Epidemiology of arterial hypertension in renal transplant patients: changes over the last decade

Josep M. Campistol1, Rafael Romero2, Javier Paul3 and Alex Gutierrez-Dalmau1

1Renal Transplant Unit, Hospital Clinic, University of Barcelona, Barcelona, Spain, 2Nephrology Department, Complexo Hospitalario Universitario de Santiago, Santiago de Compostela, Spain and 3Nephrology Department, Hospital Miguel Servet, Zaragoza, Spain

Abstract

Background. Arterial hypertension is a common clinical problem in renal transplantation, with important consequences on graft and patient survival.

Patients and methods. A total of 3365 adult patients transplanted in 1990 (N = 824), 1994 (N = 1075) and 1998 (N = 1466) with a functioning graft after the first year were included. In this study, arterial hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg and/or treatment with antihypertensive drugs. The use of angiotensin converting enzyme (ACE) inhibitors or angiotensin II (ATII) receptor blockers during the first year was recorded.

Results. The prevalence of hypertension showed a progressive and significant increase during follow-up after renal transplantation in the three periods analysed, although SBP and DBP were lower in patients who underwent transplantation in 1998. The presence of arterial hypertension at 1 year was significantly associated with recipient gender (male), donor age (<60 years), immunosuppressive therapy (cyclosporine), serum creatinine and year of transplantation. Arterial hypertension was not associated with graft survival and cardiovascular mortality. The prevalence and severity of hypertension was significantly lower in patients treated with tacrolimus vs cyclosporine. The use of ACE inhibitors or ATII receptor blockers has increased in the recent years.

Conclusions. Arterial hypertension remained a common problem in renal transplantation, although in recent years the intensity of the control seems satisfactory. The use of ACE inhibitors or ATII receptor blockers has increased significantly in the last years.

Keywords: angiotensin converting enzyme inhibitors; arterial hypertension; cyclosporine; cardiovascular mortality; graft survival

Introduction

Hypertension is a common clinical problem in renal transplant recipients: its prevalence ranges from 60 to 85% in transplant patients treated with calcineurin inhibitors [1]. Hypertension has been shown to correlate with increased cardiovascular mortality and morbidity, as well as with graft loss. Opelz et al. [2] demonstrated an inverse relationship between the severity of hypertension and graft survival. Nowadays, cardiovascular mortality is the leading cause of mortality in the renal transplant population, causing more deaths than infectious diseases [3]. Several factors have been implicated in the increase in cardiovascular mortality in this population, particularly hypertension, a greater number of diabetic patients, left ventricular hypertrophy, and progressive ageing among transplant patients [3,4]. Although control of blood pressure is essential in renal transplant recipients, many issues remain unresolved, especially the type of therapy to be used and the degree of blood pressure control [5].

The aim of the present study was to analyse the epidemiology of arterial hypertension in renal transplant patients over the last decade in Spain as well as the impact of hypertension on graft and patient survival.

Patients and methods

Study design and clinical variables

We analysed the patients included in the Spanish Chronic Allograft Nephropathy Study. As previously described [6], a cohort of 3365 adult patients who underwent renal trans-
plantation in Spain in 1990, 1994 and 1998 with a functioning graft at 1 year were included. In all patients, different types of variables were evaluated before, during and after renal transplantation. Immunosuppressive treatment was provided on an intention-to-treat basis. The use of angiotensin converting enzyme (ACE) inhibitors or angiotensin II (ATII) receptor blockers during the first year was recorded.

**Definition of variables**

Arterial hypertension was defined as a systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg and/or treatment with antihypertensive drugs. When hypertension was analysed as a risk factor for cardiovascular mortality or graft loss, three groups were considered: (i) patients with uncontrolled hypertension (SBP >140 mmHg and/or DBP >90 mmHg); (ii) patients with controlled hypertension (SBP ≤140 mmHg and DBP ≤90 mmHg) who were receiving treatment for hypertension; and (iii) patients without hypertension (SBP ≤140 mmHg and DBP ≤90 mmHg) without antihypertensive drugs.

**Statistical methods**

Descriptive results are expressed as the mean ± standard deviation. Contingency tables were employed to describe categorical variables. The projected death-censored renal allograft half-life in 1990, 1994 and 1998 was calculated under the assumption of Weibull-distributed graft survival times. Graft loss was defined as a return to dialysis or retransplantation. Predictors of death-censored graft survival were evaluated by a multiple Cox proportional hazard regression model. Only variables associated with graft survival in the univariate analysis were considered in the multivariate analysis. The incidence of arterial hypertension and that of SBP and DBP were compared among successive follow-up periods using Wilcoxon tests, with Bonferroni correction to account for multiple comparisons. Because a large number of values were missing, when studying proteinuria and creatinine in patients requiring ACE inhibitors or ATII receptor blockers during follow-up, mixed linear regression models were applied to evaluate changes through time. Predictive factors for death from cardiovascular disease were analysed by Cox proportional hazards multiple regression. Only factors found to significantly predict overall patient survival were analysed.

