Blood Pressure and the Survival of Renal Allografts from Living Donors

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Abstract. Levels of BP have been associated with increasing rates of renal allograft failure from cadaveric donors, independent of renal function. The effect of BP, a modifiable risk factor, on the failure rates of renal allografts from living donors is unknown and maybe obscured by the rate of decline of renal function from this source of organs. A nonconcurrent cohort study collecting data from 392 recipients of a renal allograft from a living donor during 1990 to 2001 was performed. Multivariable Cox regression models were fit by means of time-varying terms for systolic BP (SBP), diastolic BP (DBP), mean arterial BP (MAP), pulse pressure, and renal function during the first year after transplantation to study the association of BP and the time to allograft failure. Potential nonlinear relationships were considered by fractional polynomial terms. Recipient gender, preemptive transplantation, and time-varying terms for the natural logarithm of creatinine clearance and acute rejection were retained in the multivariable model. Including separate multivariable models with nonlinear terms for SBP ($P = 0.02$), for DBP ($P = 0.02$), or for MAP ($P = 0.05$) during the first year significantly improved the fit of the respective models and confirmed that there is an association of BP and allograft failure independent of renal function. Pulse pressure had neither a linear nor nonlinear association with allograft failure. In this nonconcurrent study, the level of BP during the first year affected the survival of renal allografts from living donors, independent of renal function. Further investigation is required to confirm the level of BP that is optimal to prevent foreshortened duration of survival.

Detecting a causal relationship between BP and the survival of renal allografts is complex because renal insufficiency is a described cause of hypertension. Several prior investigations limited to cadaveric renal allografts (CRT) have examined the relationship of BP and allograft survival conditional on a minimum duration of survival after transplantation (1–3). Investigators from the Collaborative Transplant Group studied CRT with a minimum survival of 1, 2, and 3 yr, and observed greater rates of allograft failure with increasing BPs measured at these times (2). However, adjustment for the level of allograft function at the time of BP measurements was not performed, leaving the relevance of BP to survival separate from renal function unclear. The effect of the levels of BP on CRT survival, independent of renal function, was subsequently addressed by a study of 277 recipients of a CRT that accounted for allograft function at the beginning of follow-up (3). In this study, increases of 10 mmHg in systolic BP (SBP), diastolic BP (DBP), and mean arterial BP (MAP) at 1 yr after transplantation increased the risk of allograft failure by 15%, 27%, and 30%, respectively, after adjustment for the level of allograft function.

Prior studies of the relationship of BP and CRT survival have not considered BP early within the posttransplantation period. BP levels during the first year have been considered less clinically relevant to the survival of CRT in the milieu of the more dominant insults by immunological and ischemic processes. Nonetheless, it is plausible that the levels of BP within this time frame significantly influence the survival of allografts, especially those transplanted from living donors, given the less prominent allograft injury from ischemia and immunological factors in this population. Enhancing the understanding of factors that influence the survival of renal allografts from living donors (LDRT) is of particular importance, given that living donors are the fastest growing source of renal allografts in the United States (4). The extended duration of survival of these allografts may detract from the importance of BP and lead to an underappreciation of a modifiable clinical exposure, resulting in avoidable foreshortened survival. The principal objective of this study was to assess whether the level of BP within the first year after transplantation provides predictive information, adjusted for the level of renal function, for LDRT survival.

Materials and Methods

Study Design

This nonconcurrent cohort study of recipients of renal allografts from living donors during 1990 to 2001 at the Hospital of the Uni-

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versity of Pennsylvania was designed to examine the potential association of BP during the first year after transplantation and long-term allograft survival. Data were abstracted from medical records for inpatient admissions and outpatient clinic visits at 2 wk and at 1, 2, 3, 6, 9, and 12 mo after transplantation. BP was measured during routine outpatient visits to the transplant clinic by an automated sphygmomanometer while the patient was seated. Creatinine clearances by the Cockcroft-Gault formula (5) were calculated from the serum creatinine levels and body weights recorded at each of the clinic visits. The status of allografts and of patients was verified with the United Network for Organ Sharing, and patient vital status was further confirmed using the National Death Index. This study was approved by the Institutional Review Board of the University of Pennsylvania.

