Renal allograft survival following acute rejection correlates with blood pressure levels and histopathology

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Renal allograft survival following acute rejection correlates with blood pressure levels and histopathology.

Background. Acute rejection (AR) is a strong predictor of renal graft survival, but the negative impact of AR on survival is variable, suggesting that other factors modulate this relationship. In this study, we examined the variables that correlate with graft survival after AR, particularly the impact of blood pressure (BP), graft function, and histopathology.

Methods. The study population included patients with no AR (N = 942) and patients with one (N = 407) or two (N = 156) AR during the first year post-transplant. Patients were adults who were recipients of living related (LRD, N = 410) or cadaveric grafts (CAD, N = 1095) and who were transplanted in a single institution and followed for 5.8 ± 4 years.

Results. Compared with patients without AR, those with AR were significantly younger, had more human lymphocyte antigen mismatches, and included more CAD recipients. Graft survival was analyzed beyond six-months post-transplant. In patients with AR, reduced survival correlated (multivariate) with (a) younger recipients (P = 0.01), (b) AR occurring later during the first-year post-transplant (P = 0.0006), (c) elevated serum creatinine (Cr) before (P = 0.05), at the time (P = 0.0001) of, or after AR (P = 0.0004), and (d) average BP levels after AR [systolic BP (P = 0.003 logistic, P < 0.0001 by Cox), diastolic BP (P = 0.007), mean arterial pressure (P < 0.0001)]. This latter correlation was independent of graft function and recipient race. Thus, post-AR BP levels correlated with graft survival in patients with post-AR creatinine ≤2 mg/dl (N = 408, P = 0.0009), in Caucasian recipients (P = 0.001), and in African American recipients (P = 0.01). In contrast, there was no significant correlation between BP levels and graft survival in patients without AR. AR histopathology, analyzed in patients with one AR episode, correlated with graft survival only the first six months after AR but not thereafter.

Conclusions. Graft survival after AR can be predicted independently by graft function and BP levels after the event. Patients with elevated BP post-AR have poor graft survival even if they have excellent graft function.

Key words: graft survival, transplantation, renal allograft, hypertension.

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It has been well established that acute rejection (AR) is a strong predictor of renal allograft survival [1–3]. In addition, several studies have identified other factors that appear to modulate the negative impact of AR on graft survival. For example, (a) in general, the later the AR occurs following transplantation, the more detrimental is its effect on graft survival [4, 5]. (b) Increasing numbers of AR episodes, even if they occur early after the transplant, increase the risk of graft loss [2]. (c) Graft dysfunction after AR is also an important variable that modulates the impact of AR on graft survival [6]. (d) Finally, the histopathological grade of the AR episode appears to correlate with graft prognosis [7, 8].

Recent advances in immunosuppression have caused a significant reduction in the number of patients who have AR following transplantation [9, 10]. However, the numbers of patients with AR is considerable, and the factors that determine the lower long-term graft survival in these individuals remain unclear. The ultimate goal of these studies is to identify variables that are associated with shortened graft survival after AR. Ultimately, we would like to determine whether modification of those variables alters the prognosis of patients with AR. In this study, we sought to determine the relationship between graft survival, AR, and graft function. Furthermore, these variables were analyzed in the context of other covariates shown to correlate with graft survival, including blood pressure (BP) levels and the histopathology of AR. Regarding BP, in previous studies, we showed that poorly controlled BP correlates with renal allograft survival in African Americans but not in Caucasian cadaveric graft (CAD) recipients [2]. Other studies had shown previously a relationship between hypertension and graft survival in other patient populations [11, 12], and a more recent analysis of a large number of renal allograft recipients confirmed that elevated BP levels correlate for graft survival in renal transplant recipients [13]. However, the analysis of the impact of BP on graft survival needs to be done with caution because variables
that correlate with BP, principally race and graft function, are also determinants of graft survival. Based on these considerations, one of the goals of our study was to determine whether there is in fact a correlation between BP and graft survival that is independent of other variables. To evaluate the relationship between histopathology and graft survival, we used the Banff criteria, which allows a consistent grading of the histopathology of AR [14]. Because of its initial description, these histopathological criteria have been shown to correlate with the acute changes in serum creatinine that occur during AR and perhaps also with long-term survival [7, 8]. However, the relationship between histopathology and graft survival has not been analyzed together with other clinical parameters that determine graft prognosis.