This study was approved by the ethics committee of the Hospital de Bellvitge and assures data confidentiality.

**Results**

**Epidemiology of arterial hypertension**

The incidence of arterial hypertension at 3 months, 1 and 2 years after transplantation was significantly different among the three periods analysed (1990, 1994 and 1998) (P < 0.01) (Figure 1). The prevalence of hypertension showed a progressive and significant increase during follow-up after renal transplantation in the three periods, although SBP and DBP were lower in patients who underwent transplantation in 1998. The number of antihypertensive drugs used during these periods progressively increased during the post-transplantation follow-up and patients who underwent transplantation in 1998 were treated with a greater number of antihypertensive drugs than those who underwent transplantation in 1994 and 1990.

**Risk factors for arterial hypertension**

Multiple logistic regression analysis demonstrated six different factors associated with the development of arterial hypertension at 3 months and 1 year. The presence of arterial hypertension at 3 months was significantly associated with the following factors: recipient

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension at 1 year (ref. ‘no’)</td>
<td>–</td>
<td>–</td>
<td>0.1597</td>
</tr>
<tr>
<td>Non-controlled</td>
<td>1.096</td>
<td>(0.470, 2.551)</td>
<td>0.8324</td>
</tr>
<tr>
<td>Controlled</td>
<td>1.738</td>
<td>(0.801, 3.772)</td>
<td>0.1621</td>
</tr>
<tr>
<td>No hypertension</td>
<td>1.000</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Pulse pressure (+10 mmHg)</td>
<td>1.237</td>
<td>(1.048, 1.459)</td>
<td>0.0117</td>
</tr>
<tr>
<td>Recipient age (ref. ‘&lt;60 years’)</td>
<td>3.135</td>
<td>(1.869, 5.257)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Creatinine at 3 months (+1 mg/dl)</td>
<td>2.020</td>
<td>(1.522, 2.682)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Creatinine increase from 3 months to 1 year (+1 mg/dl)</td>
<td>1.479</td>
<td>(1.014, 2.158)</td>
<td>0.0423</td>
</tr>
<tr>
<td>Proteinuria at 3 months (+1 mg/dl)</td>
<td>1.392</td>
<td>(1.084, 1.786)</td>
<td>0.0094</td>
</tr>
<tr>
<td>Proteinuria increase from 3 months to 1 year (+1 mg/dl)</td>
<td>1.247</td>
<td>(1.011, 1.539)</td>
<td>0.0390</td>
</tr>
</tbody>
</table>

Year of transplantation was not included because it was not significant. Ref., reference.
gender (male 81% vs female 74%; \( P < 0.001 \)), delayed graft function (non-delayed 76% vs delayed 84%; \( P < 0.001 \)), immunosuppressive therapy (tacrolimus 67% vs cyclosporine 80%; \( P < 0.001 \)), and year of transplantation (1990 73% vs 1994 81% vs 1998 80%; \( P < 0.001 \)). At 1 year, the presence of arterial hypertension was significantly associated with the following factors: recipient gender, donor age (< 60 years 81% vs > 60 years 88%; \( P < 0.005 \)), immunosuppressive therapy, serum creatinine (sCr< 1.2 mg/dl 73% vs sCr 1.2–2 mg/dl 82% vs sCr 2–3 mg/dl 88% vs sCr > 3 mg/dl 94%; \( P < 0.001 \)), and year of transplantation.

**Hypertension and cardiovascular mortality**

Arterial hypertension at any time after renal transplantation was not associated with cardiovascular mortality. Moreover, classifying the patients into three different groups (non-hypertension, controlled hypertension and uncontrolled hypertension) revealed no statistically significant relationship with cardiovascular mortality. The degree of systolic and diastolic hypertension at 1 year was not associated with cardiovascular mortality. Multiple regression analysis showed that pulse pressure (+10 mmHg) at 1 year, recipient age (> 60 years), serum creatinine (+1 mg/dl) and proteinuria (+1 g/24 h) at 1 year were significantly associated with cardiovascular mortality.

**Hypertension and graft survival**

Arterial hypertension at 3 months and 1 year was not significantly related to graft survival, neither SBP nor DBP. The level of systolic and diastolic arterial pressure at 3 months and 1 year was not associated with graft survival. In the multivariate analysis, only the following factors were related with graft survival: recipient age (< 60 years), last PRA (>15%), acute graft rejection, serum creatinine at 3 months (+1 mg/dl), proteinuria at 3 months (+1 g/24 h), and treatment with lipiodowering agents.

**Hypertension and immunosuppressive therapy**

The incidence of arterial hypertension was significantly lower in patients treated with tacrolimus vs those with cyclosporine at 3 months, 1 and 2 years after transplantation (\( P < 0.001 \)). Similarly, SBP and DBP values in these periods were significantly lower in patients treated with tacrolimus than in those treated with cyclosporine. Moreover, the number of antihypertensive drugs at 1 year was significantly lower in patients treated with tacrolimus than in those treated with cyclosporine (Figure 2).