Analytical Strategy

The primary outcome was allograft failure defined by the initiation of chronic dialysis, retransplantation, or death. Survival analysis, fitting Cox regression models, was used to examine the association of BP and the time to allograft failure. Time-varying terms were constructed for SBP, DBP, MAP (2/3 DBP + 1/3 SBP), and pulse pressure (PP = SBP − DBP), as well as for renal function during the first year. The incorporation of time-varying data on BP and renal function permitted investigation of the relationship of recent BP and renal function on the subsequent rate of allograft failure. Eligibility for inclusion in the multivariable model was explored in unadjusted models with $P < 0.20$ by the Wald test as the threshold criterion for inclusion. Factors were retained in the multivariable model if the addition of the variable resulted in $P \leq 0.10$ by the likelihood ratio test (6). The assumption of proportionality was examined by weighted testing of Schoenfeld residuals (7,8).

Nonlinear associations of SBP, DBP, MAP, and PP with allograft failure were explored in the Cox regression models by means of fractional polynomials (9–11). This technique affords flexibility in allowing for whole integer as well as fractional powers when examining continuous exposures. Fractional polynomials also have a primary advantage over percentile categorization of BP levels by not requiring individuals within each group to assume the mean value of BP of the categorical group, which reduces power for detecting effects if the effect of the exposure is concentrated in the ends of the distribution or if exposure effects are nonlinear (12,13). The multivariable models that included polynomial terms with or without a linear term for BP were compared with a multivariable model that included only a linear term for BP to determine which model better fit the data. $P \leq 0.05$ by the likelihood ratio test for this comparison was indicative of a nonlinear association. A similar strategy was used to allow for a nonlinear association of renal function (serum creatinine or estimated creatinine clearance) and allograft failure. The possibility that BP at particular times within the first year had greater or lesser magnitudes of associations with allograft failure was explored by fitting BP-by-time multiplicative interaction terms. Two-sided P values ≤ 0.05 were considered significant except were noted, and all analyses were performed using Stata version 7 (Stata, College Station, TX).

Results

Characteristics

There were a total of 392 recipients of a renal allograft from a living donor with a mean time of follow-up of 1050 d (range, 39 to 4297 d). Donors were more frequently white women; recipients were more frequently white men, and glomerulonephritis was the most common cause of end-stage renal disease (ESRD) (Table 1). Of the transplant pairs, 99.7% had a donor with the identical race of the recipient. The mean 5-yr allograft survival was 77.8% (95% confidence interval, 72.0 to 83.0), consistent with reported national rates of allograft survival (4).

Table 1. Transplant characteristics[a]

Recipients	
race	
white	77.8%
non-white	22.2%
gender	
male	58.7%
age	
mean (SD)	40.2 (12.3)
range	(18 to 75)
Donors	
race	
white	78.0%
non-white	22.0%
gender	
male	34.3%
age	
mean (SD)	41.8 (10.9)
range	(18 to 70)
Cause of ESRD	
diabetes mellitus	23.1%
hypertension	8.3%
glomerulonephritis	38.6%
interstitial	7.9%
polycystic	7.4%
other	14.7%
Chronic dialysis	
preemptive	25.6%
peritoneal dialysis	21.2%
hemodialysis	53.2%
Level of HLA matches	
0	9.0%
1	11.9%
2	7.5%
3	42.3%
4	8.5%
5	1.6%
6	19.3%
Relationship to donor	
sibling	49.2%
parent	18.2%
offspring	9.7%
other related	2.1%
spouse	14.6%
other unrelated	6.2%
Use of induction therapy	12.6%
Type of calcineurin inhibitor at discharge from transplantation	
none	4.9%
cyclosporine	61.8%
tacrolimus	33.3%

* ESRD, end-stage renal disease; HLA, human leukocyte antigen.