The criteria used here for the selection of a study population were designed to minimize the impact of time of AR and number of AR on graft survival. Thus, this study includes renal allograft recipients who had no AR or who had one or two AR episodes during the first-year post-transplant.

METHODS

Study population

Included are all adult kidney transplant recipients done at The Ohio State University from September 26, 1982, to June 14, 1996, who additionally met the following criteria: (a) Patients had no AR episodes any time post-transplant (N = 942), or (b) patients had one (N = 407) or two (N = 156) AR episodes during the first-year post-transplant. Patients with more than two ARs and/or with AR episodes beyond the first post-transplant were excluded from the study. Patients included 1095 recipients of CAD and 410 recipients of grafts from living donors (LRD).

The majority of patients received induction immunosuppression immediately post-transplant, which consisted of polyclonal (Minnesota ALG) or monoclonal antilymphocyte antibodies (OKT3; Ortho Biotech, Raritan, NJ, USA) until the serum creatinine was ≤2.5 mg/dl when cyclosporine was initiated. Maintenance immunosuppression consisted of triple immunosuppression with prednisone, azathioprine, and cyclosporine until 1995 when azathioprine was replaced by mycophenolate mofetil (CellCept) at a dose of 2 to 3 g/day.

The diagnosis of AR was based on both clinical and pathological information. When AR was suspected clinically, the patient was admitted to the hospital and had an allograft biopsy done soon after admission before or simultaneously with the initiation of anti-AR therapy. ARs were treated with corticosteroid only or in combination with an antilymphocyte antibody preparation. These two forms of AR treatment were used with similar frequency in nonvascular AR (31% corticosteroid alone; 69% corticosteroid and antilymphocyte antibody) or vascular AR (24% corticosteroid; 76% corticosteroid and antibody), reflecting our aggressive approach to the treatment of ARs.

Clinical parameters

For this analysis, clinical values were analyzed as follows: (a) The pre-AR creatinine (pre-Cr) was defined as the lowest serum creatinine concentration within one month prior to the AR episode. (b) The post-AR creatinine (post-Cr) was defined as the lowest serum creatinine concentration more than one month and less than three months post-AR. (c) Peak-Cr was the highest concentration of serum creatinine within one month of the diagnosis of AR. (d) The pre-AR BP (pre-BP) was the average systolic, diastolic, or mean artery pressure (MAP) from the time of transplantation to the time of diagnosis of AR. (e) The post-AR BP (post-BP) was the average systolic, diastolic, or MAP BP level achieved on the patient from two months following AR to the end of the follow-up period. BP levels were determined by the patient at home and during outpatient clinic visits. Prior to AR, a total of 69,622 BP readings was analyzed, and every patient had a minimum of 10 BP readings recorded. Following AR, a total of 51,106 BP levels were analyzed. A significant higher number of BP recordings were available in patients who had AR (47 per patient) than in patients who did not have AR (25 per patient), most likely reflecting the closer clinical follow-up of patients considered to be at higher risk. Post-transplant acute tubular necrosis (ATN) was defined as the need for dialysis during the transplant admission.

For histopathological assessment, all of the biopsies that the patient had at the time of AR were reviewed by one or two of the authors (D.D.S., F.G.C.). Only those biopsies that had less than moderate chronic allograft nephropathy (CN; such as interstitial fibrosis and tubular atrophy) [14] were included, because it was considered that the presence of moderate to severe CN would obscure the interpretation of the analysis of the impact of acute pathological changes on graft survival. Twenty patients had moderate to severe CN, and these patients were not included in this analysis. In addition, in this portion of the study, only those patients who had one AR episode were included, because in patients with two AR episodes, it was difficult to determine whether the histopathology of the first or the second AR episode had an impact on graft survival. AR intensity was graded according to the Banff criteria [14] with two modifications: (a) Patients with allograft infarction were classified separately from patients with grade III or severe rejection. This was done because we showed previously that these two groups of patients have significantly different graft survival [15]. (b) Patients with moderate vascular rejection (Banff grade IIB) were analyzed together with
patients with severe rejection (Banff grade III) because the prognosis of these two groups of patients is similar. For statistical analysis, the histopathological grade of AR was given a numerical value as follows: 1 = borderline AR (N = 37); 2 = grade I (N = 78); 3 = grade IIA (N = 42); 4 = grades IIB and III (N = 72); 5 = infarcts (N = 16). All biopsies were reviewed without the knowledge of the ultimate fate of the allograft.

