Transpl Int (1995) 8: 286–292

ORIGINAL ARTICLE

Carl Warholm
Henryk Wilczek
Erna Pettersson

Hypertension two years after renal transplantation: causes and consequences

Received: 18 July 1994
Received after revision: 26 January 1995
Accepted: 27 January 1995

C. Warholm (✉)
Karolinska Institute,
Renal Unit
Department of Medicine,
Danderyd Hospital,
S-182 88 Danderyd,
Sweden
Fax: + 46 8 753 0716

C. Warholm · H. Wilczek
Department of Transplantation,
Huddinge Hospital,
S-141 86 Huddinge,
Sweden

E. Pettersson
Department of Nephrology,
Huddinge Hospital,
S-141 86 Huddinge,
Sweden

Abstract The incidence of hypertension 2 years after renal transplantation and the possible causes of hypertension were studied retrospectively. A group of 93 patients treated with cyclosporin (CyA), azathioprine (Aza), and/or prednisolone (Pred) were compared to a group of 31 patients treated with Aza and Pred. There were more patients with hypertension in the CyA group (73 %) than in the Aza group (58 %). Hypertension before transplantation predisposed to hypertension after transplantation. After transplantation, hypertension was most common among patients with polycystic kidney disease (46 %), chronic glomerulonephritis (67 %), and diabetes (71 %).The accumulated immunosuppressive medication (CyA/Pred) did not affect the occurrence of hypertension. Hypertensive patients had significantly poorer graft function than did normotensive patients (serum creatinine level 229 μmol/l vs 162 μmol/l, $P < 0.01$). The 10-year graft survival was markedly impaired in the group with hypertension (42 % vs 65 % for normotensives, $P < 0.05$). The 10-year patient survival was 59 % vs 79 % (P = NS). The study further confirms the frequent finding that hypertension has a negative effect on graft and patient survival rates.

Key words Hypertension, kidney transplantation · Kidney transplantation, hypertension

Introduction

Hypertension, a frequent problem in dialysis patients, often continues to be a problem after renal transplantation. Prevalence figures after transplantation vary from 25 % to 80 % [2, 4, 6, 8, 10, 14, 15]. The etiology, probably multifactorial, involves immunosuppressive medication, impaired renal graft function due to either acute or chronic rejection, recurrent/de novo renal disease [2, 10, 14], transplant artery stenosis, or the presence of native kidneys [8, 10]. Post-transplantation hypertension has also been associated with kidneys from cadaveric donors (CD) [2, 8, 10] and with overweight [2, 8, 10]. Hypertension is also associated with cardiovascular disease [1, 9], which is a major cause of death after renal transplantation [2, 12, 20, 25].

Cyclosporin (CyA) became the major immunosuppressive drug in the 1980s, usually in combination with steroids and sometimes also with azathioprine. The effect of corticosteroid medication in post-transplant hypertension is still under debate [14].

The purpose of the present study was to investigate the prevalence of hypertension 2 years after renal transplantation and to assess the possible causes and consequences of elevated blood pressure. Particular emphasis has been placed on the possible influence of the following factors: original renal disease, presence of previous hypertension, duration of dialysis treatment before transplantation, ages of the kidney graft recipient and of the donor, dosage of CyA and glucocorticoid medication, graft function, overweight at transplantation and 2 years later, and morphological findings in the trans-

Table 1 Demographic data

	High-dose CyA ($n = 25$)	Medium-dose CyA ($n = 34$)	Low-dose CyA ($n = 34$)	Aza ($n = 31$)
Period	1981–1983	1985–1987	1985–1987	1973–1982
Initial CyA dose (mg/kg BW)	15–17.5	12	8	0
Pred and/or Aza	Pred	Pred	Pred and Aza	Pred and Aza
Living donor (%)	20	32	21	45
Cadaveric donor (%)	80	68	79	55
Recipient age, mean ± SD	44 ± 15	42 ± 15	46 ± 13	39 ± 14
(range)	(19–64)	(17–66)	(22–70)	(14–64)
Recipient sex M/F	14/11	20/14	17/17	15/16
Donor age, mean ± SD	42 ± 13	44 ± 18	52 ± 13	44 ± 13
(range)	(20–68)	(14–72)	(10–72)	(18–66)
Donor sex M/F	18/7	17/15	21/13	16/15

plant. Furthermore, the cause of death of the donors and its possible impact on post-transplant hypertension was studied. Finally, we calculated the actuarial graft and patient survival in relation to the blood pressure.

