Maintenance and recovery stages of postischemic acute renal failure in humans

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1Division of Nephrology, 2Department of Radiology, 3Department of Pathology, and 4Department of Transplant Surgery, Stanford University School of Medicine, 5Division of Biostatistics, Department of Health Research Policy, Stanford University, Stanford, California 94305, and 6Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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Ramaswamy, Deepa, Geraldine Corrigan, Catherine Polhemus, Derek Boothroyd, John Scandling, F. Graham Sommer, Edward Alfrey, John Higgins, William M. Deen, Richard Olshen, and Bryan D. Myers. Maintenance and recovery stages of postischemic acute renal failure in humans. Am J Physiol Renal Physiol 282: F271–F280, 2002. First published August 15, 2001; 10.1152/ajprenal.00068.2001. 2001.—Postischemic injury in 38 recipients of 7-day-old cadaveric renal allografts was classified into sustained (n = 15) or recovering (n = 23) acute renal failure (ARF) according to the prevailing inulin clearance. Recipients of long-standing allografts that functioned optimally (n = 16) and living transplant donors undergoing nephrectomy (n = 10) served as functional and structural controls, respectively. A combination of physiological and morphometric techniques were used to evaluate glomerular filtration rate and its determinants 1–3 h after reperfusion and again on day 7 to elucidate the mechanism for persistent hypofiltration in ARF that is sustained. Glomerular filtration rate in the sustained ARF group on day 7 was depressed by 90% (mean ± SD); the corresponding fall in renal plasma flow was proportionately less. Neither plasma oncotic pressure nor the single-nephron ultrafiltration coefficient differed between the sustained ARF and the control group, however. A model of glomerular ultrafiltration and a sensitivity analysis were used to compute the prevailing transcapillary hydraulic pressure gradient (ΔP), the only remaining determinant of ΔP. This revealed that ΔP varied between 27 and 28 mmHg in sustained ARF and 32–38 mmHg in recovering ARF on day 7 vs. 47–54 mmHg in controls. Sustained ARF was associated with persistent tubular dilatation. We conclude that depression of ΔP, perhaps due partially to elevated tubule pressure, is the predominant cause of hypofiltration in the maintenance stage of ARF that is sustained for 7 days.

filtration dynamics; glomerular morphometry; tubule morphometry; ultrafiltration coefficient; filtration pressure

ALLOTRANSPLANTATION OF A CADAVERIC kidney is invariably followed by a postischemic-reperfusion injury (2, 8, 18). In a substantial minority (25–30%) of cases, the injury is sufficiently profound and prolonged to require dialytic therapy because of inadequate allograft function. The precipitating ischemic insult comprises renal underperfusion during the fatal illness of the donor, followed by a period of nonperfusion from the time the kidney is procured until completion of the vascular anastomosis to the iliac vessels of the recipient. Despite the cytoprotective effects of cooling the kidney to 4°C during the protracted period of nonperfusion (often ≥24 h), the magnitude of the postischemic injury is often sufficient to delay the onset of adequate allograft function for days or weeks.

We have shown that delayed graft function is associated with all the hallmarks of postischemic acute renal failure (ARF) in native kidneys. These include a sublethal injury to proximal tubule cells, one that is associated with impairment of intercellular tight junctions and an ensuing loss of cell polarity (1, 2, 17, 18). Notwithstanding nearly normal rates of renal plasma flow (RPF) (8), the “effective” glomerular filtration rate (GFR), as determined by inulin clearance, is depressed by ~90%. This reduction is attributable, in part, to a real decline in true GFR secondary to depression of the filtration pressure. In addition, there is a transtubular backleak of inulin, which leads to an underestimation of the calculated “true” GFR (2, 18).

The aforementioned dissipation of filtration pressure has been shown by micropuncture techniques in animal models of postischemic ARF to be the consequence of a decline in the glomerular transcapillary hydraulic pressure gradient (ΔP), the outward driving force for the formation of filtrate (4, 6, 33). In an earlier study, we used novel techniques to measure the GFR and its remaining determinants 1–3 h after reperfusion of cadaveric renal allografts. We then computed ΔP using a mathematical model of glomerular ultrafiltration (2). Our computations suggested that reduction of ΔP to a level similar to the opposing glomerular intracapillary oncotic pressure (πGC) was the predominant cause of

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filtration failure in this early or “initiation stage” of the postischemic renal injury. The purpose of the present study was to extend our observations to the “maintenance” stage of the injury in transplant recipients in whom the ARF was sustained for ≥7 days. By studying consecutive renal allograft recipients 7 days after transplantation, we observed not only sustained ARF but also transition to the “recovery” stage in those recipients with lesser degrees of postischemic injury. Accordingly, in addition to studying the mechanism of the decrement in GFR in sustained ARF, we have attempted to characterize the determinants of the increment in GFR that underlie the recovery from postischemic ARF. Our findings form the basis of this report.

METHODS

Patient Population

Thirty-eight patients undergoing renal transplantation at our institution gave informed consent to a study of allograft glomerular ultrafiltration and three of its determinants, namely, RPF, afferent oncotic pressure (\(\pi_A\)), and the glomerular ultrafiltration coefficient (\(K_f\)). Each was studied according to a protocol approved previously by the Panel for Research in Human Subjects at Stanford University. They ranged in age from 37 to 64 yr, and 30 were men. The transplants were exclusively from “heartbeating,” cadaveric donors. Donor age ranged from 14 to 64 yr. Each subject was studied on two occasions: on the day of surgery (day 0) between 1 and 3 h after vascular anastomosis and reperfusion of the allograft and on postoperative day 7. GFR and each of its three measurable determinants were evaluated in all 38 subjects on day 0. Whereas GFR and \(\pi_A\) were also determined in all 38 subjects on day 7, we were limited by logistical constraints at this time to evaluating only a single additional determinant of GFR, i.e., RPF or \(K_f\) in most subjects (\(n = 29\)). Only in the remaining nine subjects were RPF and \(K_f\) determined on day 7.

