did not differ in age, sex distribution, weight, height, body mass index, and body surface area from patients receiving placebo (Table 1). No differences were found with regard to the immunological characteristics of the received renal transplant (Table 2). Cold and warm ischaemia times of the transplant were also not different between both groups. The prevalence of still functioning dialysis shunts was similar between both groups (13 in the placebo group and 15 in the nitrendipine group). Table 3 shows the course of kidney function expressed by serum creatinine, serum urea and serum uric acid. Overall, kidney function appeared to be comparable between both treatment groups at baseline and after treatment with either placebo or nitrendipine. Yet the number of patients with a rise in serum creatinine $\geqslant 0.25$ mg/dl after 12 months of treatment tended to be higher in the placebo group than in the nitrendipine group ($P<0.1$, Table 3), a finding that was significant in the multicentre study analysis [9].

The 24-h blood pressure measurements disclosed similar systolic and diastolic pressure averages throughout all study points for both groups (Table 4). Absolute blood pressure values, the change in systolic and diastolic blood pressure during follow-up, and the fall in blood pressure during the night were similar between the two groups. Thus, hypertensive blood pressure values were equally controlled in the nitrendipine and placebo group by additional drug therapy. The use of diuretics, betablockers and other antihypertensive agents was similar in the two groups (see Methods). Of note, none of the patients received an ACE-inhibitor or calcium channel blocker (other than the study medication) before or during the follow-up.

Table 1. Clinical characteristics in renal transplant recipients of both treatment groups

	Placebo ($n=22$)	Nitrendipine ($n=24$)	*P*-value
Age (years)	43.5 ± 12.4	48.2 ± 10.2	NS
Sex (m:f)	15:7	15:9	NS
Weight (kg)	71.9 ± 9.98	72.1 ± 12.6	NS
Height (m)	1.71 ± 0.10	1.68 ± 0.08	NS
BMI (kg/m^2)	24.6 ± 2.77	25.4 ± 3.82	NS
BSA (m^2)	2.84 ± 0.2	1.82 ± 0.2	NS
Normotensives	11	14	NS
Hypertensives	11	10	NS
Number of antihypertensive agents	2.64 ± 2.36	2.79 ± 2.23	NS

m, male; f, female; BMI, body mass index; BSA, body surface area.

At baseline, at the average of 6 months after renal transplantation, patients who were randomized into the placebo group had a smaller septal ($P<0.01$) and relative wall thickness ($P<0.05$) than patients randomized to receive nitrendipine treatment (Table 5). Also, patients randomized for the nitrendipine group had a somewhat greater posterior wall thickness and left ventricular mass than those patients allocated for placebo treatment. This difference in left ventricular structure at baseline emerged despite randomization. We therefore analysed the changes in each group between the baseline and follow-up examination.

The most intriguing finding of the analysis of cardiac structural changes throughout the follow-up period (Table 5) was that at equal blood pressure, control patients on nitrendipine had a similar septal (-0.83 ± 2.23, NS) and posterior (-0.10 ± 0.77, NS) wall thickness during 12 months of therapy. In contrast, posterior wall thickness ($+0.71\pm0.92$, $P<0.01$) and septal wall thickness ($+0.97\pm2.20$, $P<0.05$) increased in the placebo group. This disparate pattern of wall thicknesses between the groups was significant for septal wall thickness (ANOVA: $P=0.048$) and tended to be significant for posterior wall thickness (ANOVA: $P=0.093$). Diastolic diameter, in contrast, tended to increase in patients on nitrendipine (2.17 ± 4.33 mm, $P=0.10$) and to decrease in the placebo group (-0.83 ± 2.23 mm, $P=0.10$), which was significant between the two groups (ANOVA: $P=0.015$). Relative wall thickness remained similar in patients on nitrendipine (-0.02 ± 0.09, NS) whereas it increased significantly in the patients randomized to placebo (0.04 ± 0.06, $P<0.02$). This disparate pattern indicates that patients on placebo were more prone to develop concentric LVH, in contrast to the calcium channel blocker nitrendipine that appeared to prevent an increase in relative wall thicknesses (ANOVA: $P=0.036$) (Fig. 1).