Materials and methods

Patients

Ninety-three kidney graft recipients [23 living donor (LD) and 70 CD], transplanted between 1981 and 1987 and immunosuppressed with CyA, were investigated retrospectively. The patients had received initial doses of CyA according to three regimens [29] (Table 1), and these doses were then adjusted to obtain predetermined whole blood levels, as previously described [18, 27]. All patients had had a graft biopsy taken 2–2.5 years after transplantation. In addition to CyA, all patients received prednisolone (Pred) in an initial daily dose of 1.5–3 mg/kg body weight (BW), tapered to 10 mg within the first 6 months. Some patients also received azathioprine (Aza) in an initial daily dose of 1–2 mg/kg BW, reduced to 0.5–1 mg/kg BW within 6 weeks (Table 1).

To elucidate the possible effects of CyA treatment on blood pressure control, 31 patients (14 LD and 17 CD), transplanted between 1973 and 1982 and treated with Aza and Pred, were chosen as historical controls. The initial daily Aza dose for these patients was 2–3 mg/kg BW. The dose was then kept as high as possible with regard to the leukocyte count, but with an upper limit of 150 mg/day. Details of this treatment protocol have been reported elsewhere [22]. Transplant biopsies from the controls had been obtained 3–13 years after transplantation. Demographic data on these patients are given in Table 1.

Rejection episodes (as diagnosed by a significant rise in the serum creatinine level without other obvious cause and usually confirmed by transplant biopsy findings) were treated with methylprednisolone in a dose of 500 mg i.v. (1000 mg in the control group) on the 1st day, followed by 250 mg once daily for 3 days.

Data from the pretransplantation period were retrieved from old patient records. Bilateral nephrectomy had been performed (several years before transplantation) on one patient. Dialysis treatment and the presence of hypertension prior to transplantation, as evidenced by antihypertensive medication, were recorded. Pretransplantation data were not available for one patient. No patient had renal artery stenosis in the graft.

All patients were seen at the outpatient clinic twice weekly for the first 3 months after discharge and then at least every 6th week during the first 2 years post-transplantation.

Blood pressure

Blood pressure was recorded twice daily postoperatively until discharge and thereafter at each visit to the outpatient clinic. A standard cuff was used and blood pressure was recorded after the patient had been resting in the supine position for 10 min. Patients with repeated diastolic pressure (DBP) values above 90 mmHg were regarded as hypertensive in accordance with the WHO criteria [21, 26].

On the basis of repeated blood pressure measurements and the prescription of antihypertensive medication, the patients were classified in three groups: patients with no hypertension (no antihypertensive medication or furosemide alone; group 1), patients with well-controlled hypertension (DBP ≤ 90 mmHg with antihypertensive medication; group 2), and patients with poorly controlled hypertension (DBP > 90 mmHg despite antihypertensive medication; group 3) [6]. Two of the investigators (E. P., C. W.) analyzed all patient records independently of each other and defined the group to which each patient belonged. The concordance of these individual analyses was above 90 %.

Besides diuretics, the hypertensive patients in the CyA group had been prescribed beta blockers and/or calcium channel blockers. The patients in the Aza group were prescribed beta blockers and/or vasodilators, such as hydralazine or prazosine. ACE inhibitors were prescribed only to a few patients. The antihypertensive medication prescribed reflected common clinical practice in the Department of Transplantation Surgery during the respective periods.

Body mass index

At the time of transplantation, the height and the „dry weight" (body weight without hyperhydration) of each patient were recorded. All patients were weighed at each visit to the outpatient clinic and the body mass index (BMI; body weight in kg/height in m^2) was calculated. Patients with a BMI greater than 26 kg/m^2, regardless of sex, were considered to be overweight [13, 19].

Renal biopsy

The CyA patients had been biopsied on a yearly basis in order to evaluate the development and possible progression of histological lesions, in particular signs of chronic CyA nephrotoxicity. All biopsies were obtained according to a planned protocol for clinical and research follow-up at the clinic [28]. For the present study, the biopsy specimens taken 2 years post-transplantation were analyzed.

The biopsies had been obtained during a clinically quiescent period, without any signs of acute rejection or drug toxicity.

For comparison, 31 transplant biopsies from the control group were reviewed. These biopsies had been used as controls in earlier studies [27]. All biopsies were taken with a percutaneous technique and the biopsy specimens obtained were prepared as described elsewhere [18, 28]. A histological analysis of the biopsies with morphometric calculations was done as previously reported [27]. In short, the relative volume (volume density, V_v) of the cortical interstitium was used as a parameter for renal interstitial fibrosis with tubular atrophy. A closely related parameter, the so-called interstitial-tubuli ratio (I/T ratio), was also used.