On day 7, the subjects were divided arbitrarily into two groups according to the urinary clearance of inulin, which should be regarded as the effective, rather than the true, GFR, because it does not take into account transstubular backleak of filtrate (18). Group 1 comprised 23 subjects who were classified as recovering from ARF by virtue of an inulin clearance \(\geq 20 \text{ ml/min}\). Group 2 comprised the remaining 15 subjects who were classified as exhibiting sustained ARF because of persistent depression of inulin clearance <20 ml/min. The latter value was selected because it represented depression of GFR by 75% below the average value in a group of control subjects who provided an average of values for the renal allograft (24). Glomerular filtration dynamics were evaluated 13–66 mo after transplantation on a single occasion in these control subjects, who were 16 recipients of long-standing renal allografts that were donated by a living sibling or parent and had never undergone a known episode of rejection. A second control group comprised 10 living donors of a healthy kidney for transplantation into a relative. They provide normal values for the quantitative assessment of tubule obstruction and of those glomerular structures that determine \(K_f\). Each gave permission for two cores of kidney tissue to be taken by needle biopsy, under anesthesia, during donor nephrectomy.

Transplantation Procedures

Management of cadaveric donors. All cadaveric donors in this series died of a severe brain injury. Crystalloid fluids and dopamine (0.1–0.5 \(\mu\)g·kg\(^{-1}\)·min\(^{-1}\)) were infused in an effort to maintain systolic blood pressure at >90 mmHg and urine flow at >50 ml/h. Cadaveric organ procurement was coordinated by the California Transplant Donor Network. A neurologist in each participating center diagnosed brain death using clinical criteria. With the heart still beating, the donor was taken to an operating room, where the renal artery and vein were exposed. To minimize the warm ischemic time, the kidneys were first cooled in situ by flushing the renal circulation with cold University of Wisconsin preservation solution. The kidneys were then removed and stored in the same solution at 4°C until transplantation.

Management of transplant recipients. All 38 recipients had end-stage renal failure that had resulted in anuria and required dialytic therapy. Thirty-four recipients in the present series were receiving maintenance hemodialysis therapy, and four were receiving chronic ambulatory peritoneal dialysis. All recipients on maintenance dialysis were dialyzed within the 24 h preceding the transplantation. Peritoneal dialysis catheters were drained and capped before surgery.

General anesthesia was induced with narcotic agents and maintained with isoflurane. An indwelling bladder catheter and a central venous line were inserted after induction of anesthesia. The extraperitoneal space was entered through a lower-quadrant abdominal incision. The external iliac artery and vein were identified, skeletonized for a distance of 8 cm, and clamped proximally and distally. Methylprednisolone (1 g) and azathioprine (10 mg/kg) were then infused intravenously. The kidney graft was removed from the icd storage solution, and the renal artery and vein were anastomosed end-to-side to the corresponding recipient iliac vessels. All clamps were then released. The “rewarming time” (from the end of cold storage until completion of the anastomoses) was recorded. Mannitol (0.5 g/kg) was infused just before release of the vascular clamps. Each recipient’s bladder was filled with an irrigating solution containing neomycin, bacitracin, and heparin. The donor ureter was then spatulated, the recipient bladder mucosa incised, and a ureteroneocystotomy created. The detrusor muscle was reapproximated over the ureteroneocystotomy to create an antireflux tunnel. Crystalloid solutions were infused throughout the operative procedure to maintain central venous pressure (CVP) at >10 mmHg.

Postoperative immunosuppression. All recipients received immunosuppressive therapy with prednisone and either mycophenolate mofetil or azathioprine during posttransplantation week 1. These agents are not known to impair renal blood flow. In addition, subjects received a third immunosuppressive agent during posttransplantation week 1, i.e., cyclosporine (\(n = 34\)) or tacrolimus (\(n = 4\)). The latter two agents are renal vasoconstrictors. They were used in modest dosages to achieve whole blood trough levels of 300–400 ng/ml for cyclosporine and 10–15 ng/ml for tacrolimus.

Protocol

Evaluation of early allograft function. The GFR and its determinants were evaluated during the first 3 h after reperfusion of the allograft. Renal blood flow was determined 45–60 min after reperfusion by Doppler flow probe using an ultrasonic transit time flowmeter (model HT 107, Transonic Systems, Ithaca, NY). A snugly fitting 12- to 16-mm-diameter flow probe was placed around the renal vein. The iliac fossa was then filled with saline to optimize ultrasonic determinations. Triplicate determinations were recorded on a precalibrated digital readout at 2-min intervals. The coefficient of variation of the three measurements was 15%, and renal
blood flow was expressed as the median value. Mean arterial pressure was simultaneously determined by Dynmap and CVP by transducer. Renal vascular resistance was calculated by dividing the arteriovenous pressure drop by renal blood flow. RPF was calculated from the product of renal blood flow (RBF) and the hematocrit (Hct) of venous blood (expressed as a fraction) as follows

\[
RPF = \frac{RBF(1 - Hct)}{(1)}
\]

On completion of the foregoing hemodynamic determinations, an allograft biopsy was performed using a gun biopsy device with a 16-gauge needle (Monopart, Bard, Covington, CA). It was divided into portions for examination by light and electron microscopy. The portion for light microscopy was fixed in Zenker's fluid, dehydrated, and embedded in paraffin. The portion for electron microscopy was fixed in 2.5% glutaraldehyde buffered with cacodylate and postfixed in 2% osmium tetroxide for 60 min. The fixed tissue was then embedded in Epon after passage through a series of graded ethanols.

Once the surgical procedure was complete, the irrigating solution was rinsed out of the bladder to permit determination of the effective GFR by substitution of endogenous creatinine for inulin as a filtration marker (2). This substitution was made because anesthetic or other agents used during surgery interfered with our inulin assay. Furthermore, we have shown that creatinine and inulin clearances are in close agreement under conditions of postischemic renal injury (2, 22). Arterial and venous pressures were determined, and venous plasma was sampled for the determination of oncotic pressure (\(\pi_v\)). Two timed 30- to 60-min urine collections were then made via the Foley bladder catheter. Each urine collection was bracketed by a 10-ml sample of venous blood. Plasma and urine samples were then assayed for true creatinine levels. We also determined the osmolality and sodium concentration of each urine and plasma sample and used the urine-to-plasma osmolality ratio and the fractional excretion of sodium as indexes of tubule function. The second examination was performed on posttransplantation day 7. Arterial pressure was determined by Dynmap. A priming dose of inulin (50 mg/kg) was followed by a sustaining infusion calculated to maintain plasma inulin concentration constant at 20 mg/dl. After the 60-min equilibration period, four timed urine collections were made. A blood sample was drawn to bracket each urine collection. Venous plasma from the initial sample was used to determine \(\pi_v\). Effective GFR was calculated as the average of the four individual inulin clearances. The same urine and blood samples were used to calculate the simultaneous fractional excretion of sodium and the urine-to-plasma osmolality ratio. After clearance determinations, subjects underwent a repeat needle biopsy of the renal allograft \((n = 19)\) and/or a determination of allograft blood flow using cine-phase-contrast magnetic resonance imaging (cine-PC-MRI, \(n = 28\)). As stated previously, whereas 9 individuals underwent both of the latter examinations, the remaining 29 individuals underwent a biopsy or a cine-PC-MRI.