Of the 72 persons who had an allograft failure, 11 (15.6%) had a failure due to death from any cause.

Unadjusted Analysis of Associations with Allograft Failure

Pressures throughout the first year are presented in Figure 1. Significant correlations existed between SBP and DBP ($r = 0.59$, $P < 0.0001$), SBP and PP ($r = 0.83$, $P < 0.0001$), and MAP and PP ($r = 0.46$, $P < 0.0001$). A low correlation was observed between DBP and PP ($r = 0.04$, $P \leq 0.08$).

In Table 2, SBP measured during the first year was divided into categories. Within each SBP category, the total amount of person-time spent by individuals is presented, along with the incidence rates of allograft failure. A comparison of the crude incidence rates across categories suggests that there is a potential association between the levels of SBP and allograft failure. However, a linear relationship may not best characterize the effect of BP. Similar observations were made for DBP and MAP.

Constraining the associations of allograft failure with SBP, DBP, MAP, or PP (using time-varying terms) to a linear form revealed that SBP and PP had unadjusted associations with allograft failure that exceeded the criterion for inclusion in the multivariable model ($P \leq 0.17$ and $P \leq 0.12$, respectively) (Table 3). Nonetheless, linear and nonlinear associations of BP were still examined in the multivariable models.

Allograft failure was observed to have significant unadjusted associations with recipient gender and race, donor race, preemptive transplantation, and the levels of HLA matching (Table 3). Renal function during the first year, reflected by a time-varying term for either serum creatinine or calculated creatinine clearance, was also associated with an increasing rate of failure.

Independent Associations of BP with Allograft Failure

Multivariable models separately containing a linear term for SBP, DBP, MAP, or PP were fit. Collinearity of variables (donor and recipient race, HLA matching and unrelated donor, and calculated creatinine clearance and serum creatinine) was accommodated by alternatively fitting these variables into the multivariable model. The following variables subsequently satisfied criteria to be retained in the multivariable models: recipient gender, preemptive transplantation, unrelated donor or HLA matching, calculated creatinine clearance or serum creatinine, and acute rejection. Adjustment for either of the alternative collinear variables did not affect the models. The time-varying terms for BP did not suggest that there was an adjusted linear association of SBP ($P = 0.25$), DBP ($P = 0.23$), MAP ($P = 0.40$), or PP ($P = 0.38$) with allograft failure. The use of fractional polynomial terms revealed that the addition of a variable representing the time-varying natural logarithm (Ln) of SBP over the first year significantly improved the fit of the model ($P = 0.02$), incremental to a time-varying linear term (Table 4). Similarly, the model for MAP had an improved fit to the data when a time-varying variable representing the natural logarithm (Ln) of MAP over the first year was included in addition to a time-varying linear term, $P = 0.03$. For DBP, the final model did not include a linear term, but rather two polynomials (square root of DBP, and Ln(DBP) $\times$ square root of DBP) for DBP varying over the first year best fit the data ($P = 0.05$). An adjusted nonlinear association of PP with allograft failure was not observed ($P > 0.50$). These models confirm that during the first year, SBP, DBP, and MAP have associations with the rate of allograft failure, independent of the level of renal function at the time of BP measurement. The magnitude of collinearity between SBP and DBP resulted in unreliable estimates of each in a multivariable model that included both parameters. Fitting PP into the multivariable models did not significantly change the adjusted estimates of the effects for SBP, DBP, or MAP. The BP-by-time interaction was nonsignificant ($P > 0.50$), suggesting that the magnitude of the BP association with allograft failure was unrelated to the time of BP measurement within the first year. Forcing the year