Statistical analysis

For comparisons of proportions of patients in the various groups, the chi-square test with Yates' correction was used. In small samples, Fischer's exact probability test was used. The graft and patient survival rates were estimated by the Kaplan-Meier method [16]. The log rank test (Mantel-Cox) was used to test the equality of the survival curves. A P value below 0.05 was considered significant.

Results

Prevalence of hypertension 2 years after renal transplantation

In the CyA group, 27 % of the patients were normotensive compared to 42 % in the Aza group (P = NS; Table 2). The overall prevalence of hypertension (in all 124 patients) was 80 % among patients with chronic glomerulonephritis, 87 % among patients with polycystic kidney disease, and 76 % among the diabetic patients. In the group with chronic pyelonephritis, 44 % were hypertensive after transplantation. Details are shown in Fig. 1. The incidence of hypertension after renal transplantation, irrespective of the original disease, was slightly higher than before transplantation (73 % vs 61 %, resprectively, P = NS). The highest proportion of patients with poorly controlled hypertension – 44 % – was seen in the group of CyA patients with an initial dose of 15–17.5 mg/kg BW (Table 1).

Influence of original renal disease and hypertension before renal transplantation

There were no significant differences with regard to the underlying renal disease between the CyA and control groups with one exception: there were no diabetic patients in the Aza group. Eighteen of 31 (58 %) patients in the Aza group and 57 of 92 (62 %) patients in the CyA group were hypertensive prior to transplantation.

Of the patients with poorly controlled blood pressure after transplantation, 74 % were hypertensive before transplantation. The corresponding figure among those with well-controlled hypertension was 63 %, while only 14 % ($P < 0.001$) of the nonhypertensive patients had been hypertensive before transplantation. In the Aza group, 18 patients (58 %) were hypertensive after transplantation.

Table 2 Classification of patients into different groups with regard to blood pressure and immunosuppressive regimen

Tx group (n)	No hypertension	Hypertension	
		Well-controlled	Poorly-controlled
CyA (93)	25 (27 %)	50 (54 %)	18 (19 %)
Aza (31)	13 (42 %)	13 (42 %)	5 (16 %)
Total (124)	38 (30 %)	63 (51 %)	25 (19 %)

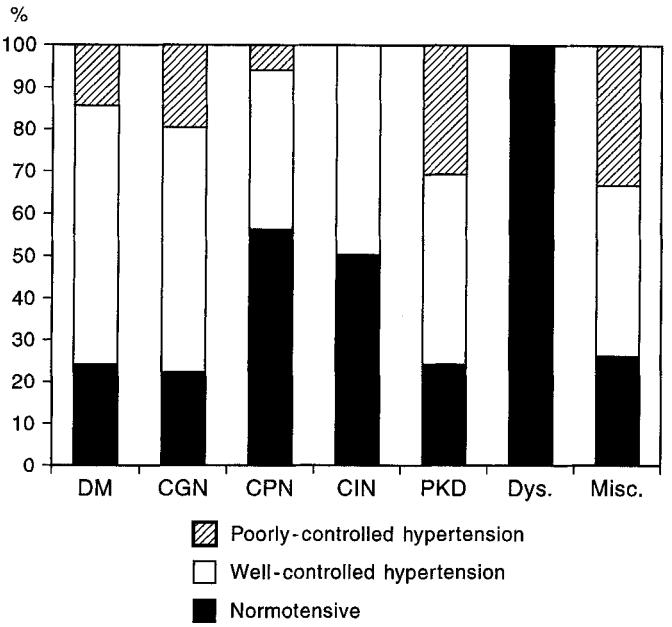

Fig. 1 Diagnoses and incidence of hypertension (*DM* diabetes, *CGN* chronic glomerulonephritis, *CPN* chronic pyelonephritis, *CIN* chronic/interstitial nephritis, *PKD* polycystic kidney disease, *Dys* dysplasia, *Misc* miscellaneous)

Duration of dialysis treatment

The median time on dialysis treatment was 6 months in all three blood pressure groups. Among the normotensive patients, 70 % received dialysis treatment prior to transplantation. The corresponding figure was 80 % among the patients with well-controlled hypertension and 91 % in the group with poorly controlled hypertension (P = NS).