Discontinuation of steroids was not associated with a significant decrease in the incidence of arterial hypertension, although SBP and DBP and the number of antihypertensive drugs were significantly lower at 1 year post-transplantation than before discontinuation.

**Use of ACE inhibitors and ATII receptor blockers**

The use of ACE inhibitors and ATII receptor blockers increased significantly during the study period, especially in patients undergoing transplantation in 1998. At 1 year, 9.7% of patients who underwent transplantation in 1990 were treated with ACE inhibitors or ATII receptor blockers vs 13.8% in 1994 and 22.2% in 1998. During the post-transplantation follow-up, the use of ACE inhibitors and ATII receptor blockers progressively increased in the three periods analysed.
A marked decrease in 24 h proteinuria was observed after the introduction of ACE inhibitors or ATII receptor blockers. When only patients with a proteinuria higher than 1 g/24 h were considered, this decrease was statistically significant (baseline 2.4 g/24 h vs 1.31 g/24 h at 1 year; \( P < 0.001 \)).

Discussion

The present study defines the high incidence and prevalence of arterial hypertension in renal transplant patients. The prevalence of hypertension progressively increased during the post-transplantation follow-up. Hypertension was present in more than 80% of patients 3 years or more after transplantation and in 85% of patients, 5 years after transplantation. All these patients were treated with a calcineurin inhibitor (cyclosporine or tacrolimus), which could have influenced the development of hypertension. Interestingly, the prevalence of arterial hypertension was higher in recent years (1994 and 1998) than previously, although the recent management of hypertension was more aggressive, with the use of a greater number of antihypertensive drugs. Moreover, the number of patients treated with ACE inhibitors or ATII receptor blockers significantly increased in the later periods when the number of antihypertensive drugs and the prevalence of patients with controlled hypertension were significantly higher than in 1990. In addition, SBP and DBP values at 1 year were significantly lower in 1998 than in 1990 and 1994. Specialists in renal transplantation are paying greater attention to the management of arterial hypertension.

The development of arterial hypertension at 3 months and 1 year after transplantation was significantly and independently associated with recipient gender (male), delayed graft function, immunosuppressive therapy (cyclosporine) and year of transplantation (1998). Interestingly, the development of post-transplantation delayed graft function was associated with a higher incidence of hypertension, probably related to poorer renal function and higher steroid doses. A more aggressive approach in patients with delayed graft function is essential to achieve optimal renal function and effective blood pressure control [7]. The role of immunosuppressive therapy in the development of hypertension has been analysed in many studies, and most have concluded that the prevalence is higher with cyclosporine than with tacrolimus [8,9]. The present study supports these results, with a significantly higher prevalence of hypertension in patients treated with cyclosporine. Moreover, SBP and DBP and the number of antihypertensive drugs were significantly lower in patients treated with tacrolimus than in those treated with cyclosporine. The lower incidence of arterial hypertension with tacrolimus could provide beneficial effects in long-term cardiovascular follow-up.

Unfortunately, we found no effect of arterial hypertension on graft survival and cardiovascular mortality. Several studies [10,11] have defined the importance of hypertension on graft survival, especially the study by Opelz et al. [2], who demonstrated that SBP and DBP values were significantly associated with graft survival. In the present study, we were unable to show any correlation because arterial hypertension was highly prevalent (>80%), but the influence of blood pressure values on graft survival might be considerable. In addition, the effect of renal function (serum creatinine) on graft survival and cardiovascular mortality was so strong that some of the remaining factors were omitted from the analysis.

Finally, in recent years the use of ACE inhibitors and ATII receptor blockers has progressively increased in post-transplantation follow-up. Although theoretically the use of ACE inhibitors or ATII receptor blockers might predominate in renal
transplant recipients with hypertension, their use is restricted to a few units that have experience with these drugs [12]. Nevertheless, calcium channel blockers are the most frequently used antihypertensive drugs in the treatment of hypertension in renal transplant recipients [13]. There are several reasons for this contradictory situation: (i) fear of the presence of renal artery stenosis in the graft, with the risk of acute renal failure; (ii) the slight elevations in serum creatinine observed simultaneously with the introduction of an ACE inhibitor or ATII receptor blocker always create doubts about acute graft rejection; and (iii) the ease and antihypertensive efficacy of calcium channel blockers in renal transplant recipients, which have some beneficial effects on cyclosporine metabolism [14]. Although calcium channel blockers are highly effective as antihypertensive drugs in this population, their tolerance is not as good. Adverse effects include oedema and facial flushing in many patients; no antiproteinuric or renoprotective effects on grafts have been described. Recent studies have confirmed the importance of ACE inhibitors or ATII receptor blockers as antihypertensive or renoprotective agents with high efficacy and good tolerance in renal transplant patients [15,16]. In the next few years, the use of these drugs will probably become widespread in renal transplant patients.

Conflict of interest statement. None declared.

References