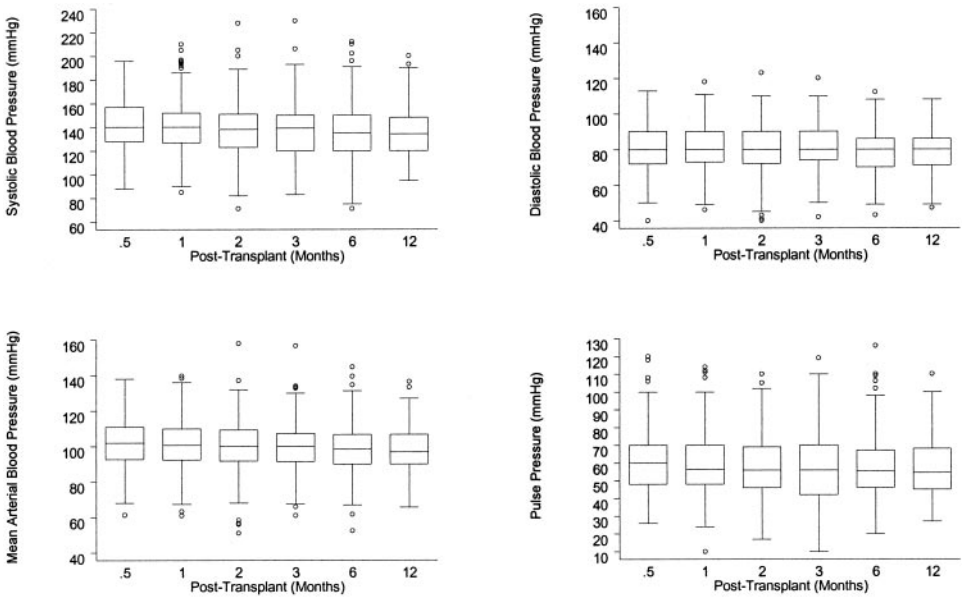

Figure 1. BPs throughout the first year after transplantation.

Table 2. Unadjusted rates of allograft failure according to categories of systolic BP in the first year and duration of exposure

Systolic BP	Person-time (d)	Incidence rate (per 1000 person-yr)	95% CI
71 to 85	1237	0.808	0.114 to 05.74
86 to 95	2547	0	0
96 to 105	13544	0.148	0.037 to 0.590
106 to 115	66257	0.075	0.031 to 0.181
116 to 125	65576	0.137	0.071 to 0.264
126 to 135	90080	0.122	0.068 to 0.221
136 to 145	96427	0.156	0.094 to 0.258
146 to 155	62059	0.161	0.087 to 0.299
156 to 165	42984	0.209	0.109 to 0.402
166 to 230	32241	0.124	0.047 to 0.331

Table 3. Unadjusted analysis of factors associated with allograft failure

	Hazard Ratio	95% CI	*P*
Recipient			
age (per 5 yr)	1.00	0.92 to 1.10	0.94
female (*versus* male)	1.68	1.08 to 2.62	0.02
non-white (*versus* white)	1.55	0.96 to 2.49	0.07
Donor			
age (per 5 yr)	1.00	0.91 to 1.11	0.97
female (*versus* male)	1.38	0.73 to 2.62	0.33
non-white (*versus* white)	1.60	0.99 to 2.58	0.05
Preemptive (*versus* non-preemptive)	0.42	0.21 to 0.81	0.01
Cause of ESRD (*versus* diabetes)			0.34
hypertension	0.81	0.41 to 1.89	
glomerulonephritis	0.56	0.32 to 0.99	
interstitial	0.89	0.39 to 2.07	
polycystic	0.33	0.08 to 1.41	
other	0.74	0.38 to 1.43	
Donor unrelated (*versus* related)	1.41	0.81 to 2.46	0.23
Six HLA match (*versus* 0 to 5 HLA Match)	0.63	0.31 to 1.27	0.20
Calcineurin inhibitor at time of discharge from transplantation (*versus* cyclosporine)			
none	0.93	0.34 to 2.57	0.89
tacrolimus	0.95	0.46 to 2.01	0.89
Acute rejection in first year[a] (*versus* None)	2.96	1.92 to 5.77	0.001
Systolic BP[a] (per 5 mm Hg)	1.05	0.98 to 1.12	0.17
Diastolic BP* (per 5 mm Hg)	1.05	0.93 to 1.18	0.43
Mean arterial BP[a] (per 5 mm Hg)	1.07	0.96 to 1.19	0.23
Pulse Pressure[a] (per 5 mm Hg)	1.06	0.98 to 1.14	0.12
Serum creatinine[a] (per 0.5 mg/dl)	1.26	1.20 to 1.33	0.001
Estimated creatinine clearance* (per 5 ml/min)	0.91	0.86 to 0.96	0.001

[a] Time-varying term throughout the first year post-transplant.

of transplantation and the type of calcineurin inhibitor administered at the time of discharge from the transplantation procedure did not affect the models.

