Determinants of Hypofiltration during Acute Renal Allograft Rejection

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Abstract. This study sought to determine the extent to which GFR is decreased during acute renal allograft rejection in human subjects and to determine the mechanism of the decrease in GFR. Eight patients with biopsy-proven acute rejection were compared with 18 recipients of optimally functioning renal allografts. GFR and renal plasma flow (RPF) were measured as the clearance of inulin and para-aminomhippuric acid, respectively. Arterial BP was determined, blood was sampled, and plasma oncotic pressure (πA) was measured. Glomeruli obtained by biopsy during rejection were subjected to morphometric analysis, for determination of $K_f$. Control morphometric values for healthy glomeruli were provided by 10 living donors from whom biopsies were obtained at the time of organ donation. The subjects in the acute rejection group exhibited a significantly reduced GFR of $17 \pm 4$ ml/min per 1.73 m², compared with $72 \pm 4$ ml/min per 1.73 m² for control subjects ($P < 0.001$). With the use of a sensitivity analysis to take into account the unknown para-aminomhippuric acid extraction ratio, the RPF rate was calculated to have likely been significantly decreased, by 45 to 70%, in the acute rejection group. Neither the plasma oncotic pressure nor the mean arterial pressure differed between the two groups. Morphometric analysis revealed no difference in the single-nephron $K_f$ values for the acute rejection group, compared with the control group. These results indicate that acute renal allograft rejection causes a profound decrease in GFR, which is attributable to a decrease in RPF alone or in combination with a decrease in the glomerular transcapillary hydraulic pressure gradient ($\Delta P$).

Acute rejection in human renal allografts is manifested as an increase in serum creatinine levels associated with typical biopsy findings. The increase in serum creatinine levels, caused by a decrease in the GFR, often responds to pulse steroid therapy or antilymphocyte antibody therapy. The incidence of acute rejection in the first 1 yr after transplantation has decreased dramatically with the advent of new immunosuppressive agents. The incidence of acute rejection as a cause of allograft loss has also decreased, resulting in a remarkable improvement in short-term graft survival rates in the past two decades (1). However, long-term graft survival rates among patients who experience acute rejection are projected to be only one-half of those for patients without episodes of rejection (2). Chronic transplant nephropathy (also called chronic rejection) has been blamed for the long-term graft loss (3). Acute renal allograft rejection, although successfully treated, has been identified as a major risk factor for chronic rejection (4–7). Despite the pivotal role of acute rejection in both short- and long-term renal allograft function, neither the extent of the reduction in GFR during acute renal allograft rejection nor the mechanisms by which it occurs have been examined.

In this study, we sought to determine the extent to which GFR is decreased during acute renal allograft rejection in human subjects. In addition, we used a combination of physiologic and morphometric techniques to estimate three GFR determinants to elucidate the mechanism of the decrease in GFR. Our findings form the basis of this report.

Materials and Methods

Patients

Eight patients with graft dysfunction attributable to biopsy-proven acute rejection were recruited into the study. Seven of the subjects had received cadaveric renal transplants and one had received a living related donor transplant. Subjects were studied before biopsy and before any changes in their immunosuppressive regimens.

Eighteen patients with well functioning transplants from living related donors were used as physiologic control subjects. The control subjects had received their transplants 12 to 144 mo before the physiologic evaluations (Table 1). The physiologic control subjects had histories of excellent graft function, and only three of the 18 had been treated for fully reversible acute rejection (one episode each). There was no significant difference in the median ages for patients in the control group and the rejection group, i.e., 42 yr (range, 29 to 62 yr) versus 39 yr (range, 28 to 64 yr). However, the median allograft age of 3 mo (range, 0.8 to 68 mo) in the acute rejection group was significantly lower than the corresponding median allograft age of 52 mo (range, 12 to 144 mo) in the control group, reflecting the early occurrence of acute rejection during the posttransplant course (Table 1). Similarly, the mean dose of cyclosporine was significantly greater in the acute rejection group (6.0 ± 1.1 mg/kg per d), compared with the control group (3.0 ± 0.5 mg/kg per d, $P < 0.05$), because the former allografts were more recently transplanted. The dose of cyclosporine had not been changed for any subject before the study.
Immunosuppression

