Arterial Hypertension and Renal Allograft Survival

Kevin C. Mange, MD
Borut Cizman, MD
Marshall Joffe, MD, PhD
Harold I. Feldman, MD, MSCE

RENAL TRANSPLANTATION HAS emerged as the treatment of choice for many patients with end-stage renal disease. However, despite marked improvements in short-term allograft function with administration of newer potent immunosuppressive medications, long-term allograft survival continues to be inadequate, with allograft failure being one of the most important reasons for (re)initiating long-term dialysis treatment in the United States.

Nonimmunological factors have been increasingly identified as potentially important mediators of reduced long-term renal allograft function known as chronic allograft nephropathy. One such factor is hypertension; higher blood pressures have been observed among patients whose allografts failed the most rapidly. These observations are consistent with the recent demonstration of a graded risk of developing end-stage renal disease with increasing levels of systolic blood pressure (SBP) and diastolic blood pressure (DBP) outside of the transplant setting. However, it has been difficult to establish the exact role of hypertension in chronic allograft dysfunction, because elevations in blood pressure frequently occur as a result of the progressive allograft failure that typifies chronic allograft nephropathy. Prior studies of the relationship between hypertension and renal failure have not been able to control for baseline renal function and therefore have left unanswered the question of whether elevations in blood pressure are a cause or a result of progressive renal dysfunction.

Further complicating the evaluation of the role of hypertension as a cause of progressive allograft dysfunction is the potential effect of certain classes of antihypertensive agents on renal function independent of their effect on blood pressure. For example, calcium channel blockers have been shown to limit the renal arteriolar vasoconstriction induced by cyclosporine and angiotensin-converting enzyme inhibitors have been shown to reduce the rate of progression of renal...
failure in native kidney disease, possibly by decreasing intraglomerular hypertension.

A clearer understanding of the etiologic role of hypertension in chronic allograft nephropathy is critical to developing optimal strategies for management of hypertension among transplant recipients. The principal objective of this study was to characterize the relationship between hypertension and subsequent kidney allograft failure, adjusting for baseline allograft function and other potential confounding factors, thereby accounting for the elevations in blood pressure that result from allograft dysfunction.

**METHODS**

We performed a historical cohort study among adult recipients of cadaveric kidneys that examined the relationship of blood pressure and long-term allograft survival adjusted for renal function. A secondary aim was to evaluate the potential impact of specific classes of antihypertensive agents on allograft survival.

**Subjects**

All patients aged 18 years or older who underwent cadaveric renal transplantation at the Hospital of the University of Pennsylvania between January 1, 1985, and December 31, 1990, were eligible for this study. From 1985 to 1990, a total of 376 cadaveric transplantations were performed at the hospital. Study subjects were limited to the 277 patients who underwent kidney transplantation without another simultaneous organ transplant and whose kidney allograft was functioning 1 year after cadaveric renal transplantation. We excluded patients whose allografts failed during the first year following transplantation because allograft failure occurring during this period is commonly due to processes (eg, surgical complications and hyperacute rejection) that are not likely to be modified by blood pressure control. The research protocol was approved by the Institutional Review Board of the University of Pennsylvania.

**Organ Procurement**

All kidney allografts were procured using standard multiorgan intravascular flush techniques and preserved at 4°C until implantation. Pulsatile perfusion was not used. In most cases, the aorta of the donors was flushed with Euro-Collins solution. Harvested kidneys were cold-stored in Euro-Collins solution (Electrolyte Solution for Kidney Preservation; Baxter Health Care, Irvine, Calif).

**Immunosuppression**

All patients received triple immunosuppression consisting of corticosteroids, cyclosporine, and azathioprine. One gram of methylprednisolone was administered intraoperatively, followed by prednisone, 1.5 mg/kg per day, tapered to 0.5 mg/kg per day by discharge. By 6 months, the prednisone dosage was lowered to 0.15 mg/kg per day. Cyclosporine administration was begun on the first postoperative day at 14 mg/kg per day to maintain a whole-blood trough level between 100 and 200 mg/L by high-performance liquid chromatography. If allograft function was delayed, the cyclosporine was lowered to 7 mg/kg per day until renal function began. Azathioprine was administered intraoperatively at a dosage of 10 mg/kg per day and then tapered to 1 mg/kg per day by day 5 postimplantation. In 1988, 27 patients with oliguria received cyclosporine-sparing therapy with antibody induction for the first 7 to 14 days after transplantation.

