Stretching of Glomerular Afferent Arterioles in the Swollen Renal Allograft Undergoing Acute Rejection

CARIN L. ALLHISER, JOHN E. STEFANIAK, LEE A. HEBERT, ANTHONY J. LAFORTA, ARTHUR L. RILEY, AND DEREK SAMPSON

SUMMARY Marked renal swelling occurs in acute renal allograft rejection. The impaired renal function in this state could be related in part to mechanical adjustments that the renal tubular and vascular network must make as they participate in the overall expansion of renal parenchymal volume. In the present study we examined whether vascular stretching occurs in the swollen acutely rejecting kidney. From each of five pairs of dogs matched for weight, a donor animal was chosen from which a control kidney was removed, weighed, and perfused at constant pressure (150 mm Hg) with polymerizing silicone rubber. The contralateral kidney was transplanted into the recipient dog which was then bilaterally nephrectomized. On the sixth posttransplant day, the transplant kidney was removed, weighed, and perfused with silicone rubber, as above. Multiple coronal sections were made of each control and transplant kidney and a total of 240 photomicrographs were taken of the coronal sections from unselected fields of outer and inner cortex. The photographic slides were then coded, randomized, and projected. Measurements were then made, from the projected images, of the glomerular afferent arteriolar length (AL), and width (AW), and the glomerular width (GW). The code was then broken and the measurements in the control and transplant kidneys collated. We found that transplant AL was significantly longer (mean ratio: transplant/control = 1.32 ± 0.06, P < 0.001) and transplant AW significantly narrower (mean ratio: transplant/control = 0.88 ± 0.04, P < 0.05). We also found that GW was slightly but significantly decreased in the transplant compared to the control kidney. We conclude that afferent arteriolar stretching occurs in swollen renal allografts and accounts, at least in part, for the impaired renal function observed in acutely rejecting renal allografts. Circ Res 44: 216-222, 1979

MARKED expansion of renal parenchymal volume above normal commonly occurs in states of acute renal injury, such as ischemic damage or transplant rejection (Abrams, 1972; Fletcher et al., 1969). In previous studies, we provided indirect evidence that the renal swelling in these states is due, principally, to an increase in compliance of the kidney (Hebert et al., 1975) and that compliance-mediated (as opposed to pressure-mediated) expansion of renal parenchymal volume may impair renal function (Hebert et al., 1975, 1978 in press). One mechanism by which compliance-mediated expansion of renal parenchymal volume could affect renal function is that the renal vasculature might become stretched, as the vascular network participates in the overall expansion of renal parenchymal volume. In the present study we assessed this possibility by comparing glomerular afferent arteriole dimensions in control and transplant kidneys. This vascular segment was chosen because its anatomic limits can be readily defined and measured because it is a major resistor in the renal vascular circuit (Abe et al., 1970).

Methods

Surgical Preparation

Five pairs of male mongrel dogs, each pair matched for weight, were studied. Each pair was anesthetized with intravenous sodium pentobarbital (30 mg/kg), and endotracheal tubes were inserted and connected to a constant volume, positive-pressure ventilator which was adjusted according to a nomogram to achieve normal levels of ventilation. From each pair of dogs, a donor and a recipient were selected arbitrarily and were prepared for surgery under sterile conditions. In the donor dog, both kidneys were freed of their nonhilar perirenal attachments and either the right or left kidney was chosen as the control kidney. The donor kidney then was removed if the kidneys appeared different in size. The hilar vessels of the control kidney then were double-clamped and incised between the clamps. The excised kidneys were freed of their nonhilar perirenal attachments and either the right or left kidney was chosen as the control kidney. The dog was rejected as a donor if the kidneys appeared different in size. The hilar vessels of the control kidney then were double-clamped and incised between the clamps. The excised kidney was weighed and prepared for silicone rubber infusion (Microfil, Canton Bio-Medical Products). The contralateral kidney (transplant kidney) was excised in a similar fashion and perfused with iced, heparinized Ringer's-lactate solution until the venous effluent was clear (about 250 ml). This kidney then was...
transplanted into the iliac fossa of the recipient dog with vascular anastomoses to the iliac vessels and with the ureter connected to the bladder. The recipient’s native kidneys were then removed and the abdominal incision closed. During the surgical procedure, the donor animal received intravenously 0.5-1.0 liter of Ringer’s lactate and the recipient animal received intravenously 2 liters of Ringer’s lactate. The serum creatinine was measured in the donor and the recipient on the day of kidney transplantation and daily in the recipient animal, thereafter. On the 6th posttransplant day, the recipient dog was anesthetized and the renal allograft removed (as described above), weighed, and prepared for silicone rubber infusion.