The cine-PC-MRI procedure has been described by us in detail elsewhere (24). PC-MRI depends on the use of magnetic field gradients to acquire velocity information, in image format, from phase data. When PC-MRI data are acquired at specific phases of the cardiac cycle, the technique is known as cine-PC-MRI. If the phase-contrast acquisition is encoded for motion through the imaging plane, the product of the average velocity in a region encompassing a blood vessel and the vessel area yields the flow rate. The computed flow rates at each point in the cardiac cycle are then averaged and scaled to yield the average flow rate through the vessel (ml/min).

MRI scanning was performed using a 1.5-T (General Electric Medical Systems, Milwaukee, WI) whole body MRI scanner, a 9-in.-diameter receive coil positioned over the transplant kidney, and the body coil used for RF transmission. The plane of acquisition for the cine-PC-MRI was defined using gradient-recalled-echo images of the allograft vein, with the acquisition plane set as perpendicular as possible to the transplant renal vein near the anastomosis with the external iliac vein. For the cine-PC-MRI acquisitions, the following conditions were employed: electrocardiogram gating, respiratory compensation, pulse repetition time of 25 ms, echo time of 12 ms, slice thickness of 4 mm, and a maximum flow encoding velocity of 50 cm/s. Total acquisition time for each cine-PC-MRI sequence was 2.5 min, precluding breath holding. However, respiratory motion is trivial in the renal allograft because of its pelvic location, and we previously showed that renal blood flow measured by cine-PC-MRI is similar to that determined by \(p\)-aminohippurate (PAH) clearance in our control subjects, whom we assume to have a normal renal PAH extraction ratio (24). After acquisition of data, an analysis of renal blood flow was performed off-line. Dedicated software was used to compute and integrate renal blood flow from the product of velocity and renal vein cross-sectional area through 16 equal phases of the cardiac cycle. RPF was calculated from renal blood flow using Eq. 1. Renal vascular resistance was again calculated from the arteriovenous pressure drop (mean arterial pressure – CVP) divided by renal blood flow. Because the central venous line had been removed from all subjects before postoperative day 7 and fluid balance had been restored to normal at this time, we assumed a CVP of 5 mmHg in each instance.

Laboratory determinations. Concentrations of inulin in urine and plasma were determined by the autoanalyzer method of Fieldbo and Stamey using resorcinol as the colorimetric reagent. The concentration of creatinine in urine and plasma was determined by an automated rate-dependent picrate method using a creatinine analyzer (Creatinine Analyzer 2, Beckman Instruments, Fullerton, CA). This method minimizes the influence of slow-reacting, non-creatinine chromagens and thus provides an estimate of the true creatinine concentration. Concentrations of sodium were determined by ion-selective electrode (NOVA 11, NOVA Biomedical, Waltham, MA) and osmolality by a vapor pressure osmometer (model 5500, Wescor, Logan, UT). The oncotic pressure in venous plasma was taken to be the same as that entering the glomerular tuft (\(\pi_v\)) and was measured directly by membrane osmometry using a colloid osmometer (model 4400, Wescor), as described by us previously (7).

** Morphological Studies**

Glomerular morphometry. Sections (1-μm thick) of the paraffin-embedded biopsy material were cut and stained with periodic acid-Schiff reagent. A dedicated computer system (Southern Micro Instruments, Atlanta, GA) consisting of a videocamera, monitor, light microscope, and digitizing tablet was used to perform measurements (2). The average number of glomeruli examined per day 0 biopsy was 18 in the recovering group and 12 in the sustained ARF group. Corresponding numbers of glomeruli in day 7 biopsies were 6 and 6, respectively. The average number of glomeruli in the control group was 21. The outline of each Bowman's capsule and glomerular tuft in the cross section was traced onto the digitizing tablet at ×900 magnification. The cross-sectional areas within Bowman's capsule (\(A_{BC}\)) and of the glomerular tuft (\(A_c\)) were computed using area perimeter analysis. The
difference between $A_{BC}$ and $A_A$ yielded the area of Bowman’s space ($A_{BS}$). Glomerular volume ($V_G$) was calculated from $A_A$ and corrected to account for the tissue shrinkage associated with paraffin embedding using a linear shrinkage factor ($f_s$) (2)

$$V_G = \frac{\beta}{d} A_A f_s^{-3}$$

where $\beta$ is a dimensionless shape coefficient ($\beta = 1.38$ for spheres) and $d$ is a “size distribution coefficient,” which is introduced to account for variations in glomerular size. We used $d = 1.1$, which corresponds to a distribution of sizes with a standard deviation of 25% of the mean size (2). We have determined that, in our experimental procedure for tissue fixation, $f_s = 0.86$.