Table 1. Patient characteristicsa

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 18)</th>
<th>Acute Rejection (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yr)</td>
<td>42 (29 to 62)</td>
<td>39 (28 to 64)</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>9/9</td>
<td>6/2</td>
</tr>
<tr>
<td>Median age of graft (mo)</td>
<td>52 (12 to 144)</td>
<td>3 (0.8 to 68)</td>
</tr>
<tr>
<td>Type of graft</td>
<td>18 LRT</td>
<td>7 CRT, 1 LRT</td>
</tr>
<tr>
<td>CSA dose (mg/kg per d)</td>
<td>3.0 ± 0.5</td>
<td>6.0 ± 1.1b</td>
</tr>
</tbody>
</table>

a LRT, living related donor transplant; CRT, cadaveric renal transplant; CSA, cyclosporin A.  
b P < 0.05.

To spare the members of the physiologic control group the risk of a biopsy, a different set of control subjects were used for the morphometric studies. The control morphometric values for healthy glomeruli were provided by 10 living donors from whom biopsies were obtained at the time of organ donation. These biopsies were obtained before clamping of the renal vessels and were not subject to ischemic injury.

Immunosuppression

The subjects in the acute rejection group were maintained on standard triple-immunosuppression therapy with cyclosporine, prednisone, and mycophenolate mofetil. Twelve of the 18 physiologic control subjects received immunosuppression therapy with cyclosporine, prednisone, and azathioprine. The remaining control subjects had been weaned from cyclosporine and were treated with only prednisone and azathioprine, because of a rejection-free posttransplant course. There was no significant difference between the physiologic function of the control subjects treated with cyclosporine and that of the control subjects maintained on a cyclosporine-free regimen.

Physiologic Evaluations

Clearance studies in control subjects and subjects with rejection were performed in the General Clinical Research Center at Stanford University Medical Center. In the acute rejection group, the studies were performed before allograft biopsy or any treatment for acute rejection. Inulin clearance measurements were equated with GFR, and para-aminohippuric acid (PAH) clearance measurements were used for estimations of renal plasma flow (RPF). Priming doses of inulin (50 mg/kg) and PAH (12 mg/kg) were administered. Thereafter, inulin and PAH were administered by continuous infusion, to maintain constant plasma levels of 20 and 1.5 mg/dl, respectively. One hour after the priming infusion, arterial BP was determined by using standard sphygmomanometry, and blood was sampled for the measurement of plasma oncotic pressure. Four spontaneously voided, timed, urine collections were made, each bracketed by blood samples drawn from a peripheral vein. GFR was expressed as the average of the four timed inulin clearance values. A range of values for RPF was approximated by dividing the corresponding PAH clearance values by a range of possible values for the renal arteriovenous PAH extraction ratio. Because the latter quantity was not determined and because proximal tubule damage during acute rejection may decrease PAH extraction, we performed a sensitivity analysis to examine the effects of variations in PAH extraction on calculated RPF values. The concentrations of inulin and PAH were determined with automated assays (8,9). The concentrations of albumin in serum and urine were determined by immunochemical methods and plasma oncotic pressure was assessed by membrane osmometry, as described previously (10).

Morphometric Evaluations

Light Microscopy. One of two biopsy cores was fixed in Zenker’s fluid, dehydrated, and embedded in paraffin. Serial sections of 1- to 2-μm thickness were stained with periodic acid-Schiff reagent. All glomeruli in these sections were analyzed at the light-microscopic level. A dedicated computer system (Southern Micro Instruments, Atlanta, GA) with a video camera, monitor, microscope, and digitizing tablet was used to perform the measurements. The outline of each glomerular tuft in the section was traced onto the digitizing tablet at ×900 magnification, and the mean tuft cross-sectional area (A_{gt}) was determined by using computerized planimetry (11). Glomerular volume (V_G) was calculated from A_{gt} by using the formula

\[ V_G = \beta d(A_{gt})^{1/2}(f_s,f_i)^{-3} \]  

(1)

where \( \beta \) is a dimensionless shape coefficient (\( \beta = 1.38 \) for spheres), \( d \) is a size distribution coefficient used to adjust for variations in glomerular size (12), and \( f_s \) and \( f_i \) are correction factors for the tissue shrinkage associated with paraffin embedding and immersion fixation, respectively (13). We used \( d = 1.1 \), which corresponds to a distribution of glomerular sizes with a SD of approximately 25% of the mean size (12). We have determined that the values of the shrinkage factor for our embedding procedure and that for immersion fixation are \( f_s = 0.86 \) and \( f_i = 0.85 \), respectively (13). The median number of complete glomeruli in the biopsy cores was seven (range, three to 14) in the acute rejection group and 19 (range, four to 40) in the living donor control group.