**Silicone Rubber Infusion**

Silicone rubber was prepared in a 4:5 ratio of silicone rubber to diluent with 5% (by volume) of catalyst added to cause polymerization. The silicone rubber was infused via a canula placed in the renal artery within 3 minutes after nephrectomy. The infusion was controlled by a constant infusion pump which was continually adjusted to maintain the infusion pressure at about 150 mm Hg. The infusion pressure was monitored by means of a Statham pressure transducer which was attached via a side arm to the renal artery catheter.

Silicone rubber infusion was continued until filling of superficial cortical vessels and/or efflux of silicone rubber from the renal vein was noted. The infusion was stopped, the hilar structures clamped, and the kidney stored at 4°C for 24 hours to allow the silicone rubber to harden.

**Preparation and Photography of Silicone Rubber-Injected Specimens of Kidney**

The kidney injected with silicone rubber was cut into coronal sections about 0.5 cm thick and placed in alcohol to remove water from the specimen. This was done by placing the specimens in 25% ethyl alcohol on the first day and then increasing the concentration of alcohol to 50% on the second day, 75% on the third day, 95% on the fourth day, and absolute alcohol on the fifth day. On the sixth day, the specimens were placed in methyl salicylate for clearing. The specimens were photographed, while in the methyl salicylate solution, through a Leitz microscope using a 3.5 magnification objective. A Pentex-Asahi 35 mm camera with Kodak Pana- tomic X film was used.

Filling of the transplant kidney vasculature with the silicone rubber tended to be patchy compared to filling observed in the control kidney. Thus, to insure that the photographs of the control kidney cortex corresponded to areas photographed in the transplant kidney cortex, the transplant kidney was photographed first. The corresponding areas in the control kidney cortex then were photographed. Photographs were taken first of the inner cortex closest to the hilum and then, moving circumfer-entially about 4 cm at a time, until the entire inner cortex was photographed. The outer cortex then was photographed in the same fashion. There was no selection of the fields, except that prior to the taking of each photograph, the field was inspected to determine if the vasculature in that field was filled with silicone rubber. If any filling with silicone rubber was present, the field was photographed. If no vascular filling with silicone rubber was present, the field was moved circumferentially about 4 mm at a time until a field with vascular filling with silicone rubber was found.

**Analysis of Photographs**

The photographic negatives of the kidney specimens were set in conventional 35-mm mountings, numbered, randomized, and then placed in a carousel by a person who was not involved in the interpretation of the slides. The slides then were projected onto a screen 277 cm from the projector lens. To determine the degree of magnification of the projected image, a hemocytometer grid with lines 0.2 mm apart was photographed with the same arrangement used to photograph the kidney specimens. The distance between the projected grid lines was 40.0 mm. Thus, the total magnification of the projected image was 200 X.

From each photographic slide of the tissue specimens, the following determinations were made from the projected images.

**Glomerular Afferent Arteriolar Length (AL)**

The length of each glomerular afferent arteriole, with a visible origin and connection with a glomerulus, was measured from the origin of the arteriole on its feeding artery to its glomerular termination (see Fig. 1). This was done with a hand-held device which measured, in millimeters the distance a rotating wheel moves in tracing the measured distance (Selsi map measurer, West Germany). The measurement of AL tends to underestimate the true glomerular afferent arteriolar length for two rea-

![Figure 1](https://example.com/fig1.png)

**Figure 1** Schematic representation of the microanatomic measurements made in this study. AL = afferent arteriolar length; GD = glomerular distance; GW = glomerular width. In addition, we measured afferent arteriolar width (AW) at the midpoint of all arterioles which were in focus.
Gross Anatomic Findings