Epon-embedded cores of day 7 biopsies for electron microscopy contained no glomeruli in a single subject. Glomeruli from the remaining 18 subjects (9 from each group) were subjected to morphometric analysis. The corresponding tissue from the day 0 biopsy was examined in parallel to permit a paired comparison in these 18 individuals. Toluidine blue-stained 1-μm sections of the Epon-embedded material were examined to select the two glomeruli closest to the center of the block. Ultrathin (60–70 nm) sections of these glomeruli were cut, stained with uranyl acetate and lead citrate, and photographed. A complete montage of each glomerulus was prepared at ×2,820 magnification. Point and intercept counting was then used to determine the peripheral capillary surface area ($S$), which was defined as the interface between the peripheral capillary wall and epithelium and calculated as

$$S = S_V V_G$$

where $S_V$ is the surface density of peripheral capillary wall (expressed as length of peripheral capillary wall per unit cross-sectional area of glomerulus). Eight electron photomicrographs ($\times 11,280$) were then obtained from each of the two glomerular profiles to evaluate the thickness of the glomerular basement membrane and frequency of epithelial filtration slits (13). The harmonic mean basement membrane thickness ($\delta_{bm}$) was calculated for each individual from the measured (apparent) harmonic mean thickness ($\delta_{m}$) as follows

$$\delta_{bm} = \frac{8}{3\pi} \delta_m$$

where $8/(3\pi)$ is a correction factor to account for the random angle of sectioning. The filtration slit frequency (FSF) was determined by counting the total number of slits captured on the electron photomicrographs and dividing this number by the corresponding length of the peripheral capillary wall. The mean distance between filtration slits ($W$) was computed as follows

$$W = \frac{2}{\pi} \frac{1}{FSF}$$

where $2/\pi$ is a correction factor derived by Drumond et al. (13) to account for the random angle of sectioning. Tissue morphometry. Abnormalities of tubule structure were assessed by light microscopy using 1-μm sections stained with periodic acid-Schiff reagent. An 11 × 11 square grid was inserted into the eyepiece of the microscope. Point and intercept counting of seven grid fields at ×900 magnification was used to calculate the cross-sectional area of the lumens of all tubules in the seven fields. The percentage of proximal tubule cells that had exfoliated was also estimated. Point counting was used to count 500–1,000 tubule cells in each subject and to estimate the fraction of such cells that had sloughed off the tubular basement membrane and entered the tubular lumen (2).

Calculations

Glomerular capillary oncotic pressure. We computed $\pi_{GC}$ from the arithmetic mean of $\pi_A$ and $\pi_E$, which are the respective oncotic pressures of plasma entering the afferent and efferent arterioles, respectively. The $\pi_A$ was assumed to be the same as that measured directly in systemic venous blood. The $\pi_E$ was calculated as follows

$$\pi_E = \frac{\pi_A}{1 - FF}$$

where FF is the filtration fraction. That $\pi_{GC}$ can be equated with the arithmetic mean of $\pi_A$ and $\pi_E$ assumes a linear rise in oncotic pressure as plasma flows axially along the glomerular capillaries, an assumption that we have shown to be accurate to within 0.5 mmHg (7).

Glomerular ultrafiltration coefficient. The overall $K_f$ for the transplanted kidney is the product of the glomerular capillary hydraulic permeability ($k$) and the total surface area available for filtration in all glomeruli. The total surface area was computed from the single nephron value ($S_f$, determined as described above) and estimates of the total number of nephrons. The baseline value of the total number of nephrons was taken to be 0.7 or $1.0 \times 10^6$ (14, 25). The effective hydraulic permeability was estimated from the individually measured values of basement membrane thickness, FSF, and $W$ by using the structural-hydrodynamic model of Drumond and Deen (12). Briefly, that model approximates the glomerular capillary wall as consisting of a large number of repeating structural units, each unit being based on a single filtration slit. Within a structural unit are representations of the individual layers of the capillary wall, namely, the fenestrated endothelium, the basement membrane, and the epithelial filtration slits with slit diaphragms. By solving the differential equations describing viscous flow through each of these layers and using the concept of resistances in series, a value for $k$ is obtained. In addition to the values of basement membrane thickness, FSF, and $W$ measured in the present study, a number of other quantities are needed as inputs for the calculations of $k$. The other quantities, which include the intrinsic (Darcy) permeability of the glomerular basement membrane and the dimensions of various other structures, were estimated from data reported for normal rats, as described in detail previously (13). The values of the other inputs used here are identical to those given by Drumond et al. (see Table 1 in Ref. 13).

Glomerular transcapillary hydraulic pressure difference. The $\Delta P$ was computed from GFR, RPF, $\pi_A$, and $K_f$ (10), as described in detail by Alejandro et al. (2). In the model employed, the glomerular capillary network is idealized as a number of identical capillaries in parallel, and steady-state mass balance equations are used to compute variations in plasma flow rate and protein concentration with distance along a representative capillary. It was assumed that $\Delta P$ is constant along a capillary.

Statistical Analysis

Because the distribution of many of the measured variables was not Gaussian, comparisons between and among groups of measurements were made with one- or two-sample...
Table 1. Glomerular filtration dynamics

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Sustained</th>
<th>Recovery</th>
<th>Day 0</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GFR, ml/min</strong></td>
<td>80 ± 20</td>
<td>7 ± 6*</td>
<td>17 ± 11†</td>
<td>8 ± 8*</td>
<td>50 ± 20†‡</td>
</tr>
<tr>
<td><strong>RPF, ml/min</strong></td>
<td>384 ± 121</td>
<td>225 ± 53*</td>
<td>243 ± 97*</td>
<td>239 ± 98*</td>
<td>336 ± 139</td>
</tr>
<tr>
<td><strong>FF, %</strong></td>
<td>22 ± 5</td>
<td>3 ± 3*</td>
<td>9 ± 6†</td>
<td>4 ± 4*</td>
<td>18 ± 12†‡</td>
</tr>
<tr>
<td><strong>πa, mmHg</strong></td>
<td>23.7 ± 2.2</td>
<td>23.2 ± 3.3</td>
<td>21.3 ± 3.3*</td>
<td>23.8 ± 4.0</td>
<td>20.8 ± 2.2†‡</td>
</tr>
<tr>
<td><strong>MAP, mmHg</strong></td>
<td>103 ± 10</td>
<td>100 ± 12</td>
<td>97 ± 14</td>
<td>104 ± 12</td>
<td>113 ± 9‡</td>
</tr>
<tr>
<td><strong>Renovascular resistance, mmHg·min⁻¹⁻¹</strong></td>
<td>168 ± 48</td>
<td>278 ± 60*</td>
<td>315 ± 146*</td>
<td>346 ± 158*</td>
<td>288 ± 132*</td>
</tr>
</tbody>
</table>

Values are means ± SE. GFR, glomerular filtration rate; RPF, renal plasma flow; FF, filtration fraction; πa, afferent oncotic pressure; MAP, mean arterial pressure. *P < 0.017 vs. control; †P < 0.017 vs. sustained group on given day; ‡P < 0.05, paired difference on day 7 vs. day 0.