Electron Microscopy. For transmission electron microscopy, tissue was fixed in 2% paraformaldehyde in 0.1 M cacodylate buffer and embedded in Epon. Toluidine blue-stained sections were then surveyed, to locate patent glomeruli entirely within the block. Ultrastructural analysis was performed on two glomerular profiles for each subject. Ultrathin sections (60 to 70 mm) of the glomeruli were stained with lead citrate and uranyl acetate. A complete montage of each glomerulus at ×2820 magnification was prepared, and line-intercept counting was used to calculate the fractional surface density (S_V) at the subendothelial aspect of the peripheral capillary wall by standard stereologic methods (12), where \( S_V \) is defined as the length density of the peripheral capillary wall from mesangial function to mesangial function. Six to eight images of peripheral capillary loops chosen at approximately uniform intervals from each of the glomerular profiles were then photographed at ×11,280 magnification, for evaluation of the frequency of epithelial filtration slits and the thickness of the peripheral glomerular basement membrane. Filtration slit frequency was determined by counting the total number of epithelial filtration slits and dividing that value by the total length of the peripheral capillary wall at the epithelial interface (14). The harmonic-mean basement membrane thickness (δ_{bmn}) was calculated for each individual, using the method of orthogonal intercepts (15).

\[ \delta_{bmn} = 8/3 \pi \times \delta'_{bmn} \]  

(2)

In this equation, \( \delta'_{bmn} \) is the apparent mean and 8/3 \( \pi \) is a factor to correct for the angle of sectioning.

Calculations

The total filtration surface area \( S \) was calculated from the equation

\[ S = S_V \times V_G \]  

(3)
where $S_v$ is the fractional surface density and $V_{ct}$ is the glomerular tuft volume, as defined above. The intrinsic hydraulic permeability of the glomerular capillary wall ($k$) was estimated from the filtration slit frequency and the basement membrane thickness by using the hydrodynamic model of viscous flow described by Drummond et al. (16).

In that model, the capillary wall consists of a large number of repeating structural units, each of which is based on a single filtration slit. The width of such a structural unit ($W$) is calculated from the filtration slit frequency (FSF) by using the equation

$$W = \frac{2}{\pi} \times \frac{1}{\text{FSF}}$$  \hspace{1cm} (4)

where $2/\pi$ is a stereologic factor that accounts for the random angle of sectioning.

By considering the capillary wall as a system of resistances in series, the overall hydraulic permeability can be calculated from the permeability of each component layer with the equation

$$K = \left( \frac{1}{k_{en}} + \frac{1}{k_{bm}} + \frac{1}{k_{ep}} \right)^{-1}$$  \hspace{1cm} (5)

where $k_{en}$, $k_{bm}$, and $k_{ep}$ are the hydraulic permeabilities of the endothelium, basement membrane, and epithelium, respectively.

The permeability of the epithelial layer was calculated by using the formula

$$k_{ep} = \frac{W_s}{W \times K_s}$$  \hspace{1cm} (6)

where $W_s$ is the fraction of the basement membrane area occupied by filtration slits and $W$ is the slit width ($W_s = W/W$). The permeability of the basement membrane ($k_{bm}$) was calculated by using equation 21 described by Drummond and Deen (17). Because resistance to water flow imposed by endothelial fenestrae is negligible, $1/K_{en}$ was ignored.

The single-nephron ultrafiltration coefficient ($K_f$) was calculated from the product of the filtration surface area ($S$) and the hydraulic permeability of the walls of patent glomerular capillaries ($k$) in the glomeruli, which were examined ultrastructurally.