The results for the 'normotensive' and 'hypertensive' group categorized arbitrarily according to casual blood pressure readings indicate that the beneficial effect was in particular evident for the hypertensive patients (ANOVA, $P=0.018$, see Table 6).

No clear-cut result over time as well as throughout the study period was obtained for the parameters of diastolic function (Table 5). Table 7 depicts the results of the blood analyses at baseline and follow-up. Both treatment groups were comparable with regard to blood glucose, serum triglycerides, and serum cholesterine throughout the entire study period. Also, no

Table 2. Renal characteristics in patients with renal transplants of both treatment groups

Treatment		Placebo ($n=22$)	Nitrendipine ($n=24$)	*P*-value
HLA-Mismatch A (0:1:2)		3:12:7	1:15:8	NS
HLA-Mismatch B (0:1:2)		4:15:3	7:12:5	NS
HLA-Mismatch Dr. (0:1:2)		13:8:1	17:6:1	NS
Cyclosporin-dosage (mg/day)		213±29	218±45	NS
Cyclosporin A-level	mono (ng/ml)	135±61.6	134±49.5	NS
	poly (ng/ml)	271±91.0	319±106	NS
Glucocorticoid dose (mg/day) (methyl-prednisolon)		4.82±1.59	5.49±2.52	NS
CMV-Mismatch	donor	6(−)/15(+)	8(−)/15(+)	NS
	recipient	12(−)/10(+)	11(−)/13(+)	NS
Age of the donor (years)		33.2±17.2	33.7±15.4	NS
Δ Age donor-recipient (years)		−10.2±16.8	−14.5±19.2	NS
Cold ischaemic time (min)		1415±284	1520±399	NS
Warm ischaemic time (min)		37±9	37±7	NS

Δ, difference.

Table 3. Results of kidney function at baseline and after therapy in both patient groups

	Placebo ($n=22$)	Nitrendipine ($n=24$)	*P*-value
Serum creatinine (mg/dl) 6 months after RT	1.44±0.47	1.40±0.30	NS
Serum creatinine (mg/dl) after 18 months of treatment	1.47±0.38	1.43±0.51	NS
Change in serum creatinine (%)	3.94±20.2	5.99±36.5	NS
Serum urea (mg/dl) 6 months after RT	52.6±21.0	53.0±15.9	NS
Serum urea (mg/dl) after 18 months of therapy	53.5±17.2	56.0±22.5	NS
Change in serum urea (%)	7.78±34.0	15.6±50.4	NS
Serum uric acid (mg/dl) 6 months after RT	8.37±2.80	8.61±1.8	NS
Serum uric acid (mg/dl) after 18 months of therapy	8.94±2.12	8.93±2.49	NS
Change in serum uric acid (%)	6.60±21.8	4.41±21.6	NS
Number of patients Δ serum creatinine >0.25 mg/dl	13:6	17:2	=0.10

RT, renal transplantation.

Table 4. 24-Hour blood pressure values

	Placebo ($n=22$)	Nitrendipine ($n=24$)	*P*-value
24-Hour blood pressure at baseline			
Systolic (mmHg)	134±12.9	135±15.0	NS
Diastolic (mmHg)	84.7±10.2	84.8±7.45	NS
Heart rate (bpm)	74.9±10.7	71.7±9.79	NS
Tension time index (s*mmHg)[a]	36.1±3.99	36.8±4.29	NS
24-Hour blood pressure at follow-up			
Systolic (mmHg)	131±10.4	131±13.9	NS
Diastolic (mmHg)	83.0±5.35	84.7±7.72	NS
Heart rate (bpm)	71.3±10.4	69.1±8.45	NS
Tension time index (s*mmHg)[a]	35.9±3.62	36.6±4.59	NS
24-Hour blood pressure change between baseline and follow-up examination			
Δ Systolic (mmHg)	−1.63±9.85	1.93±9.56	NS
Δ Diastolic (mmHg)	−1.50±5.83	1.21±8.22	NS
Δ Heart rate (bpm)	−1.33±7.66	−2.91±8.49	NS
Δ Tension time index (s*mmHg)[a]	−0.34±2.79	0.84±2.90	NS

[a]For details see [13].

differences were found with regard to plasma renin activity, plasma angiotensin II or serum aldosterone levels.