The mean control kidney weight was 55.2 ± 5.5 g. These kidneys were infused with an average of 5.2 ± 0.4 ml of silicone rubber at the time when filling of the superficial cortical vessels became evident and the infusion was stopped. In all control kidneys there was good filling of both outer and inner cortex. This was shown by comparing, by unpaired t-test, the mean value for AL from all control kidney measurements to the mean value for AL from all transplant kidney measurements. In addition, for each dog we calculated the ratio (mean AL, transplant kidney/mean AL, control kidney), for both outer and inner cortex. Each ratio was greater than 1.00 (range, 1.06-1.60). There was no difference between the mean ratios for outer and inner cortex; thus the ratios for outer and inner cortex were combined, averaged, and this mean ratio compared to 1.00, as shown in Table 1 (bottom line). This analysis also shows that the AL of the transplant kidneys is significantly greater than AL of the control kidneys. The data for GD were analyzed in the same way as the data for AL. As can be seen from Table 1, the interpretation of the GD data is the same as the interpretation of the AL data.

The finding of increased afferent arteriolar length and greater distance between the glomeruli and its feeding artery is largely the result of stretching (an increase in true length) of the glomerular afferent arteriole. That is, it seems unlikely that the increase in AL and GD are the result simply of uncoiling of the afferent arterioles (an increase in afferent arteriolar length visible to the camera, but no increase in the true length of the afferent arteriole). This interpretation follows from the fact that, as depicted in Figure 3, most afferent arterioles in normal kidneys are straight or nearly straight and none is highly coiled. This interpretation receives quantitative support by examining the relationship between AL and GD, shown in Table 1. As can be seen, AL and GD are nearly equal, indicating that on the average, glomerular afferent arterioles follow a nearly straight path from the feeding artery to the

Microanatomic Findings

Figure 3 shows selected photomicrographic fields of silicone rubber-injected control and transplant kidneys. Note that in the control kidneys the glomeruli tend to lie close to their feeding artery and are connected to the feeding artery by a relatively short and sometimes gracefully arched afferent arteriole. By contrast, in the transplant kidneys the glomeruli appear to be pulled away from their feeding artery and some of the afferent arterioles appear to be stretched and narrowed.

Table 1 compares the microanatomic measurements of the control kidneys to that of the transplant kidneys. The actual dimensions of the renal structures are shown in micrometers. As can be seen, transplant kidney AL is significantly longer than control kidney AL, in both outer and inner cortex. This was shown by comparing, by unpaired t-test, the mean values for AL from all control kidney measurements to the mean value for AL from all transplant kidney measurements. In addition, for each dog we calculated the ratio (mean AL, transplant kidney/mean AL, control kidney), for both outer and inner cortex. Each ratio was greater than 1.00 (range, 1.06-1.60). There was no difference between the mean ratios for outer and inner cortex; thus the ratios for outer and inner cortex were combined, averaged, and this mean ratio compared to 1.00, as shown in Table 1 (bottom line). This analysis also shows that the AL of the transplant kidneys is significantly greater than AL of the control kidneys. The data for GD were analyzed in the same way as the data for AL. As can be seen from Table 1, the interpretation of the GD data is the same as the interpretation of the AL data.

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glomerulus. Thus, uncoiling of the glomerular afferent arteriole cannot account for the large increases in AL observed in the transplant kidney (Table 1).

It also seems unlikely that any systematic error in the selection of glomerular afferent arterioles for measurement can account for the finding of greater AL and GD in transplant vs. control kidneys. In fact, if anything, the techniques used tend to underestimate the increase in AL and GD in transplant kidneys. This interpretation is based on the fact that control kidneys have more short glomerular afferent arterioles, and short afferent arterioles are difficult to find, particularly in control kidneys, because of the tendency to more abundant vascular filling with silicone rubber (Fig. 3). Thus, in the control kidney data for AL and GD, there is underrepresentation of glomeruli with short afferent arterioles because these afferent arterioles are difficult to identify, and thus often were not measured. Consequently, the mean control kidney AL shown in Table 1 is probably greater than the true mean AL for control kidneys. The greater difficulty in finding measurable glomerular afferent arterioles in the material obtained from control kidneys also accounts for the fact that there are fewer measurements in the control kidneys, compared to the transplant kidneys, as shown in Table 1.

The data on AL are also of interest because they show that in the control kidney the average AL of inner cortex is significantly greater than the average AL of outer cortex (P < 0.001).