### Statistical Analyses

Results are expressed as means ± SEM or median values as appropriate. An unpaired $t$ test was used to compare the physiologic findings for the acute rejection group and the control group. Depending on whether the distribution was gaussian or nongaussian, an appropriate test was used to test the significance of differences in glomerular structure between the biopsies with acute rejection and the control biopsies.

### Results

**Physiologic Studies**

Rejection episodes were histologically characterized by tubulitis in all eight instances. As judged by Banff 1997 diagnostic criteria, three of the subjects exhibited type IA or IB acute rejection. The remaining two subjects exhibited type IIA acute rejection, in which mild to moderate intimal arteritis was observed with the tubulitis (18). The baseline prerejection serum creatinine level in the acute rejection group was $2.0 \pm 0.1$ mg/dl. The mean serum creatinine level had increased to $4.0 \pm 0.6$ mg/dl at the time of biopsy-proven rejection but subsequently improved to $3.0 \pm 0.6$ mg/dl after therapy for the rejection episode. Glomerular filtration dynamics for the subjects with acute rejection and the control subjects are summarized in Table 2. The subjects in the control group exhibited an inulin clearance of $72 \pm 4$ ml/min per $1.73$ m$^2$. The subjects in the acute rejection group exhibited a significantly reduced mean inulin clearance of $17 \pm 4$ ml/min per $1.73$ m$^2$ ($P < 0.001$). The RPF values for the subjects with acute rejection and the control subjects are summarized in Table 3. With the assumption of a normal PAH extraction ratio of 0.9, the RPF of the control group averaged $377 \pm 73$ ml/min per $1.73$ m$^2$, compared with only $114 \pm 28$ ml/min per $1.73$ m$^2$ ($P < 0.005$) in the experimental group with acute rejection.

Because proximal tubule damage during acute rejection may decrease PAH extraction, we also calculated the RPF rate for the acute rejection group by assuming PAH extraction ratios ranging from 0.7 to 0.3. The resultant RPF rate remained significantly lower for the acute rejection group with PAH extraction ratios of 0.5 to 0.9. Only with PAH extraction ratios of $\leq 0.3$ would RPF not be significantly decreased in the acute rejection group (Table 3).

In contrast to the decreased glomerular flow rates, renovascular pressures in subjects with acute rejection were similar to those in control subjects. The onotic pressure averaged $24.4 \pm 3.9$ mmHg for the subjects with acute rejection, compared with $24.5 \pm 2.0$ mmHg for the control subjects ($P = \text{NS}$). The mean arterial pressure of $98 \pm 15$ mmHg in the subjects with acute rejection was similar to the control value of $104 \pm 10$ mmHg ($P = \text{NS}$) (Table 2).

### Glomerular Morphometric Features

The results of the morphometric studies are summarized in Table 4. Morphometric analysis revealed the filtration surface density and the glomerular volume to be similar in the subjects with acute rejection and the control subjects. Consequently, there was no significant difference in the capillary filtration

### Table 2. Glomerular dynamics

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Acute Rejection</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR (ml/min per 1.73 m$^2$)</td>
<td>72 ± 4</td>
<td>17 ± 4</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Oncotic pressure (mmHg)</td>
<td>24.4 ± 4.0</td>
<td>24.5 ± 2.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>98 ± 15</td>
<td>104 ± 10</td>
<td>0.3</td>
</tr>
</tbody>
</table>

### Table 3. Sensitivity analysis of RPF corrected for PAH extraction

<table>
<thead>
<tr>
<th>Condition</th>
<th>PAH Extraction Ratio</th>
<th>Corrected RPF (ml/min per 1.73 m$^2$)</th>
<th>$P$ Value, Acute Rejection versus Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.9</td>
<td>377 ± 73</td>
<td></td>
</tr>
<tr>
<td>Acute rejection</td>
<td>0.9</td>
<td>114 ± 28</td>
<td>$&lt;0.005$</td>
</tr>
<tr>
<td></td>
<td>0.7</td>
<td>147 ± 36</td>
<td>$&lt;0.005$</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>206 ± 51</td>
<td>$&lt;0.005$</td>
</tr>
<tr>
<td></td>
<td>0.3</td>
<td>344 ± 84</td>
<td>0.71</td>
</tr>
</tbody>
</table>