The graphs in Figure 2 combine the information from the models in Table 4 in order that the terms for BP can be jointly interpreted to provide an indication of the magnitude of the association between varying levels of BP and the adjusted rate of allograft failure. The lower 95% confidence limits of the adjusted hazard ratios exceeded 1 when during the first year SBP was below 75 mmHg and above 159 mmHg; when DBP

Table 4. Multivariable analysis

	Mean Arterial BP			Systolic BP			Diastolic BP		
	HR (per mm Hg)	95% CI	*P*	HR (per mm Hg)	95% CI	*P*	HR (per mm Hg)	95% CI	*P*
First term for BP	1.05	1.02 to 1.09	0.002	1.03	1.01 to 1.05	0.004	0.01[a]	0.001 to 0.28	0.007
Second term for BP	0.19[b]	0.08 to 0.49	0.001	0.27[b]	0.12 to 0.60	0.002	2.39[c]	1.27 to 4.49	0.007
Unrelated donor (*versus* related)	1.80	0.91 to 3.56	0.09	1.82	0.92 to 3.58	0.09	1.69	0.85 to 3.37	0.13
Recipient gender (*versus* male)	1.79	1.03 to 3.11	0.04	1.75	1.01 to 3.04	0.05	1.81	1.04 to 3.16	0.04
Preemptive transplant (*versus* non-preemptive)	0.39	0.19 to 0.81	0.01	0.39	0.18 to 0.81	0.01	0.39	0.19 to 0.83	0.01
Estimated creatinine clearance (per Ln [ml/min])	0.53	0.38 to 0.75	0.001	0.53	0.37 to 0.74	0.001	0.53	0.37 to 0.74	0.001
Acute rejection in the first year (*versus* none)	3.31	1.40 to 7.83	0.007	3.16	1.33 to 7.50	0.009	3.51	1.46 to 8.40	0.005

[a] Per $\sqrt{(\text{mmHg})}$.

[b] Per Ln(mm Hg).

[c] Per $\sqrt{(\text{mmHg})} \times \text{Ln(mmHg)}$.

was below 43 mmHg and above 98 mmHg; and when MAP was below 56 mmHg and above 113 mmHg.

A series of ancillary analyses was performed to evaluate the sensitivity of the primary observations to various assumptions. First, analyses were repeated considering death from any cause as a censoring event. Second, the level of allograft function in the follow-up period immediately preceding the measurement of BP was considered instead of contemporaneous renal function to evaluate for potential overadjustment for renal function, leading to underestimation of associations. Third, time-varying indications of an occurrence of acute rejection during the follow-up period were included in multivariable models to account for the transient elevations of BP and renal function resulting from episodic rejections, creating an overestimation of associations. In all supplemental analyses, the primary observations were robust to varying assumptions.

Discussion

This study demonstrates that among recipients of renal allografts from living donors, BP throughout the first year after transplantation is an important determinant of allograft failure, independent of renal function. Furthermore, pressures at the times measured throughout the first year had equivalent importance to the rate of failure. These results are consistent with earlier studies demonstrating that BP later within the first year or later affects allograft function among recipients of CRT (1–3).