Wilcoxon statistics or, where there were three groups to compare (control, sustained, and recovering ARF), by their extension, the Kruskal-Wallis statistic. The latter is a non-parametric substitute for the one-way, fixed-effects analysis of variance (19). Each of the three-group comparisons done separately for days 0 and 7 was supplemented by three pairwise comparisons of groups using the two-sample Wilcoxon statistic. For these comparisons, significance was judged according to the Bonferroni technique (20). Thus P < 0.017 for a particular comparison meant P < 0.05 for the set of three comparisons. For five variables (urine flow, fractional sodium excretion, urine-to-plasma osmolality ratio, and cold and warm ischemic times), there were no control data, so two-sample Wilcoxon statistics with standard notions of significance were used. Matching on a patient-by-patient basis within each ARF group allowed us to compute changes between day 0 and day 7 for each group. These changes were evaluated with paired, one-sample Wilcoxon signed-ranks tests.

RESULTS

Initial Allograft Function

Initial allograft function was measured 1–3 h after reperfusion. The duration of cold ischemia averaged 921 ± 369 min in the group destined to exhibit recovering ARF and 1,221 ± 349 min in the group destined to exhibit sustained ARF (P = 0.014). The corresponding durations of rewarming times, during performance of the vascular anastomosis, were 29 ± 9 and 32 ± 10 min, respectively [P = not significant (NS)]. In keeping with their classification according to the inulin clearance on day 7, those in the recovering ARF group tended to have a significantly higher effective GFR on day 0 than those classified as sustained ARF (Table 1; P = 0.0017). Moreover, initial GFR was profoundly and significantly depressed below the control value (80 ± 20 ml/min) in both groups, averaging 17 ± 11 and 7 ± 6 ml/min, respectively.

RPF and πa were also similar in the two ARF groups. The πa tended to be lower than in the control group, a finding that should enhance, and not depress, GFR (Table 1). RPF was also below control: by 37% in the recovering group (P = 0.0009) and by 41% in the sustained group (P = 0.00003; Table 1). As indicated by profound and significant depression of corresponding values of the filtration fraction to only 9 ± 6% (P = 0.00001) and 3 ± 3% (P = 5 × 10⁻⁶) in the recovering and sustained ARF groups, respectively, compared with 22 ± 5% in controls, the modest depression of RPF does not explain the extent of initial glomerular hypofiltration in the two ARF groups. The value for k was significantly depressed below control levels by a similar amount in the recovering and sustained ARF groups on day 0: 2.4 ± 0.4 vs. 1.9 ± 0.3 (P = 0.005) and 1.8 ± 0.4 × 10⁻⁹ m²·s⁻¹·Pa⁻¹ (P = 0.002), respectively (Table 2). The low k, in turn, was a consequence of foot process broadening with an ensuing reduction in FSF (Table 2). A trend to enhanced filtration surface area, owing to enlargement of glomerular volume after transplantation, offset the low k, however (Table 2). As a result, Kf did not differ from the control value of 4.6 ±

Table 2. Glomerular structure and modeling

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Sustained</th>
<th>Recovery</th>
<th>Day 0</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vv, μm³×10⁶</strong></td>
<td>1.7 ± 0.5</td>
<td>2.0 ± 1.1</td>
<td>2.4 ± 0.9</td>
<td>2.5 ± 1.3</td>
<td>2.9 ± 1.8</td>
</tr>
<tr>
<td><strong>Sw</strong></td>
<td>0.10 ± 0.01</td>
<td>0.11 ± 0.02</td>
<td>0.11 ± 0.02</td>
<td>0.10 ± 0.03</td>
<td>0.10 ± 0.03</td>
</tr>
<tr>
<td><strong>FSF, no./mm GBM</strong></td>
<td>1,094 ± 165</td>
<td>796 ± 132*</td>
<td>832 ± 131*</td>
<td>880 ± 118*</td>
<td>998 ± 166*</td>
</tr>
<tr>
<td><strong>Thickness of basement membrane</strong></td>
<td>412 ± 86</td>
<td>415 ± 118</td>
<td>393 ± 96</td>
<td>455 ± 90</td>
<td>426 ± 62</td>
</tr>
<tr>
<td><strong>k, m⁻¹·Pa⁻¹×10⁻⁹</strong></td>
<td>2.4 ± 0.4</td>
<td>1.8 ± 0.3*</td>
<td>1.9 ± 0.3*</td>
<td>1.9 ± 0.2*</td>
<td>2.2 ± 3.2†</td>
</tr>
<tr>
<td><strong>S, m²×10⁵</strong></td>
<td>1.8 ± 0.6</td>
<td>2.0 ± 1.2</td>
<td>2.6 ± 1.2</td>
<td>2.4 ± 1.5</td>
<td>3.0 ± 2.2</td>
</tr>
<tr>
<td><strong>SN Kf, nl·min⁻¹·mmHg⁻¹</strong></td>
<td>4.6 ± 1.8</td>
<td>3.9 ± 2.1</td>
<td>5.4 ± 2.8</td>
<td>5.2 ± 3.4</td>
<td>7.0 ± 5.3‡</td>
</tr>
</tbody>
</table>

Values are means ± SE. Vv, glomerular volume; Sw, filtration surface density; FSF, filtration slit frequency; k, glomerular capillary hydraulic permeability; S, capillary surface area; SN Kf, single-nephron ultrafiltration coefficient; GBM, glomerular basement membrane. *P < 0.017 vs. control; †P < 0.05, paired difference on day 7 vs. day 0.
1.8 nl·min⁻¹·mmHg⁻¹, averaging 5.4 ± 2.8 and 3.9 ± 2.1 nl·min⁻¹·mmHg⁻¹ in the recovering and sustained groups, respectively (P = NS; Table 2). Thus the present findings confirm precisely our earlier observations that changes in \( \pi_A \), RPF, and \( K_f \) do not explain GFR depression in the immediate wake of an ischemic-reperfusion injury to the renal allograft. That tubules also suffer a severe initial injury is indicated by excretion of a massive fraction of the filtered sodium load (≥20% on average) and isosthenuria in each ARF group (Table 3).