**Study Data**

The primary outcome was allograft failure as defined by return to dialysis, repeat transplantation, or death. Allograft outcomes were obtained from the United Network for Organ Sharing and medical records. Potential confounding variables were abstracted from subjects’ charts: HLA antigens recorded as the number of HLA-A, HLA-B, and HLA-DR mismatches; panel of reactive antibodies as a continuous variable from 0% to 100%; age; sex; ethnicity (white, African American, Hispanic, or other); primary cause of renal failure (diabetes mellitus, hypertension, glomerulonephritis, or other); delayed allograft function defined as the need for dialysis within 1 week of transplantation; and the number of acute rejections within the first year.

Serum creatinine and SBP and DBP were recorded at 12 months. Twelve months was chosen a priori because we hypothesized that by this time following transplantation additional episodes of acute rejection with their associated destabilizing effect on renal function would be uncommon. In addition, by 12 months immunosuppressive therapy is usually stabilized.

Mean arterial blood pressures (MABPs) were calculated by the formula (SBP − DBP)/3 + DBP. Glomerular filtration rates were estimated using creatinine clearances calculated using the formula described by Cockcroft and Gault: 

\[
\text{MCCr} = \frac{(140 – \text{age}) \times \text{weight}}{(72 \times \text{serum creatinine})} \times 0.85 \text{ (for women)}
\]

where SBP is systolic blood pressure, DBP is diastolic blood pressure, and weight is in kilograms. Serum creatinine and MABPs were calculated at 1 year after transplantation additional episodes of acute rejection with their associated destabilizing effect on renal function would be uncommon. In addition, by 12 months immunosuppressive therapy is usually stabilized.

**Statistical Analysis**

The primary analysis examined the relationship between SBP, DBP, and MABP at 1 year following transplantation and long-term allograft survival. Initially, baseline characteristics at 1 year after transplantation including ethnicity, age, sex, percentage reactive antibodies, HLA mismatches, and primary cause of renal disease were described by mean, median, and SD for continuous variables and frequencies for nominal variables.

We used the Cox proportional hazards model to examine the relationship of blood pressure and other baseline covariates to allograft survival. We first examined the unadjusted associations of these variables with allograft survival. Variables that had a nominally significant relationship to allograft survival (P≤0.20) were considered as candidates.
for multivariate model building. We fit these multivariate models by first adding covariates in a forward stepwise manner and then removing variables that did not retain statistical significance (P < .10) by means of a backward algorithm. The potential nonlinear relationship of SBP, DBP, and MABP to allograft failure was explored using indicator variables for the quartiles of the pressure measurements. To account for possible nonlinearity of blood pressure in our models, quadratic terms were also examined. In addition, a number of interactions were explored, including those between blood pressure and race as well as between blood pressure and diabetes.

The proportionality assumption underlying Cox proportional hazards regression was tested in 2 manners. First, ln(−ln(S(t))) curves were examined to affirm that the survival functions remained parallel over time.12 Second, a χ² test based on weighted residuals was performed.13 Both approaches confirmed the proportionality assumption for each of our measures of blood pressure in unadjusted and adjusted models.

In an exploratory analysis of antihypertensive agents and allograft survival, subjects exposed to an angiotensin-converting enzyme inhibitor were compared with those subjects who were not exposed to this agent, and subjects exposed to a calcium channel blocker were compared with those patients who were not similarly exposed. Multivariate models were fit to evaluate the association of antihypertensive agent class and allograft survival using methods similar to those for the principal analysis of blood pressure and kidney allograft function.

All statistical analyses were performed using Intercooled Stata, Version 5.0 (Stata Corp, College Station, Tex).

RESULTS

Descriptive Analyses

Among the 277 patients eligible for this study, more than 60% were men and had kidney disease due to glomerulonephritis (TABLE 1). The majority of the recipients were white (71.5%); 23.8% were African American, and 4.7% were either Asian or Hispanic. Few recipients were highly immunologically sensitized (mean panel reactive antibodies were 10.9%, and 10.5% of recipients had prior kidney transplants), although more than 90% received kidneys that were mismatched at more than 3 HLA loci. Delayed allograft function occurred for 46.4% of recipients, and 62.6% of recipients had an episode of acute rejection within the first year following transplantation. The mean (SD) follow-up time was 5.73 (2.4) years. By the end of the study, 13.0% of patients had died with a functioning allograft, 20.5% had received another transplant or returned to dialysis, and 66.5% had not experienced an end point by the time of their last known follow-up. The mean (SD) duration of follow-up for this latter group was 6.12 (3.22) years. At 12 months following transplantation, the mean (SD) creatinine clearance for all study subjects was 0.88 (0.37) mL/s (53 [22] mL/min) and the average (SD) MABP was 104 (13) mm Hg.