The largest study of BP and allograft survival from the Collaborative Transplant Group analyzed data from 29,751 recipients of CRTs. These investigators observed that SBP and DBP significantly predicted allograft failure among cohorts with minimum survival times (*e.g.*, 1 yr, 2 yr, 3 yr). Limiting the observations from this large study was the lack of consideration for the level of renal function at the time of BP measurements that might explain the observations, leaving unanswered the direction of the causal relationship. An earlier study that averaged MAP during the first 6 mo after transplantation among recipients of cadaveric allografts detected an increased risk of failure with MAP after consideration of renal function, but the effect was limited to African American recipients (1). Several other investigations have explored the importance of BP, measured at various times relative to transplantation, to allograft survival, but time-varying measures of BP and allograft function were not considered in the analyses (14,15). Ultimately, one study that examined recipients of cadaveric organs that had survived a minimum of 6 or 12 mo confirmed the effect of BP on the long-term survival of CRTs, independent of renal function (3).

Unlike previous investigations of BP and allograft failure that were limited primarily to organs from cadaveric donors as well as in the investigation of the nature of this relationship, this study considered a curvilinear association analogous to prior demonstrations of nonlinear associations of BP with other clinical events (16–18). Allowing for nonlinearity precluded the erroneous conclusion of no association of BP and survival of allografts from living donors. The significant collinearity of pressures within subjects did not permit reliable estimation of separate effects of SBP and DBP in this observational study, as described in an earlier population-based study (19).

PP has been associated with outcomes in nontransplant populations (20–22), but not consistently (18). The lack of an independent relationship and the insignificant contribution to rates of allograft failure from PP within our study suggest that predictive information for allograft failure is related predominantly to the levels of SBP or DBP rather than to the difference between pressures. The unimportance of PP is likely related to