Analysis of the data

Data throughout the manuscript are expressed as mean ± sd of the mean. Values were compared by Student’s t-test or by nonparametric tests if the values were not normally distributed. Proportions were compared by chi-square analysis. Graft survival was censored at the time of patient death and analyzed by Kaplan–Meier plots and Cox regression. Correlations between graft survival and other variables were calculated by logistic regression analysis.

RESULTS

Characteristics of the patient population

Table 1 displays these data. Compared to patients without AR, patients with AR were significantly younger (P = 0.005), included a significantly higher number of CAD transplants (P = 0.0001), and had a significantly higher number of human lymphocyte antigen (HLA) mismatches (P = 0.002 for the whole group, P = 0.01 for CAD). The prevalence of post-transplant ATN was low, but it was significantly higher in patients with AR (10%) than in patients without AR (7%, P = 0.02). In contrast, there were no significant differences between patients with or without AR in donor, recipient variables, or pre-AR graft function. In 95% of patients with one AR and in 93% of patients with two AR, the episode occurred during the first three months post-transplant.

Graft and patient survival

After an average follow-up of 5.8 ± 4 years, 26% of patients without AR died compared with 25 and 27% among patients who had one or two AR episodes, respectively. Graft survival was not significantly different between patients with one (25% grafts lost) or two AR episodes (30%, P = 0.2). However, graft survival in patients with one or two AR episodes was significantly worse than in patients without AR (11% grafts lost, chi-square analysis, P < 0.0001). By Cox regression, graft survival time was not different in patients who had one or two AR episodes (Fig. 1), but graft survival in these two groups of patients was significantly different from that of patients without AR episodes.

Correlates of long-term graft survival in patients with acute rejection

Table 2 displays the variables that correlate significantly with graft survival beyond six-months post-transplantation in patients with AR. As can be seen by univariate analysis, the following variables correlated with worse long-term graft survival: (a) younger recipients [2], (b) AR occurring later post-transplant, such that increasing time post-transplant when the AR occurs is associated with progressively worse prognosis, (c) higher levels of serum creatinine concentration before (pre-Cr), during (peak-Cr), or after the AR episode (post-Cr). The correlation between pre-Cr and graft survival was also significant when patients with post-transplant ATN were excluded from the analysis. (d) Higher levels of BP after AR (post-BP) was also a correlate. The relationship between post-BP and graft survival was significant for systolic BP (P = 0.003, logistic regression), diastolic BP (P = 0.007), and MAP (P < 0.0001). By multivariate analysis (Table 2), recipient age, time of the AR, graft function, particularly after AR, and post-BP levels correlated with graft survival.

When the analysis above was calculated considering graft survival time as the dependent variable, the results were similar. Thus, shorter graft survival time correlated by both univariate and multivariate Cox analysis with (a) AR that occurred late during the first year post-transplant (P < 0.0001), (b) serum creatinine level pre-AR (<0.00001), peak-Cr (P < 0.0001) or post-Cr (P < 0.0001), and (c) post-BP (P < 0.0001, multivariate analysis).

The histopathological grade of the AR episode, analyzed in patients with one AR episode, did not correlate with long-term allograft survival. In addition, the following variables did not correlate significantly with graft survival: donor and recipient variables (race, age, and gender), HLA matching, plasma renin activity reactivity, origin of the graft (LRD vs. CAD), and number of AR
Fig. 1. Kaplan–Meier plots of death censored graft survival in patients without acute rejection (AR; ¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿¿ ¿

Table 2. Correlations between graft survival beyond 6 months post-transplant and clinical parameters in patient with AR