The relationship between blood pressure and the level of renal function measured by the creatinine clearance at 1 year (in quartiles) is shown in TABLE 2. The MABP, mean SBP, and mean DBP for each of the quartiles of renal function are provided. For each of these measures of blood pressure, lower creatinine clearance was associated with higher blood pressures.

Analysis of Allograft Survival

As an initial exploration of the unadjusted effect of blood pressure on allograft survival, Kaplan-Meier curves were generated separately for tertiles of SBP, DBP, and MABP (FIGURE). Systolic blood pressure (P = .009) and MABP (P = .02) had statistically significant unadjusted associations with allograft survival, whereas the association of DBP did not achieve conventional levels of significance (P = .20).

The unadjusted association between potential confounding variables and allograft failure was examined in bivariate proportional hazards models (TABLE 3). Variables consid-

©2000 American Medical Association. All rights reserved.
continued to predict allograft survival.

 representations of blood pressure con-
tained at 1 year, the rate ratio for each of these
variables for discrete levels of blood
pressure was 15%, 27%, and 30% reductions,
respectively, in the rate of allograft surv-
vival. When we fit models that com-
bined measures of blood pressure, there
was little evidence of an improved abil-
ity of our models to predict allograft sur-
vival, particularly for SBP and MABP.

TABLE 3. Unadjusted Rate Ratios Between Various Variables and Allograft Failure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rate Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male vs female)</td>
<td>0.99 (0.66-1.49)</td>
<td>.97</td>
</tr>
<tr>
<td>Ethnicity (nonwhite vs white)</td>
<td>3.05 (2.03-4.58)</td>
<td>.01</td>
</tr>
<tr>
<td>Age, per year</td>
<td>0.99 (0.97-1.01)</td>
<td>.27</td>
</tr>
<tr>
<td>Native kidney disease (no diabetes vs diabetes)</td>
<td>0.68 (0.43-1.09)</td>
<td>.12</td>
</tr>
<tr>
<td>Prior renal transplant (any vs none)</td>
<td>2.45 (1.50-4.00)</td>
<td>.01</td>
</tr>
<tr>
<td>Prior blood transfusion, No. (≥5 vs &lt;5)</td>
<td>1.01 (0.97-1.05)</td>
<td>.56</td>
</tr>
<tr>
<td>HLA mismatches, No. (≥3 vs &lt;3)</td>
<td>0.81 (0.50-1.28)</td>
<td>.36</td>
</tr>
<tr>
<td>HLA-DR mismatches (any vs none)</td>
<td>0.71 (0.42-1.21)</td>
<td>.21</td>
</tr>
<tr>
<td>Cold ischemia time, per hour</td>
<td>0.98 (0.95-1.01)</td>
<td>.15</td>
</tr>
<tr>
<td>Antibody induction (yes vs no)</td>
<td>1.58 (1.28-2.05)</td>
<td>.01</td>
</tr>
<tr>
<td>Delayed graft function (yes vs no)</td>
<td>1.46 (1.09-1.96)</td>
<td>.09</td>
</tr>
<tr>
<td>Acute rejection (any vs none in first year)</td>
<td>2.35 (1.45-3.83)</td>
<td>.01</td>
</tr>
<tr>
<td>Creatinine clearance at 12 mo, per 0.17 mL/s</td>
<td>0.85 (0.56-1.28)</td>
<td>.56</td>
</tr>
<tr>
<td>Systolic blood pressure at 12 mo, per 10 mm Hg</td>
<td>1.22 (1.09-1.36)</td>
<td>.01</td>
</tr>
<tr>
<td>Diastolic blood pressure at 12 mo, per 10 mm Hg</td>
<td>1.25 (1.01-1.55)</td>
<td>.05</td>
</tr>
<tr>
<td>Mean arterial blood pressure at 12 mo, per 10 mm Hg</td>
<td>1.36 (1.11-1.65)</td>
<td>.01</td>
</tr>
<tr>
<td>Body surface area, per m²</td>
<td>1.77 (0.63-4.98)</td>
<td>.28</td>
</tr>
</tbody>
</table>

*CI indicates confidence interval. Rate ratios were calculated with Cox proportional model.