Factors influencing hypertension after transplantation

Immunosuppression and rejection episodes

There was no difference in HLA A, B or DR matching between the groups. The average number of rejections and the dosage of methylprednisolone were equal in the study group and the control group. The accumulated CyA dose and CyA concentration in blood at the time of biopsy did not differ significantly between the normotensive and hypertensive CyA patients.

There was no significant difference between the three hypertensive groups with regard to the accumulated prednisolone dose 2 years after transplantation (normotensive group 7.3 g, patients with well-controlled blood pressure 7.3 g, and patients with poorly controlled blood pressure 7.8 g).

Recipient and donor ages

The mean donor age was 49 ± 6 years among the patients with poorly controlled hypertension, as compared to 42 ± 7 years among the normotensives and 47 ± 5 years among the patients with well-controlled hypertension (P = NS). The highest proportion of living donors – 45 % – was seen in the Aza group. The mean recipient age was 46 ± 4, 42 ± 2, and 42 ± 6 years, respectively (P = NS).

Cause of donor death

Analysis of the cause of donor death revealed that the highest proportion of donors who died of subarachnoid hemorrhage – 52 % (12/23 donors) – was found in the group with poorly controlled hypertension. The corresponding figures for the normotensive and well-controlled hypertensive groups were 18 % and 28 %, respectively. Details are shown in Table 3.

Body mass index (BMI)

In the CyA group, eight patients (9 %) were overweight at transplantation, i.e., had a BMI above 26. Two years after transplantation, this group had increased to 30 (32 %). In the control group, ten patients (32 %) were overweight at transplantation and nine (28 %) 2 years post-transplantation. The differences were not significant. There were more patients with a BMI above 26 among the CyA patients with hypertension than among the normotensives, but the difference was not significant.

Table 3 Cause of donor death relative to incidence of hypertension after transplantation (*SAH* subarachnoid hemorrhage)

Cause of donor death	No hypertension	Hypertension	
		Well-controlled	Poorly-controlled
SAH	7 (18 %)*, **	17 (27 %)***	12 (52 %)
Other causes	27 (71 %)	36 (57 %)	6 (26 %)
Not stated	4 (11 %)	10 (16 %)	5 (22 %)
Total (n = 124)	38	63	23

* P = NS compared to well-controlled; ** $P < 0.005$ compared to poorly controlled; *** $P < 0.03$ compared to poorly controlled

Renal function

There was a correlation between impaired renal function and prevalence of hypertension. The mean creatinine value was 162 μmol/l among the normotensives, 181 μmol/l in the group with well-controlled hypertension, and 229 μmol/l ($P < 0.01$) in the group with poorly controlled hypertension. The highest average serum creatinine – 246 μmol/l – was seen in the group of CyA patients who had poorly controlled hypertension. Average serum creatinine values were lower among the Aza patients. Further details are shown in Table 4.

Renal allograft biopsy findings

Kidney biopsies taken 2 years after transplantation showed that the degree of interstitial fibrosis, expressed as the relative volume of the renal cortical interstitium (volume density, V_v) or the interstitial/tubular ratio (I/T ratio) [28], did not differ between the study group and the controls. Nor was there any difference in the V_v (34 % vs 38 % vs 37 %) or I/T ratio (1.0 vs 1.2 vs 1.1) when comparing the groups according to our blood pressure classification. No signs of acute rejection or recurrence of the original underlying disease were seen in any of the biopsies. Vascular sclerosis, indicating chronic rejection, was seen in 3 out of 38 (7.9 %) patients in the normotensive group. The corresponding figures were 9 out of 63 (14.3 %) patients in the group with well-controlled blood pressure and 4 out of 23 (17.4 %) patients in the group with poorly controlled hypertension. The differences are not statistically significant.

Actuarial graft and patient survival

The 5-year graft survival was 92 % in the normotensive patients; it was 76 % and 65 % in the hypertensive patient groups, respectively. The actuarial 10-year graft survival was clearly affected by the presence of poorly controlled hypertension (Fig. 2): it was 65 % in the nor-

Table 4 Serum creatinine levels at the time of the transplant biopsy. Values given represent mean ± SD μmol/l. Values in parentheses indicate the number of patients

Tx group (n)	No hypertension	Hypertension		
		Well-controlled	Poorly-controlled	All
	(1)	(2)	(3)	(4)
CyA (93)	166 ± 80 (25)*, ***	192 ± 75 (50)**	246 ± 106 (18)	206 ± 87 (68)
	P = NS	$P < 0.05$	P = NS	$P < 0.05$
Aza (31)	154 ± 82 (13)	140 ± 68 (13)	168 ± 48 (5)	148 ± 63 (18)
Total (124)	162 ± 79 (38)*	181 ± 76 (63)**	229 ± 101 (23)	194 ± 86 (86)