Discussion

In the current study, additional treatment with the calcium channel blocker nitrendipine in renal transplant recipients, was able to prevent the development of left ventricular hypertrophy during the 12 months of follow-up. In contrast, patients without nitrendipine treatment, i.e. in the placebo arm of the study, showed an increase in posterior and septal wall thicknesses over time. This disparate pattern of left ventricular structure also became significant in the time course for relative wall thickness, which was the most valid parameter for concentric left ventricular hypertrophy [16]. Under consideration of the prognostic importance of left ventricular hypertrophy, with the worst prognosis for concentric hypertrophy [3,18] and the preliminary results of two prospective studies, a possible cardioprotective effect can be attributed to the calcium channel blocker nitrendipine in renal transplant recipients. This indicates that reversal of left ventricular hypertrophy appears to be a desirable therapeutic goal in order to reduce increased cardiovascular risk in patients with left ventricular hypertrophy [3,4].

Previous studies that have investigated the cardiac consequences of renal transplantation report a proportional regression of left ventricular hypertrophy within 1 month after kidney transplantation, in parallel to a decrease in left ventricular volumes and cardiac index, which reflects the rapid resolution of a pre-transplant

Table 5.
Echocardiographic findings in both groups of renal transplant recipients

	Baseline			Follow-up			Change during follow-up		
	Placebo	Nitrendipine	*t*-test	Placebo	Nitrendipine	*t*-test	Placebo	Nitrendipine	ANOVA
Posterior wall thickness (mm)	10.3 ± 1.52	11.2 ± 1.78	0.075	11.1 ± 1.32	11.1 ± 1.53	NS	0.71 ± 0.92	−0.10 ± 1.77	0.093
Septal wall thickness (mm)	11.5 ± 2.32	13.7 ± 2.25	0.003	12.4 ± 1.94	12.7 ± 2.37	NS	0.97 ± 2.20	−0.83 ± 2.23	0.048
Diastolic diameter (mm)	49.5 ± 6.18	47.6 ± 5.39	NS	48.3 ± 5.63	49.1 ± 6.32	NS	−1.18 ± 3.25	2.17 ± 4.33	0.015
Relative wall thickness (–)	0.42 ± 0.08	0.48 ± 0.08	0.037	0.46 ± 0.07	0.44 ± 0.09	NS	0.04 ± 0.06	−0.02 ± 0.09	0.036
Left ventricular mass (g/cm^2)	139 ± 36.7	163 ± 42.8	0.060	149 ± 40.2	149 ± 40.2	NS	9.81 ± 28.9	4.95 ± 33.5	NS
Fractional fibre shortening (%)	38.2 ± 14.9	35.3 ± 6.28	NS	37.6 ± 7.18	37.6 ± 7.18	NS	2.52 ± 6.65	1.49 ± 6.24	NS
Diastolic function (A/E-Ratio)	1.07 ± 0.27	1.14 ± 0.28	NS	1.08 ± 0.28	1.04 ± 0.28	NS	0.01 ± 0.18	−0.10 ± 0.27	NS
Diastolic function: percentage of atrium contribution for the ventricle filling (%)	37.4 ± 8.91	36.3 ± 7.56	NS	37.9 ± 8.97	32.2 ± 10.7	0.096	1.16 ± 9.84	−3.65 ± 8.72	0.151