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Univariate analysis</th>
<th>Multivariate analysis*</th>
</tr>
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<tbody>
<tr>
<td>Recipient age</td>
<td>0.04</td>
<td>Pre-Cr</td>
</tr>
<tr>
<td>Time of AR</td>
<td>&lt;0.0001</td>
<td>Peak-Cr</td>
</tr>
<tr>
<td>Pre-Cr</td>
<td>0.002</td>
<td>Post-Cr</td>
</tr>
<tr>
<td>Peak-Cr during AR</td>
<td>&lt;0.0001</td>
<td>—</td>
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<tr>
<td>Post-Cr</td>
<td>&lt;0.0001</td>
<td>—</td>
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<tr>
<td>Post-BP (MAP)</td>
<td>&lt;0.0001</td>
<td>0.0005</td>
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* Because all of the values of serum creatinine are related to each other, the pre-Cr, the peak-Cr and the post-Cr values were analyzed in separate multivariate models.

Blood pressure, graft function, and long-term graft survival after acute rejection

The results of the multivariate analysis displayed earlier in this article indicate that the relationship between graft survival and post-BP is statistically independent from graft function. However, post-BP and post-Cr correlate significantly with each other (r = 0.21, P < 0.0001 by Spearman), suggesting that there is an interdependence between the impact of graft function and BP on graft survival. To assess these relationships further, we re-analyzed graft survival after AR selecting only those patients who had a post-Cr < 2 mg/dl (N = 408). By multivariate analysis (logistic regression), the following variables correlated with worse graft survival: (a) younger recipient (P = 0.003), (b) elevated post-AR BP (systolic BP, P = 0.0009; MAP, P = 0.003), and (c) increasing time post-transplant (P = 0.02), such that the graft prognosis progressively worsens as the time post-transplant when the AR occurs increases. In this subgroup of patients, the post-Cr concentration did not correlate with graft survival. Figure 2 graphically displays the relationship between average systolic BP levels post-AR and graft survival in the subgroup of patients with post-Cr < 2 mg/dl. As can be seen, progressive increases in post-systolic BP, beyond 130 mm Hg, were associated with progressive declines in graft survival. It should be noted that the serum creatinine concentration was not significantly different among the groups of patients displayed in Figure 2: SBP < 130 (1.5 ± 0.5 mg/dl, N =
Average systolic BP post-acute rejection, mmHg

Fig. 2. Graft survival (%) in patients with acute rejection (AR) and a post-AR serum creatinine concentration ≤2 mg/dl. The X-axis displays the average systolic blood pressure (BP) following AR (P = 0.0009, logistic regression).

In contrast to the findings described above, in patients without AR, there was no significant correlation between graft survival and the average BP level during the first- or second-year post-transplant or during the entire follow-up period (P = 0.6).

Post-BP levels also correlated with graft survival time. Figure 3 displays death-censored graft survival plots in patients without AR or with AR, the latter divided according to the post-AR systolic BP level (P < 0.0001, Cox). Statistical analysis of subgroups of patients defined by their average post-BP indicated that graft survival time was not significantly different between patients without AR and those with AR and a post-AR average systolic BP <130 mm Hg. However, patients with AR and higher levels of post-BP had significantly shorter graft survival than patients without AR.

**Correlations between acute rejection histopathology and graft survival**

As noted earlier in this article, in patients with one AR episode, the histopathology of AR did not correlate with renal allograft survival beyond six-months post-transplantation. However, when renal allograft survival any time post-transplant was analyzed, the AR Banff score correlated with graft survival by univariate analysis (P = 0.003) but not by a multivariate analysis, which included other correlates of survival such as graft function, recipient age, and post-BP. Figure 4 displays the graft survival at any time post-transplant in four groups...
look for other factors that may account for that variability, because those additional factors may be amenable to treatment. Indeed, the demonstration that post-AR BP correlates with graft survival suggests the possibility that aggressive antihypertensive therapy may effectively prolong graft survival in patients with early AR.