Late Allograft Function

Late allograft function was measured on day 7. There was negligible change in effective GFR between day 0 and day 7 in the sustained ARF group (7 ± 6 vs. 8 ± 5 ml/min). The following measured determinants of GFR also remained constant: RPF = 225 ± 53 vs. 239 ± 98 ml/min, \( \pi_A = 22.3 ± 3.3 \) vs. 23.8 ± 3.9 mmHg (Table 1), \( k = 1.8 ± 0.3 \) vs. 1.9 ± 0.3 × 10⁻⁹ m·s⁻¹·Pa⁻¹, and \( S = 2.0 ± 1.2 \) vs. 2.4 ± 1.5 × 10⁻⁵ m² (Table 2; all \( P = NS \)). Numerical increases in PSF and glomerular volume accounted for the trend to higher \( k \) and \( S \) on day 7 (Table 2). The computed \( K_f \) increased from 3.9 ± 2.1 to 5.2 ± 3.4 nl·min⁻¹·mmHg⁻¹, but this difference also failed to reach significance.

The recovering ARF group was characterized by a large increase in effective GFR between day 0 and day 7: 17 ± 11 vs. 50 ± 20 ml/min (\( P = 0.00003 \)). Whereas \( \pi_A \) remained relatively constant, RPF increased between the two examinations, albeit not significantly and less than in proportion to the corresponding change in GFR (Table 1). There was, however, a large and significant increase between day 0 and day 7 in \( K_f \): 5.4 ± 2.8 vs. 7.0 ± 5.3 nl·min⁻¹·mmHg⁻¹ (\( P < 0.02 \); Table 2). A significant (\( P = 0.02 \)) increase in \( k \) by 14% as foot process conformation was restored to normal contributed to the higher \( K_f \) (Table 2). Also contributing was a trend toward glomerular hypertrophy (Table 2) with an ensuing numerical enhancement of filtration surface area to a mean value that exceeded that in controls by 72% (Table 1). Noteworthy is that, despite their improving GFR, the recovering ARF group continued to exhibit postischemic tubule injury on day 7 similar to that in the sustained ARF group, as judged by a persistently high fractional sodium excretion and isosthenuria (Table 3).

Evaluation of Ultrafiltration Pressure

We applied the values for effective GFR, RPF, \( \pi_A \), and \( K_f \) to a model of ultrafiltration to elucidate a potential role for changes in \( \Delta P \) in the protracted hypofiltration of sustained ARF and improving GFR of recovering ARF. The results of such modeling are summarized in Table 4. A sensitivity analysis has been used to take into account the effects of uncertain nephron number and transtubular backleak of filtrate. Under the tabulated conditions, \( \Delta P \) is computed to vary between 47 and 54 mmHg in controls but to be severely depressed into the 25- to 28-mmHg range in sustained ARF on days 0 and 7. The corresponding range is similarly depressed in the recovering group on day 0 (26–31 mmHg) but increases to 32–43 mmHg on day 7 (Table 4). We recently provided evidence that ~50% of filtrate leaks back in sustained ARF but that there is no backleak in recovering ARF (18). With correction of the measured inulin clearance in the former group to allow for backleak, \( \Delta P \) on day 7 is 27–28 mmHg in sustained ARF compared with 32–38 mmHg in recovering ARF. The latter remains substantially lower than the computed value in controls (47–54 mmHg, Table 4).

Using morphometric techniques superior to those used by Dunnill and Halley (14), Nyengaard and Bendtsen (25) suggest that 0.7 × 10⁶ is likely a more accurate estimate of mean glomerular number per kidney.

### Table 3. Tubule function and structure

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Sustained</th>
<th>Recovering</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urine flow, ml/min</strong></td>
<td>2.0 ± 1.9</td>
<td>5.4 ± 4.3↑</td>
<td>1.5 ± 1.7</td>
</tr>
<tr>
<td><strong>U/P osmolality</strong></td>
<td>1.02 ± 0.07</td>
<td>1.02 ± 0.07</td>
<td>1.03 ± 0.11</td>
</tr>
<tr>
<td><strong>Fractional Na excretion, %</strong></td>
<td>27 ± 16</td>
<td>22 ± 12</td>
<td>10 ± 9↑</td>
</tr>
<tr>
<td><strong>Fractional Bowman’s space, %</strong></td>
<td>22 ± 6</td>
<td>34 ± 11*</td>
<td>34 ± 10*</td>
</tr>
<tr>
<td><strong>Tubule luminal area, μm²</strong></td>
<td>362 ± 127</td>
<td>548 ± 205</td>
<td>704 ± 206*</td>
</tr>
<tr>
<td><strong>Exfoliated cells, %</strong></td>
<td>3.7 ± 3.5</td>
<td>3.7 ± 3.6</td>
<td>4.0 ± 2.5</td>
</tr>
</tbody>
</table>

Values are means ± SE. U/P osmolality, urine-to-plasma osmolality ratio. *\( P < 0.017 \) vs. control; †\( P < 0.017 \) vs. sustained group on given day; ‡\( P < 0.05 \), paired difference on day 7 vs. day 0.

### Table 4. Computed ΔP

<table>
<thead>
<tr>
<th>Condition</th>
<th>Control</th>
<th>Sustained</th>
<th>Recovery</th>
<th>Sustained</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 × 10⁶ Glomeruli</td>
<td>47</td>
<td>25</td>
<td>26</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>0% Backleak</td>
<td>54</td>
<td>25</td>
<td>29</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>50% Backleak</td>
<td>27</td>
<td>31</td>
<td>28</td>
<td>43</td>
<td></td>
</tr>
</tbody>
</table>

Transcapillary hydraulic pressure gradient (ΔP) is expressed in mmHg.
ney than $1.0 \times 10^6$. Using the former value and assuming 50% backleak in sustained ARF but no backleak in controls and recovering ARF, we have selected a “best-case” value for $\Delta P$ in each group (Fig. 1). It can be compared with the opposing mean glomerular intracapillary oncotic pressure, which we have computed using Eq. 5 (Fig. 1). Whereas net ultrafiltration pressure (best-case $\Delta P - \pi_{GC}$) approximates 27 mmHg in controls, the corresponding pressure falls to only ~4 mmHg in sustained ARF on days 0 and 7 (Fig. 1). A similarly low initial ultrafiltration pressure approximates 5 mmHg on day 0 in the recovering ARF group. The best-case $\Delta P$ suggests that ultrafiltration pressure increases to 12 mmHg in the recovering ARF group on day 7, however. Although the latter is not yet as high as in controls, this increment, combined with the significant 30% increase in computed $K_c$ appears to account for the corresponding increment in GFR on day 7.