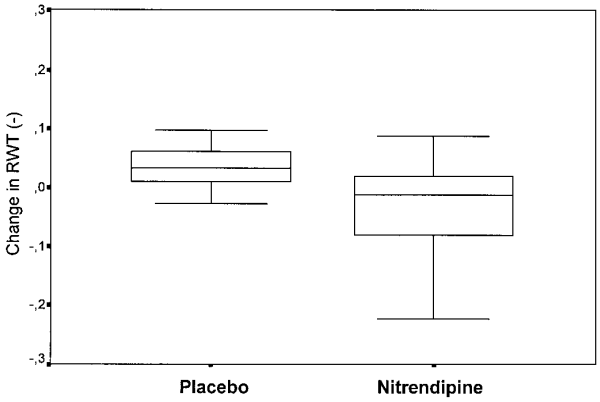

Fig. 1. Changes in relative wall thickness as a parameter for concentric left ventricular hypertrophy throughout the follow-up (mean, 95% Cl [boxes] and ± 1SD are given).

Table 6. Changes of relative wall thickness (RWT) according to the status 'normotensive' and 'hypertensive'

	Placebo	Nitrendipine	Changes in RWT ANOVA
Normotensives[a]			
before therapy	0.41 ± 0.09	0.43 ± 0.07	NS
after therapy	0.45 ± 0.07*	0.44 ± 0.07	
Hypertensives[a]			
before therapy	0.44 ± 0.07	0.52 ± 0.08	$P = 0.018$
after therapy	0.48 ± 0.06**	0.46 ± 0.11$^+$	

$^+P < 0.10$; $*P < 0.05$; $**P < 0.01$ (two-tailed before versus after).
[a]Based on casual BP values, not on 24-h ambulatory BP.

Table 7. Endocrine analysis, serum lipid and blood glucose levels at base-line and after therapy

Treatment	Placebo	Nitrendipine	*P* value
Renin (ngAl/ml/h) at baseline	3.01 ± 6.21	1.16 ± 0.57	NS
Renin (ngAl/ml/h) at follow-up	5.29 ± 6.64	5.09 ± 6.29	NS
Angiotensin II (pg/ml) at baseline	19.5 ± 18.4	14.6 ± 20.8	NS
Aldosterone (pg/ml) at baseline	350 ± 489	284 ± 294	NS
Blood glucose (mg/dl) at baseline	89.9 ± 12.4	86.3 ± 10.6	NS
Blood glucose (mg/dl) at follow-up	88.3 ± 14.8	86.1 ± 9.15	NS
Triglycerides (mg/dl) at baseline	222 ± 123	235 ± 134	NS
Triglycerides (mg/dl) at follow-up	219 ± 110	221 ± 120	NS
Cholesterol (mg/dl) at baseline	290 ± 58	257 ± 79	NS
Cholesterol (mg/dl) at follow-up	279 ± 63	260 ± 70	NS

RT, renal transplantation.

high cardiac output state [19]. However, in the following months after transplantation we observed an increase in wall thicknesses in our placebo group, which was prevented by the administration of nitrendipine. This was found in normotensive and hypertensive subjects at least for relative wall thickness, the classic parameter for concentric left ventricular hypertrophy. A limitation of our study is the fact that despite randomization, patients in the nitrendipine group had a significantly greater septal and relative wall thickness at baseline than patients randomized to the placebo group. Other echocardiographic parameters, clinical characteristics of our patients, specific renal transplant and kidney function data were comparable between both groups at baseline. The strength of our study is the double-blind nature of our study design, a requirement so far fulfilled only by a minority of published trials examining left ventricular hypertrophy [7].

Noteworthy is that the therapy with nitrendipine and the effects on left ventricular structure were blood pressure independent as all patients with high blood pressure had received other drugs for blood pressure control. Although the mechanism in humans remains to be determined, intracellular accumulation of calcium exerts growth stimulating effects, which may directly stimulate myocardial growth [20,21]. It remains to be further examined whether the prevention of LVH after kidney transplantation is only related to calcium channel blockers or also to other drugs (for example ACE-inhibitors). Overall, we found at the beginning, as well as in the follow-up phase, a similar distribution of other antihypertensive agents. In particular, none of the patients were on ACE-inhibition known to reduce left ventricular hypertrophy most effectively [7] during the treatment phase.