* $P < 0.01$ vs 3; ** $P < 0.05$ vs 3; *** $P < 0.01$ vs 4

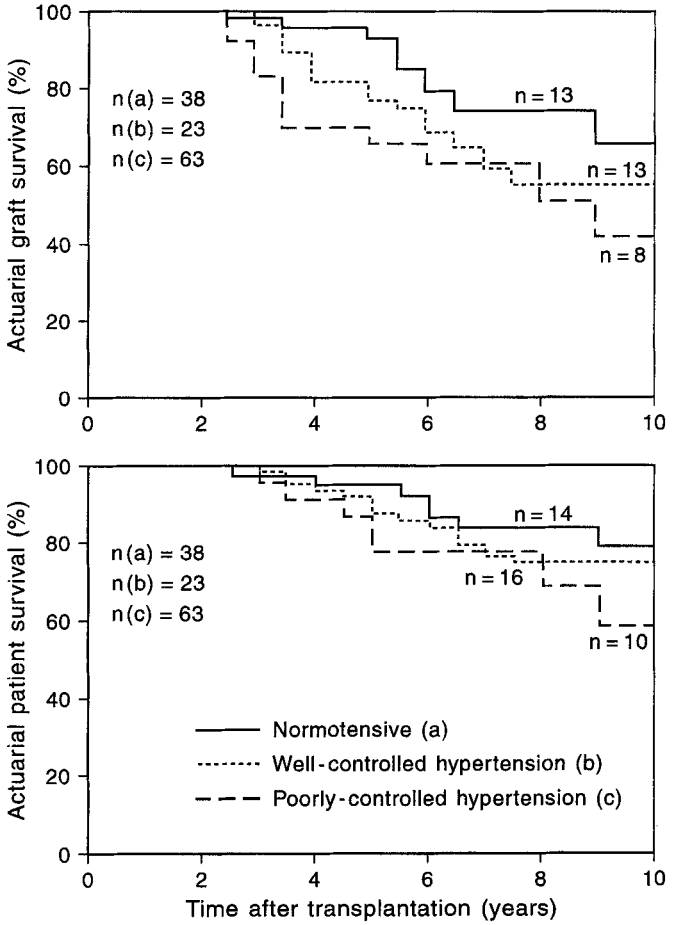

Fig. 2 Actuarial graft (%) and patient (%) survival in normotensive, well- controlled and poorly controlled hypertensive patients

motensive group and 51 % among the patients with well-controlled hypertension (P = NS), but only 42 % in the group with poorly controlled hypertension ($P < 0.05$ compared to normotensives). In the group with poorly controlled hypertension, seven patients (30 %) died with a functioning graft. The corresponding number of patients in the well-controlled and normotensive groups was 13 (21 %) and 9 (24 %), respectively. Recalculation, regarding these grafts as lost to follow-up on the date of patient death, revealed no statistically significant difference in graft survival between the groups. The 5-year patient survival numbers were 95 %, 87 %, and 78 % (P = NS). The 10-year patient survival was 79 %, 67 %, and 59 %, respectively (P = NS; Fig. 2).

Discussion

In this study there were more patients with hypertension in the CyA group (73 %) than in the Aza group (58 %) 2 years after transplantation. This finding is in agreement with those of other studies [5, 10, 14, 21]. Kidney transplantation contributed to 11 % of the overall incidence of hypertension in CyA-treated patients and to no extent at all in Aza treated patients. However, the patients in the Aza group were not entirely comparable to the CyA group because they had survived with good graft function for an average of 7.5 years. Therefore they may not reflect the true incidence of hypertension in a group of Aza-treated patients. There was also a large number of living donors in this group. Most of the patients were hypertensive prior to transplantation, a finding to be expected in a population of patients with end-stage renal disease [3, 15]. This was especially apparent among those with diabetes (75 %) and with chronic glomerulonephritis (67 %), also reported in other studies [15].