One possible mechanism by which postischemic renal injury could lower $\Delta P$ is obstruction of tubule lumens by exfoliated cells, cell debris, and/or casts with a subsequent increase in the upstream pressure in Bowman’s space (11, 21). Tubule morphometry provides equivocal information about this possibility. Fractional Bowman’s space area and tubule luminal cross-sectional area were significantly higher in the recovering group on day 0 than in controls: 34 ± 10 vs. 22 ± 6% ($P = 0.003$) and 704 ± 206 vs. 362 ± 127 $\mu m^2$ ($P = 0.003$), respectively (Fig. 2). Corresponding values in the sustained group on day 0 were similar at 34 ± 11% for fractional Bowman’s space area ($P = 0.006$ vs. controls) and intermediate at 548 ± 205 $\mu m^2$ for tubule luminal area ($P = NS$ vs. controls). Each of the latter values remained unchanged in the sustained group on day 7. In contrast, increasing GFR and $\Delta P$ in the recovering group on day 7 were associated with a significant reduction in tubule luminal area ($P = 0.004$) toward normal values (Table 2; Fig. 2). There was a parallel, albeit nonsignificant, reduction in fractional Bowman’s space area (Table 2; Fig. 2). Despite the apparent distension of Bowman’s space and tubule lumens, however, intratubular casts were rarely observed, and there was only scant tubule cell exfoliation. On day 0 the percentage of exfoliated cells in the recovering (4.0 ± 2.5%) and sustained groups (3.7 ± 2.6%) was similar to that associated with nephrectomy in the control group (3.7 ± 3.5%). The percentage of exfoliated cells by day 7 was not significantly different in the sustained group (2.6 ± 2.1%) but declined significantly by 75% to 1.0 ± 1.0% in the recovering group ($P = 0.02$; Table 3). Thus, although tubule and Bowman’s space distension correlate with GFR and computed $\Delta P$ depression during posttransplantation week 1, corresponding evidence of substantial cell exfoliation as a potential cause of downstream tubule obstruction is scanty.

**DISCUSSION**

We recently showed that transtubular backleak contributes to lowering of the urinary clearance of inulin during the maintenance stage of postischemic ARF in the renal allograft (18). We used a differential solute clearance technique to evaluate the renal handling of nonreabsorbable polysaccharide molecules of graded size. Our analysis suggested that normal tubule impermeability to the filtration markers inulin and dextran was lost and that ~50% of filtered inulin leaked back across damaged tubule walls (18). A morphometric and histochemical analysis pointed to a paracellular pathway for backleak between proximal tubule cells owing to impairment of tight junctions and cell-cell adhesion (18). Correcting the observed urinary inulin clearance in the present study by our previous estimate of the

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**Fig. 2.** Tubule luminal area (A) and fractional Bowman’s space area (B) in controls and recovering ARF group on days 0 and 7. *P < 0.017 vs. controls; **P < 0.05, paired difference between day 7 and day 0.
inulin backleak rate results in computation of a mean true GFR that is only 20% of the corresponding value observed in our control subjects with excellent allograft function.

The present study was designed to determine what accounts for the remaining disparity (~60–70 ml/min) between GFR “corrected” for backleak in sustained (maintenance stage) ARF and the control value for GFR. To do this, we determined GFR and three of its four determinants: RPF, πA, and Kf. We then subjected the foregoing quantities to mathematical modeling and a sensitivity analysis to estimate ΔP, the single remaining determinant of GFR (2). Our findings indicate that πA and Kf after 7 days of sustained ARF do not differ from control values. Furthermore, although it is modestly lowered below control by 38% on average, depressed RPF cannot be invoked to explain the observed hypofiltration. The extreme depression of filtration, even after correction for backleak (4 vs. 22% in controls), indicates that GFR depression in sustained ARF is disproportionate to the corresponding depression of RPF. Precisely the same findings for GFR, RPF, πA, and Kf during the initiation stage of ARF on day 0 indicate that a remarkable constancy of GFR and its aforementioned three determinants accompanies the phenomenon of sustained ARF on day 7 (Tables 1 and 2). It is evident by exclusion, and our model of glomerular ultrafiltration confirms, that a profound lowering of ΔP is the predominant cause of GFR depression in the initiation and maintenance stages of sustained postischemic ARF (Fig. 1).

Our finding that RPF is well preserved in the initiation (day 0) and maintenance (day 7) stages of sustained ARF is not widely recognized. This is because injury to proximal tubules inactivates the organic anion transporter, thereby precluding the use of PAH, the standard clearance marker for RPF in humans (8). Profound impairment of tubular PAH secretion results in substantial underestimation of RPF by the urinary clearance of PAH (5, 8, 15, 23). Although the number of observations is small, more invasive techniques have been used to reliably estimate RPF in the presence of ARF in humans. These include application of an electromagnetic flowmeter to the renal artery (3, 23) or cannulation of the latter vessel to measure flow by dye dilution (29) or by washout of inert radioactive gases (16). Each of these studies has reported reductions in RPF that were modest and of proportions remarkably similar to those observed by us in the present study. We have carefully validated the accuracy of our noninvasive cine-PC-MRI technique by comparison with PAH clearance in the healthy kidney, in which the organic anion transporter is unimpaired (24, 32). To the extent that the former method is also accurate in the presence of ARF, it is interesting to note the similarity of RPF in the sustained ARF group on day 7 when cine-PC-MRI was used (239 ± 98 ml/min) to that on day 0 during surgery, as determined directly by Doppler flow probe (225 ± 153 ml/min). That RPF is unlikely to have changed substantially between the two examinations is consistent with unchanging levels of corresponding serial determinations of GFR and its remaining determinants (Tables 1 and 2).