To assess the stability of our results, we performed a sensitivity analysis in which we considered patient death as a censoring event rather than as a failure. The rate ratios for SBP, DBP, and MABP were 1.12 (95% confidence interval [CI], 0.95-1.31), 1.45 (95% CI, 1.09-1.91), and 1.33 (95% CI, 1.04-1.70), respectively. We also explored for interactions between blood pressure and ethnicity as well as between blood pressure and diabetes mellitus, but were not able to detect any.

Use of Antihypertensive Agents

We could not detect a relationship between the exposure to angiotensin-converting enzyme inhibitors or to calcium channel blockers within 3 to 12 months posttransplantation and allograft survival in unadjusted analyses or in analyses adjusted for blood pressure and creatinine clearance (P > .20 for all analyses). Additionally, we detected no interaction between blood pressure and angiotensin-converting enzyme inhibitors or creatinine at 12 months.

COMMENT

This historical cohort study demonstrated that SBP, DBP, and MABP at 1 year posttransplantation are statistically and clinically significant predictors of long-term renal allograft survival independent of baseline renal allograft function. The association between blood pressure and al-

©2000 American Medical Association. All rights reserved.
lograft survival appeared linear without a definite threshold value below which improvements in allograft outcomes no longer occurred. For every increase of 0.17 mL/s (10 mL/min) in calculated creatinine clearance at 1 year, the adjusted rate of allograft failure decreased by 36%. After adjusting for this potent influence of baseline renal function on allograft survival, we continued to observe a 30% elevation in the rate of allograft failure for every 10-mm Hg increase in MAPB. The results were stable in a number of sensitivity analyses. Our findings provide evidence that chronic elevations in blood pressure cause progressive renal dysfunction and that this association is not simply a result of the occurrence of hypertension resulting from progressive renal dysfunction associated with chronic allograft nephropathy.

The plausibility of a relationship between chronically elevated blood pressure and allograft function arises from growing evidence of an association between progressive renal disease and hypertension outside of the setting of transplantation. One prior study investigated the rate of decline of renal function among individuals who were enrolled in the Multiple Risk Factor Intervention Trial (MRFIT). Baseline blood pressure and serum creatinine levels and follow-up data for a 6-year period were available for all eligible patients. A multivariate analysis demonstrated that both baseline renal function on allograft survival.4 Unadjusted analyses demonstrated that blood pressure greater than 150/90 mm Hg at 1 year after transplantation to allograft survival.3 Unadjusted analyses demonstrated that blood pressure greater than 150/90 mm Hg was associated with reduced allograft survival. However, when a multivariable survival model was fit that adjusted for estimated glomerular filtration rate, blood pressure was no longer a significant predictor of allograft survival. Although these findings suggested that hypertension was a result rather than a cause of allograft dysfunction, the small size of this study and the categorization of blood pressure into only 2 groups limit its interpretation. Furthermore, the exclusion of patients with diabetes mellitus and the probable absence of African American patients limit the generalizability of these results.

Finally, Cosio et al performed a multivariate analysis of renal allograft survival in which they studied 547 cadaveric transplant recipients and demonstrated a relationship between MABP (averaged over the first 6 months after transplantation) and allograft survival only in African American recipients. Although these analyses were adjusted for the serum creatinine at 6 months, the instability of renal function and blood pressure due to frequent episodes of acute rejection in this time frame may have been the reason no association was observed in white recipients. Our analyses demonstrate that elevated blood pressure adversely affects allograft survival for both African American and white recipients.