Although the accumulated CyA doses after 2 years did not differ significantly between the normotensive and the hypertensive patients , there was a larger proportion of patients with a high initial dose of CyA who had uncontrolled hypertension. We find it remarkable that the negative effects of a high initial dose of CyA on renal function was seen 2 years after transplantation. It is possible that interstitial fibrosis will occur earlier with a high initial dose of CyA. CyA is known to have a vasoconstrictive action on both afferent and efferent arterioles, and to cause sodium retention [10, 24]. The role of glucocorticoids in hypertension after transplantation is controversial [10, 14]. In contrast to

the findings of Dubovsky and Russell [10], we found no significant difference in the accumulated steroid dosage when we compared normotensive patients with those having hypertension.

The incidence of rejections in patients who were hypertensive was not significantly higher in the present study, in contrast to the study by Huysmans et al. [15]. However, we cannot exclude the possibility that the hypertensive patients had more severe rejections, causing a decrease in the number of functioning nephrons, which would result in a rise in the serum creatinine level.

More patients with a BMI above 26 were found among the hypertensive patients than among the normotensives, but the differences were not significant. Being overweight is considered to contribute to hypertension [2, 8, 11], but we could not demonstrate a correlation in our material, even with a BMI limit of 26 kg/m^2.

Renal function, as measured by the serum creatinine level, was significantly worse among the patients with poorly controlled hypertension. Patients with a marked reduction in renal function are likely to be hypertensive [4]. Rejection episodes may result in ischemic areas in the graft. An increased local production of renin in ischemic areas of the kidney has been demonstrated in patients with chronic renal disease, although the total plasma renin activity was low to normal [24]. Renin secretion has been shown to be intact in the transplanted kidney [7]. Activation of the renin-angiotensin system could thus explain the higher incidence of hypertension in patients with decreased renal function after transplantation. On the other hand, prolonged exposure to elevated systemic blood pressure is damaging to glomerular function and results in nephrosclerosis. Exposure of the graft to an elevated systemic blood pressure for 2 years, the time span of our study, is probably long enough to cause a measurable decrease in renal function. An abnormal pattern of renin-containing cells in the cyst walls of polycystic kidneys has been demonstrated in adult polycystic kidney disease [24]. This finding may have contributed to hypertension in the patients with this disease in our study.

Contrary to the findings of other authors [17], we found no correlation between the degree of interstitial fibrosis (volume density, V_v or I/T ratio) and hypertension. This lack of correlation was somewhat surprising, but a possible explanation is that the lesions studied reflect a focal type of changes in the kidney. Although there was more interstitial fibrosis among hypertensive patients, there was a large variation within the groups and no significant difference was seen. Only a small proportion of the patients had signs of vascular sclerosis in their biopsies, and there was no statistical difference between the groups. Thus, chronic rejection did not seem to occur more frequently among patients with hypertension than in normotensive patients in this study.

Patients who were hypertensive, especially those with poorly controlled hypertension, had a marked decrease in actuarial graft survival. This is in accordance with the findings of Cheigh et al. [6]. It is interesting to note that the highest proportion of donors who died of spontaneous intracranial bleeding was found in the group with poorly controlled blood pressure. If one speculates that the intracranial bleeding in these donors was mostly due to hypertension, it is possible that a propensity towards hypertension pre-existed in the donor. Patients who are hypertensive are at increased risk for cardiovascular disease [1]. This is especially true of renal transplantation patients, in whom cardiovascular disease remains the most common cause of death [12, 23]. Although no statistically significant difference in patient survival was found between the groups, there was a tendency towards lower survival rates in patients with severe hypertension. Graft survival was, however, significantly reduced in this group as compared to patients with no hypertension ($P < 0.05$). Therefore, one may speculate that cardiovascular mortality, resulting in patients dying with a functioning kidney graft, contributed to the poor kidney graft survival in patients with severe hypertension. In order to further elucidate this question, recalculation was performed with grafts that were lost due to patient death looked upon as lost to follow-up on the day of patient death.When graft survival was calculated under this assumption, patients with poorly controlled hypertension no longer differed statistically from patients with no hypertension. This finding suggests that among patients with severe hypertension, cardiovascular mortality that results in patient death with a functioning graft plays a more important role in the poor, long-term graft outcome than does the detrimental effect of hypertension itself.

In conclusion, the present study has demonstrated that hypertension is a frequent problem after renal transplantation. The presence of hypertension before transplantation in patients on dialysis seems to predispose the patient to post-transplant hypertension, as does post-transplant immunosuppression with CyA. Recipients of kidneys from donors who died of spontaneous intracranial bleeding also seem to be more prone to develop post-transplant hypertension.

Acknowledgement This study was supported by a grant (to C. W.) from the Sandoz Company, Täby, Sweden.

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