The process of recovery from allograft ARF is also characterized by relative constancy of πA and RPF (Table 1). In contrast to ARF that is sustained, however, the recovery stage is accompanied by a substantial increment in Kf on day 7. This is attributable partly to a significant increase in glomerular hydraulic permeability as foot process conformation is restored toward normal (Table 2). Also contributing is adaptive glomerular enlargement (see glomerular volume, Table 2) at this time, with an ensuing enhancement of filtration surface area (Table 2). The resulting 30% increase in Kf above day 0 levels is insufficient to account by itself for the observed increase in GFR. Applying the observed values of πA, RPF, and Kf to the model of ultrafiltration reveals that it is also necessary to invoke a substantial increase in ΔP to explain the observed level of GFR on day 7 as the allograft recovers from the postischemic injury. Finn and Chevalier (15) used the micropuncture technique to demonstrate that the recovery from postischemic ARF in the rat is associated with progressive and parallel increases in GFR and ΔP over a period of >8 wk. It seems likely that a similar process of recovery lasting several weeks also applies to postischemic injury of the human renal allograft. Presumably, subsequent increases in ΔP to a normal, or even supernormal, range should eventuate beyond day 7. In combination with parallel increases in Kf and RPF due to adaptive hypertrophy and hyperperfusion of glomeruli in the uninephric condition, respectively, such increases in ΔP should lead eventually to the marked elevation of single-kidney GFR that is observed in our control group of uninephric transplant recipients with optimally functioning allografts of long standing (24).

There are two potential mechanisms for the depression of ΔP that we compute in our subjects with allograft ARF. One is a rise in pressure in Bowman’s space consequent on downstream obstruction of tubules (4, 6, 15, 33). The other is a fall in perfusion pressure of glomerular capillaries consequent on afferent arteriolar vasoconstriction. Micropuncture studies of the aforementioned pressures suggest that each contributes to ΔP depression in the initiation and maintenance stages of postischemic ARF in rats and dogs (4, 6, 15, 33). Finn and Chevalier (15) extended their observations into the recovery stage. They found that early recovery, 2 wk after injury, was associated with a parallel but partial improvement in GFR and ΔP owing to a decline in Bowman’s space pressure. Only beyond 2 wk was continued recovery of GFR and ΔP attributable to a late rise in glomerular capillary pressure. The elevation of Bowman’s space pressure in the maintenance stage of ARF was associated with sluggish tubule fluid flow, distension of the tubule lumen, and extensive necrosis and exfoliation of proximal tubule cells. The decline in Bowman’s space pressure in the recovery stage, on the other hand, was associated with less tubule luminal distension and a reduction of intraluminal cells and casts (15).
Because hydraulic pressures in Bowman’s space and glomerular capillaries cannot be determined in humans, only the above-described morphological features can be used to provide indirect insights into the mechanism of \(\Delta P\) depression in our subjects with allograft ARF. Significant or nearly significant \(P = 0.03–0.06\) distension of Bowman’s space and tubule lumens in the initiation and maintenance stages and reduced distension in the recovery stage could be interpreted as consistent with intratubular obstruction and an upstream rise in pressure in Bowman’s space. In contrast to posts ischemic ARF in the rat, however, our morphometric analysis indicates that tubule cells exhibiting overt necrosis or exfoliation are sparse in this form of human ARF (Table 3), a finding that has been demonstrated by others and by us previously (2, 18, 27, 31). Unlike other forms of posts ischemic ARF in humans, intratubular casts, another potential source of luminal obstruction (26–28, 30), are also rare in allograft ARF in our experience (18). We wish to emphasize, however, that we cannot exclude the presence of casts or other structural changes that favor obstruction in inner medullary or papillary segments of tubules, because such segments are not sampled during a renal biopsy. Nevertheless, it is conceivable that a high rate of tubule fluid flow, rather than mechanical obstruction, leads to elevation of proximal tubule pressure and is solely responsible for the distension of Bowman’s space and tubule lumens observed by us in the initiation and maintenance stages of allograft ARF. That proximal tubule fluid flow rate could have been very high in our subjects is suggested by the enormous fraction of filtered sodium that was excreted in the initiation and maintenance stages of allograft ARF (Table 3). We previously used fractional lithium excretion as a surrogate for the fraction of filtered sodium delivered out of the proximal tubule to the macular densa (17). We showed that proximal reabsorption of sodium was profoundly depressed. This phenomenon is consistent with a high rate of tubule fluid flow and could have a mechanical effect to elevate pressure in and distend the proximal tubule.

Increased delivery of sodium to the macula densa could, of course, also activate tubuloglomerular feedback and lower \(\Delta P\) by mediating afferent vasoconstriction with a downstream fall in glomerular capillary hydraulic pressure (34). Table 1 shows that although RPF in the maintenance stage of ARF was depressed by only 38% on average, the corresponding increase in mean renovascular resistance was by a factor of \(2: 346 \pm 158\) vs. \(168 \pm 48\) units in controls \(P = 0.0009\). This change seems large enough, particularly if accompanied by selective afferent vasoconstriction alone or in combination with efferent vasodilatation, to account for the apparent reduction of computed \(\Delta P\).

In the absence of methods to determine Bowman’s space and glomerular capillary pressures in the human kidney, the potential contribution of tubule obstruction or afferent vasoconstriction to the filtration failure that typifies ischemic allograft ARF in humans cannot be determined. Nevertheless, a consideration of proximal tubule compliance suggests that our measured changes in luminal area are consistent with the changes we inferred for \(\Delta P\). Converting the luminal areas in Table 3 to diameters gives 21.5 \(\mu\)m for control, 26.4 \(\mu\)m for sustained day 0, 29.9 \(\mu\)m for recovery day 0, 25.9 \(\mu\)m for sustained day 7, and 22.8 \(\mu\)m for recovery day 7. As reported by Cortell et al. (9), proximal diameter varies linearly with pressure, with a slope of 0.45 \(\mu\)m/mmHg. For example, for recovery day 7 vs. day 0, the diameter reduction is 29.9–22.8 = 7.1 \(\mu\)m.

The corresponding reduction in proximal tubule pressure, based on the rat compliance data, is 7.1/0.45 = 16 mmHg. Because that matches or exceeds the increases in \(\Delta P\) in our Table 4, it tends to give credence to the idea that increases in proximal tubule pressure, secondary to tubule obstruction and/or increased flow, are a major contributor to acute reduction and eventual recovery of \(\Delta P\). Any additional contribution by afferent vasoconstriction must remain a matter for speculation.

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