The patient selection strategy used here permitted a clear separation of the effect of AR number on graft survival from other factors. However, our attempt to eliminate the impact of the time of AR on graft survival failed because even among AR that occurred during the first-year post-transplant, graft survival is worse the later the rejection occurs, an observation that is consistent with previous studies [4, 5]. The reason for this correlation is not entirely clear. However, based on these and previous results [6], it is reasonable to suggest that this relationship is due to the fact that the impact of AR on graft survival is at least in part determined by the function of the allograft prior to the AR episode. In support of this hypothesis, we show here that the serum creatinine concentration of pre-AR correlates with long-term graft survival post-AR. Also consistent with this interpretation is that the pre-Cr concentration is higher in patients with late AR than in those with early AR.

These results strongly suggest that the relationship between high BP levels and shorter graft survival post-AR is independent of both the race of the recipient and the level of graft function. Thus, (a) these correlations are statistically independent of each other. (b) The correlation between BP and survival was shown in Caucasians and African Americans when analyzed separately, and (c) when only patients with excellent graft function following AR (post-Cr ≤2 mg/dl) were selected, BP levels continued to be a significant predictor of graft survival. The impact of BP levels is such that among patients with post-Cr <2 mg/dl, graft survival was not different in patients without AR and in patients with AR as long as their average post-AR systolic BP was <130 mm Hg. It should be emphasized that the calculation of post-AR BP levels includes the achieved level of BP control, most often with treatment, throughout the life of the graft. In contrast to these findings, we could not demonstrate a relationship between BP levels and graft survival in patients without AR, and these results are in disagreement with a recently published study [13]. The reasons for the discrepancy may include the fact that the study by Opelz, Wujciak, and Ritz, because it included a larger number of patients, had more statistical power to detect the impact of BP on survival of grafts without AR, which, as suggested by that study, if present is likely to be mild. However, in addition, in our opinion, that large multicenter study did not effectively separate the impact of BP from the impact of graft function on graft survival. It seems reasonable to postulate that the deleterious effects of BP on graft survival are particularly pronounced in
certain populations of renal allograft recipients, including patients with AR and African American recipients [2].

The retrospective nature of the present study does not permit a conclusion that elevated BP levels are, at least in part, the cause of the shortened graft survival in patients with AR. However, this interpretation of the data is consistent with prospective studies done in patients with native renal diseases in which it has been shown that BP control has impressive beneficial effects slowing down the progression of renal insufficiency, particularly in patients with proteinuria [16, 17]. If these prospective studies can be reproduced in renal transplant recipients, BP control may prove to be an effective means to prolong renal graft survival, particularly in groups of recipients at high risk for graft loss. The potential beneficial effects of BP control on renal graft survival and the level of BP required to achieve this effect need to be evaluated in prospective studies. However, until those studies are completed, and based on the results of our study, it is reasonable to suggest that average systolic BP levels following AR should be maintained at least at 130 mm Hg.

The present study shows that the histopathological grade of AR correlates with graft survival during the first few months following the event, but not thereafter. This conclusion is in partial disagreement with previously published studies [7, 8]. However, previous studies and ours differ in several important aspects, including three that we believe are particularly relevant: (a) In this analysis, we included only patients with a single AR episode while this criteria was not applied to previous studies. This difference may be particularly relevant because, as shown before, the severity of AR increases with the number of AR [8]. (b) In addition, we separately analyzed the survival of patients with infarcts from those with vascular rejection. The prognosis of patients with infarcts is much worse than that of other recipients [15]. Thus, the inclusion of these patients in the analysis makes the prognosis of vascular AR appear to be much worse than it is actually, and (c) previous studies did not separate the impact of AR on short- and long-term graft survival. The lack of correlation between AR histopathology and long-term survival may not be surprising when considering the impact of other variables such as BP and graft function. With regards to the latter, a previous study showed no significant correlation between the histopathology of AR and nadir Cr post-AR [8]. In our opinion, the results of this study do not diminish the value of the renal biopsy during AR. However, it is clear that additional studies are needed to identify histological markers that are better predictors of the long-term consequences of AR.

These results emphasize the need for caution in defining an AR episode as “mild” or “severe” based only on histopathology. For example, among the patients included in this study, only those with a post-Cr ≤2 mg/dl and an average systolic BP <130 mm Hg had a graft survival time that was not statistically different from that of patients without AR. It is significant that only 10% of the patients in this study met these criteria. Furthermore, as can be seen in the graft survival plots, it may take several years to determine the impact of AR on survival.

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