Absolutely no differences were observed with regard to ambulatory blood pressure measurements, including the tension time index, which represents a more accurate non-invasive assessment of the haemodynamic load imposed on the left ventricle than blood pressure readings *per se* [13]. Also, it has been recently described that kidney transplantation leads to a normalization of circadian blood pressure profiles [22]. In this context it has been proposed that the marked decrease in blood pressure during sleep in renal transplant recipients may impose a lower haemodynamic load on the cardiovascular system and thereby lead to a reduction of cardiovascular morbidity and mortality, a finding well-known in essential hypertension [23,24]. In the current study, a similar fall of blood pressure was observed between the two groups at the follow-up examination.

Recently, a meta-analysis of randomized double-blind studies on reversal of left ventricular hypertrophy in essential hypertension demonstrated that calcium channel blockers decreased (duration-adjusted) left ventricular mass by 9% compared with a 7% decrease caused by diurectics, a 6% decrease caused by betablockers, and a 13% decrease caused by ACE-inhibitors [7]. No significant difference was found in a direct comparison between ACE-inhibitors and calcium channel blockers, whereas between calcium channel blockers and betablockers a trend that favoured the efficacy of calcium channel blockers was found. One double-blind randomized controlled clinical study in essential hypertension compared ACE-inhibitors with calcium channel blockers and found a nearly identical reduction of left ventricular hypertrophy in both parts of the treatment [25]. Overall, better results for regression of left ventricular hypertrophy have been reported with the use of non-dihydropyridine calcium channel blockers than dihydropyridine calcium channel blockers [26]. In this context, it has been speculated that dihydropyridine calcium channel blockers, which have a rapid onset and a short duration of action, tend to increase sympathetic activity, which may limit the regression of left ventricular hypertrophy when used for the treatment of hypertension. However, studies comparing the effect of shorter acting formulations with longer acting substances found a greater reduction of left ventricular mass under the longer acting compound in patients with uncomplicated essential hypertension [6]. In addition, calcium channel blockers lead to a decrease of left ventricular mass compared with placebo-treated patients with essential hypertension [27,28].

Hyperlipidaemia and diabetes mellitus were found to predict left ventricular hypertrophy independently of arterial hypertension, body mass index, age, sex and coronary heart disease in an epidemiological survey including 1.42 million Germans [29]. Various studies in patients with essential hypertension were able to demonstrate that calcium channel blockers have a neutral effect on the metabolic system and do not lead to significant rises in serum lipid or blood glucose concentrations [30]. Our own results underline these findings, and show no difference in blood glucose and lipid levels in renal transplant recipients receiving nitrendipine when compared with patients on placebo. Thus, these factors cannot be an explanation for our finding of a blood pressure independent impact on left ventricular hypertrophy with calcium channel blockers.

Experimental and clinical data have led to the assumption that the renin angiotensin aldosterone system might help to modulate the degree of left ventricular hypertrophy in essential hypertension [11,31,32]. In our study, however, determination of plasma renin activity, angiotensin II, and aldosterone before and after therapy showed no differences in hormone levels. Accordingly, our data do not support that there is a renin–angiotensin–aldosterone system dependent effect on left ventricular structure within our study groups.

In conclusion, our double-blind randomized placebo-controlled study in renal transplant recipients found that treatment with the calcium channel blocker, nitrendipine, can prevent the development of concentric left ventricular hypertrophy that was observed in the placebo control group. This observation favours, next to that of the previously described nephroprotective effect of nitrendipine, the use of long-acting calcium channel blockers as first-line antihypertensive agents after kidney transplantation.

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Received for publication: 3.7.96
Accepted in revised form: 17.3.97