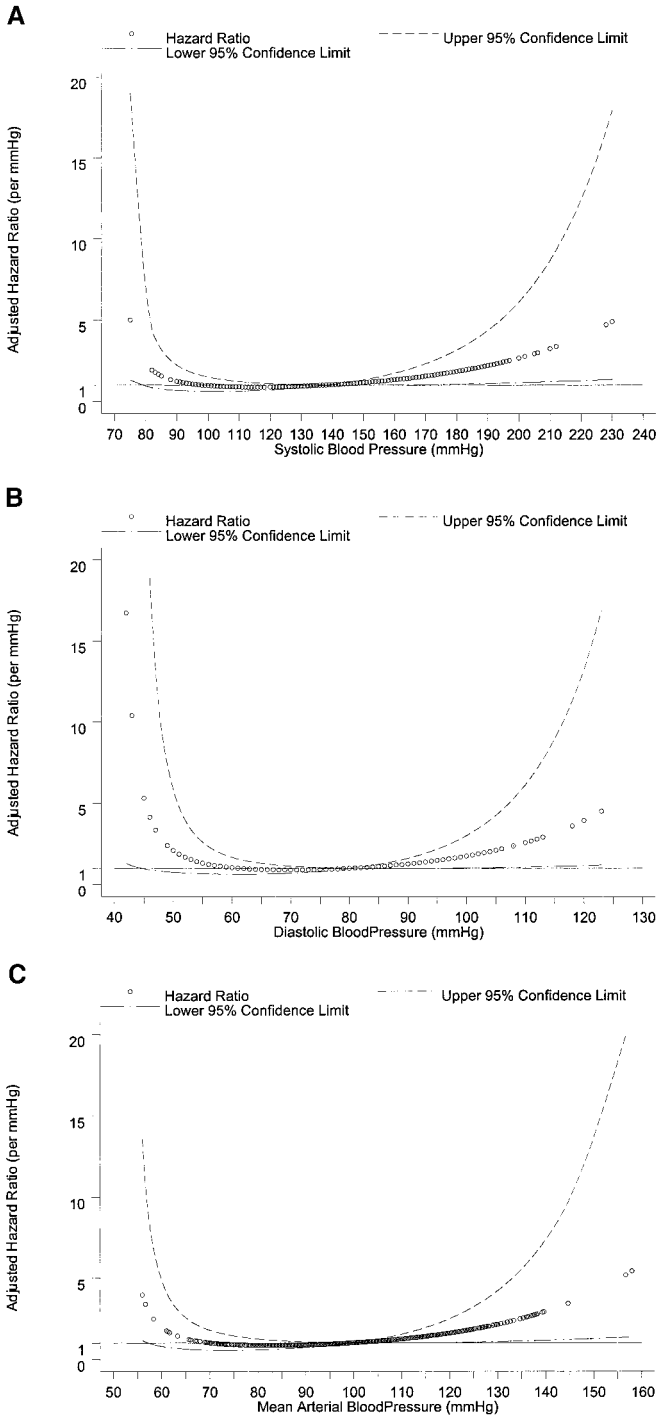

Figure 2. (a) Systolic BP during the first year and allograft failure. (b) Diastolic BP during the first year and allograft failure. (c) Mean arterial BP during the first year and allograft failure. All hazard ratios are adjusted for variables in Table 4.

the distribution of characteristics in this study population as well as to the magnitudes of proposed effects of PP. In comparison to the findings of an association of PP with the rate of progression to ESRD among nontransplanted individuals with type II diabetes and nephropathy in the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study, the present transplantation population under study was younger (40.2 yr *versus* 60.2 yr), 23.1% had diabetes, and less than 25% of the subjects had a PP that exceeded the threshold PP (>70 mmHg) above which the risk for ESRD progression was significantly associated within the RENAAL study.

We can simply speculate to explain the form of BP relationships depicted in Figure 2. It is plausible, and consistent with an animal model of denervated renal allografts (23), that autoregulation of renal blood flow is impaired in renal allografts such that below a range of flow there is chronic ischemia, above which the elevated pressure may ultimately lead to arteriolosclerosis and fibrosis. This hypothesis is further supported by data demonstrating pressure-dependent renal blood flow among humans who have chronic renal disease (24). The persistence of a curvilinear association in analyses that assigned death to be a censoring event argues that mortality from any cause does not explain the observations made in this investigation. Furthermore, the patients who had SBP below the first percentile (SBP <91 mmHg) were not unusual in other clinical parameters that might suggest that comorbidities determined their risk for allograft failure indirectly through the level of BP. For example, these individuals had BP readings repeated over several clinic visits that confirmed their exposure; they tended to be have diabetes, and they had a mean weight of 139.3 lb and a mean serum creatinine of 1.2 mg/dl at their outpatient visits during the first year after transplantation.

Appreciating the existence of a relationship between BP and survival of allografts from LDRT independent of renal function is important. The complex relationship between renal function and BP and the duration of survival of allografts from living donors likely obscured whether or not the level of BP affected allograft survival. This study, in conjunction with earlier studies, provides substantive evidence that BP, a modifiable risk factor, is significantly associated with the risk of allograft failure. Interestingly, this association appears not be simply linear in form. The nature of this relationship observed in this study suggests that inadequate control of BP as well as overzealous control may not be tolerated by the transplanted kidney, which has impaired autoregulation of perfusion pressure, leading to shortened survival.

There are several limitations to this study. First, we did not collect data on the type and number of therapeutic agents for hypertension used by the subjects. This study, focusing on BP, would account mechanistically for these agents, and any effect of these medications on allograft failure would then be independent of level of BP and would have been unlikely to be detected in this observational study. We cannot exclude the notion that there maybe further association of the types of BP-lowering agents and allograft failure. Second, BP beyond the first year was not considered in these analyses. The analyses cannot refute that BP within the first year may rather be an indication of the level of BP later in the posttransplantation period that may also be a relevant period causally related to allograft failure. Third, data about the presence of protein in the urine of subjects were not routinely collected during this study period. There exists the possibility that the effect of the level of

BP may be related to the daily excretion of urinary protein. Last, the design of this study included the use of multivariable adjustment procedures, but residual confounding from factors that do not correlate with the factors studied cannot be excluded.

In conclusion, this study confirmed that in recipients of renal allografts from the most rapidly growing source of donors in the United States, BP during the first year after transplantation, independent of renal function, affects the rate of allograft failure. The optimal level of BP and the antihypertensive regimen to achieve these levels to reduce rates of failure remain to be determined in clinical trials.

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