* RPF, renal plasma flow; PAH, para-aminohippuric acid.
surface area (S) (2.8 ± 0.5 versus 2.4 ± 0.3 × 10^5 μm^2, P = 0.5). Similarly, there was no significant difference in either the basement membrane thickness or the frequency of filtration slits between the groups. The corresponding hydraulic permeability (k) values were therefore not significantly different, averaging 2.3 ± 0.1 × 10^{-9} m/s per Pa in the acute rejection group and 2.4 ± 0.1 × 10^{-9} m/s per Pa in the control group (P = 0.7). Single-nephron Kf values (the product of k and S) were accordingly similar in the two groups, averaging 5.5 ± 0.5 nl/min-mmHg in the acute rejection group and 4.6 ± 0.6 nl/min-mmHg in the control group (P = 0.5).

**Discussion**

To the best of our knowledge, this study represents the first time that the GFR has been evaluated during episodes of acute rejection. Our physiologic control group of 18 living related donor transplant recipients provided us with an ideal value for the GFR with optimal graft function. The control subjects exhibited a mean single-kidney GFR of 72 ± 4 ml/min per 1.73 m^2, which was greater than the corresponding value for healthy binephric individuals, despite chronic exposure to cyclosporine. This elevation of GFR in the control group presumably reflects posttransplant compensatory hyperfiltration in response to the uninephric state.

In contrast, the GFR in subjects with acute rejection was profoundly decreased, to 25% of the ideal value observed in the control group. The magnitude of GFR is dependent on four determinants, i.e., RPF, glomerular transcapillary hydraulic pressure gradient (∆P), afferent oncotic pressure, and ultrafiltration coefficient (Kf). We have been able to exclude two of these determinants as causes of the low GFR in the acute rejection group. Afferent oncotic pressure values, as measured by membrane osmometry, were not different between the control and acute rejection groups (Table 2). Furthermore, morphometric analysis of glomeruli revealed that values for each of the determinants of Kf, namely hydraulic permeability (k) and the calculated filtration surface area (S), were unaltered from control values during the acute rejection episode. We thus infer that the single-nephron Kf is not significantly decreased and cannot be implicated in the observed hypofiltration. By exclusion, therefore, the decrease in GFR must be attributable to a decrease in the RPF rate and/or a decrease in the glomerular transcapillary hydraulic pressure gradient (∆P). The possible reduction in the RPF rate that we observed is unlikely to be solely an effect of cyclosporine treatment, because serum creatinine levels in the acute rejection group were increased in the absence of any increase in the cyclosporine dose. Indeed, the cyclosporine dose at the time of acute allograft rejection was often lower than the maintenance dose, possibly predisposing the patients to the observed rejection episodes.

Because all patients in this small series exhibited tubulitis, it is possible that the PAH extraction ratio was decreased. Because determination of this quantity is invasive, requiring cannulation of the allograft renal vein and of an artery, we resorted to a sensitivity analysis (Table 3). That analysis demonstrated that, unless the PAH extraction ratio was decreased to ≤0.3, the RPF rate must have been decreased. Specifically, with PAH extraction ratios of 0.5 to 0.9, the RPF rate would have been between 114 ± 28 and 206 ± 51 ml/min per 1.73 m^2, compared with 377 ± 73 ml/min per 1.73 m^2 in the control group (P < 0.005) (Table 3). Although the possibility of a PAH extraction ratio of ≤0.3 cannot be excluded, a decrease of that magnitude suggests urinary PAH excretion resulting from filtration only, with complete inhibition of tubular PAH secretion. Ivanyi et al. (19) demonstrated, by segmental analysis of infiltrating mononuclear cells, that tubulitis is predominately a distal process. In contrast, the organic anion transporter, which transports PAH from peritubular blood into tubular fluid and urine, is located on the basolateral membrane of proximal tubule cells (20,21). In the absence of direct proximal tubule injury, the PAH extraction ratio would not be expected to decrease below 0.5, indicating that RPF was likely decreased during the acute rejection.