Our secondary analysis of the effect of calcium channel blockers and angiotensin-converting enzyme inhibitors on allograft outcomes independent of their blood pressure–lowering effects did not detect an independent effect. However, a number of limitations hamper our ability to conclude that there is no effect of these agents on

Table 4. Multivariate Proportional Hazards Model of Systolic Blood Pressure and Allograft Survival*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rate Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnicity (nonwhite vs white)</td>
<td>2.52 (1.46-4.34)</td>
<td>.01</td>
</tr>
<tr>
<td>Native kidney disease (no diabetes vs diabetes)</td>
<td>0.42 (0.22-0.79)</td>
<td>.01</td>
</tr>
<tr>
<td>Prior kidney transplant (any vs none)</td>
<td>2.89 (1.40-5.95)</td>
<td>.01</td>
</tr>
<tr>
<td>Acute rejection (any vs none in first year)</td>
<td>2.65 (1.30-5.41)</td>
<td>.01</td>
</tr>
<tr>
<td>Systolic blood pressure at 12 mo, per 10 mm Hg</td>
<td>1.15 (1.02-1.31)</td>
<td>.02</td>
</tr>
<tr>
<td>Creatinine clearance at 12 mo, per 0.17 mL/s</td>
<td>0.74 (0.62-0.88)</td>
<td>.01</td>
</tr>
</tbody>
</table>
* CI indicates confidence interval.

Table 5. Adjusted Rate Ratio of Allograft Survival for Systolic, Diastolic, and Mean Arterial Blood Pressure From Multivariate Proportional Hazards Models

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rate Ratio (95% CI)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure at 12 mo, per 10 mm Hg</td>
<td>1.15 (1.02-1.30)</td>
<td>.02</td>
</tr>
<tr>
<td>Diastolic blood pressure at 12 mo, per 10 mm Hg</td>
<td>1.27 (1.01-1.60)</td>
<td>.04</td>
</tr>
<tr>
<td>Mean arterial blood pressure at 12 mo, per 10 mm Hg</td>
<td>1.30 (1.05-1.61)</td>
<td>.02</td>
</tr>
</tbody>
</table>
* CI indicates confidence interval. Rate ratios adjusted for the covariates included in the model described in Table 4.
allograft outcomes. First, we could not control for time-varied use of these medications during clinical follow-up. Plausibly, the use of these medications later in the posttransplantation course than we examined is important for allograft function. Furthermore, we could not exclude confounding by indication. In particular, it is possible that use of these agents differed according to levels of renal function because of demonstrated or hoped for effects on renal function. Finally, the precision of our estimates of effect was low.

A number of additional limitations of our study deserve mention. First, the results are applicable only to patients whose allografts have continued to function for more than 1 year. Although we hypothesized that it is unlikely that blood pressure control within the first year of transplantation significantly impacts allografts that fail during the first year, we were not able to examine this hypothesis specifically. Second, we had access to blood pressure readings from 1 clinic visit. While this limited our ability to characterize fully the exposure to hypertension experienced by our patients over the entire follow-up period, this lack of information is likely to have biased our analysis against finding a relationship between blood pressure and allograft function. Indeed, the limited data on blood pressure imply that the relationship between blood pressure and allograft survival may be more potent than we observed. Errors in the measurements of blood pressure are not likely to be associated with subsequent allograft failure, and such nondifferential misclassification would have caused underestimation of the relationship between allograft failure and blood pressure. Third, despite our attempts to control for both immunological and nonimmunological factors influencing allograft function, the possibility remains that we did not fully control for all confounding variables. Finally, studies of the progression of native renal disease have provided evidence that the impact of blood pressure on the progression of kidney dysfunction is greatest among patients with at least moderate elevations in protein excretion. Optimally, we would have been able to examine this issue, but data on protein excretion were not available.

In summary, we have demonstrated that blood pressure has a profound impact on allograft outcomes and this effect persists after controlling for baseline renal function. No threshold level of blood pressure was identified below which renal allograft survival failed to improve. Furthermore, we were unable to identify any specific demographic or disease subgroup in which this relationship was not relevant. We were not able to detect an association of specific classes of antihypertensive medications and allograft survival. Ultimately, clinical trials comparing treatment groups randomized to different levels of blood pressure control will be required to confirm the relationships we have described in this study and explore whether more intensive control of blood pressure prolongs renal allograft survival.

Funding/Support: The research reported in this article was supported in part by NIH training grant DK-07006, NIH Center grant DK-45191, National Institutes of Health; and by administrative/educational funds from the Dialysis Clinic Inc Research, Education, and Development Fund. Dr Feldman is an Established Investigator of the American Heart Association.

REFERENCES

13. Gramsch PM, Therneau TM. Propotional hazards tests and diagnostics based on weighted residu-

638 JAMA, February 2, 2000—Vol 283, No 5
©2000 American Medical Association. All rights reserved.