The remaining determinant of GFR, i.e., the glomerular capillary transmembrane pressure gradient (∆P), cannot be assessed in human subjects. It represents the difference between the hydraulic pressure in the glomerular capillaries and the opposing hydraulic pressure in Bowman’s space. In postischemic acute renal failure, obstruction of tubule lumina by exfoliated cells has been demonstrated to decrease ∆P by elevating the upstream pressure in Bowman’s space (22). Tubule cell exfoliation is not a feature of acute rejection, however, and was not observed for any subject in this study. That finding makes elevation of Bowman’s space pressure during the rejection episode unlikely. Therefore, if ∆P is indeed reduced in acute rejection, it is more likely a consequence of a

**Table 4. Glomerular morphometric parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (n = 10)</th>
<th>Acute Rejection (n = 8)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filtration surface density (S_v) (μm^2/μm^3)</td>
<td>0.100 ± 0.003</td>
<td>0.117 ± 0.009</td>
<td>0.1</td>
</tr>
<tr>
<td>Glomerular volume (V_g) (μm^3 × 10^6)</td>
<td>2.7 ± 0.3</td>
<td>2.7 ± 0.3</td>
<td>0.9</td>
</tr>
<tr>
<td>Basement membrane thickness (δ_bm) (nm)</td>
<td>412 ± 27</td>
<td>416 ± 38</td>
<td>0.9</td>
</tr>
<tr>
<td>Filtration slit frequency (no./mm)</td>
<td>1094 ± 52</td>
<td>1078 ± 54</td>
<td>0.8</td>
</tr>
<tr>
<td>Hydraulic permeability (k) (1 × 10^{-9} m/s per Pa)</td>
<td>2.4 ± 0.1</td>
<td>2.3 ± 0.1</td>
<td>0.7</td>
</tr>
<tr>
<td>Capillary filtration surface area (S) (1 × 10^5 μm^2)</td>
<td>2.4 ± 0.3</td>
<td>2.8 ± 0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Single-nephron K_f (nl/min-mmHg)</td>
<td>4.6 ± 0.6</td>
<td>5.5 ± 0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>
decrease in glomerular capillary hydraulic pressure. The latter, in turn, could be a result of afferent arteriolar constriction, a phenomenon that would prevent normal transmission of arterial pressure into glomerular capillaries. If $\Delta P$ is decreased, then the phenomenon of afferent arteriolar vasoconstriction could be uniquely responsible for the GFR decrease, because it could also explain the likely reduction calculated for RPF. It is noteworthy that cyclosporin A selectively constricts afferent arterioles (23). Its higher dosage in the acute rejection group, compared with the control group (Table 1), could contribute to the large disparity in GFR between the two groups that we observed (Table 2). The natural history of azotemia suggests that the acute rejection observed in biopsies is the major cause of the observed hypofiltration, however. As stated previously, in no case was the azotemic episode preceded by an increase in the maintenance dosage of cyclosporin A. Furthermore, treatment of rejection resulted in a subsequent decrease in the level of azotemia, despite continuing cyclosporin A therapy throughout the episode, at each individual’s maintenance dosage. Rather, it is conceivable that a cytokine released by the infiltrating cells is a specific or disproportionate constrictor of afferent arterioles and is responsible for the alteration in glomerular hemodynamics that seems to underlie the observed hypofiltration.

So-called “protocol” biopsies, i.e., biopsies performed routinely according to a prearranged protocol, have revealed morphologic evidence of acute rejection in the absence of alterations in the level of azotemia (and presumably corresponding changes in GFR) (24). The phenotype and activation status of cells infiltrating the graft have been reported to be similar in acute rejection associated with enhanced azotemia and in silent rejection (25). One striking difference, however, is the finding of elevated levels of allograft inflammatory factor-1 in clinically evident acute rejection but normal levels in clinically silent rejection. Although allograft inflammatory factor-1, a product of macrophages, has no known vasoactive properties, it is possible that other vasoconstrictor cytokines are released during acute rejection when GFR is decreased but not when GFR remains stable. Future identification of such vasoactive factors and subsequent attempts to target them for pharmacologic blockade could lead to specific forms of therapy that are capable of ameliorating the decrease in GFR associated with acute rejection.

Acknowledgments

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