The GW data shown in Table 1 confirm previous observations that the glomeruli of inner cortex are larger than the glomeruli of outer cortex (Schneider et al., 1972). We also found that the glomeruli tended to be smaller in the transplant kidneys compared to the control kidneys. Although this could not be shown by unpaired t-testing of the control kidney data vs. the transplant kidney data, it was shown by determining for each kidney the ratio (GW, transplant kidney/GW, control kidney) for both outer and inner cortex. When these ratios were pooled, the mean ratio was significantly less than 1.00 (0.97 ± 0.009, P < 0.02). The finding of a
Figure 3 Photomicrographs of exemplary cortical fields in silicone rubber-injected control and transplant kidneys. In the control kidney specimens, the arrows identify individual or groups of afferent arterioles which demonstrate that many afferent arterioles are slightly curved, or pursue a mildly undulating course. In addition, in the left lower panel, note the difficulty in clearly identifying the origin and termination of short afferent arterioles in fields which have abundant vascular filling with silicone rubber. In the transplant kidneys, the arrows identify individual or groups of afferent arterioles which demonstrate that many afferent arterioles have a "straight as a string" appearance, suggesting stretching of the afferent arterioles. Also, most of the glomeruli appear to lie at a distance from their respective arteries, making the origin and termination of most afferent arterioles relatively easy to identify.

Tendency for smaller glomeruli in the transplant kidneys is consistent with the hypothesis that the glomeruli was underperfused because of an increase in afferent arteriolar resistance.

Table 1 also shows that the afferent arterioles of the transplant kidney are narrowed compared to those of the control kidney. This was shown by comparing, by unpaired t-test, the mean value for AW from all control kidney measurements to the mean value for AW from all transplant kidney measurements. In addition, for each dog we calculated the ratio (mean AW, transplant kidney/mean
TABLE 1  Microanatomic Measurements in Control Kidneys (CK) and Transplant Kidneys (TK)

<table>
<thead>
<tr>
<th></th>
<th>Glomerular afferent arteriolar length (AL, µm)</th>
<th>Glomerular diameter (GD, µm)</th>
<th>Glomerular width (GW, µm)</th>
<th>Glomerular afferent arteriolar width (AW, µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outer cortex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control kidneys</td>
<td>172 ± 11</td>
<td>161 ± 11</td>
<td>143 ± 2</td>
<td></td>
</tr>
<tr>
<td>n = 91 (28)</td>
<td>P &lt; 0.001*</td>
<td>P &lt; 0.001*</td>
<td>0.3 &lt; P &lt; 0.4*</td>
<td></td>
</tr>
<tr>
<td>Transplant kidneys</td>
<td>248 ± 8</td>
<td>229 ± 8</td>
<td>140 ± 2</td>
<td></td>
</tr>
<tr>
<td>n = 211 (39)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Inner cortex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control kidneys</td>
<td>236 ± 9</td>
<td>214 ± 9</td>
<td>163 ± 2</td>
<td></td>
</tr>
<tr>
<td>n = 212 (76)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Transplant kidneys</td>
<td>288 ± 9</td>
<td>258 ± 8</td>
<td>158 ± 2</td>
<td></td>
</tr>
<tr>
<td>n = 371 (97)</td>
<td></td>
<td></td>
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<tr>
<td>Mean of the mean ratio from each experiment. Data from outer and inner cortex pooled.</td>
<td>1.32 ± 0.06</td>
<td>1.33 ± 0.06</td>
<td>0.97 ± 0.009</td>
<td>0.88 ± 0.04</td>
</tr>
</tbody>
</table>

n = number of measurements (number of slides analyzed).
* Unpaired t-test, comparing all measurements in control kidneys to all measurements in transplant kidneys.
† Comparing mean ratio to 1.00.

AW, control kidney) for both outer and inner cortex. There was no difference between the mean ratios for outer or inner cortex; thus the ratios for outer and inner cortex were combined, averaged, and this mean ratio compared to 1.00, as shown in Table 1 (bottom line). This analysis also shows that the AW of the transplant kidneys is significantly less than the AW of the control kidneys. Thus, the afferent arterioles of the transplant kidneys are stretched and narrowed.

**Changes in Renal Function**

The serum creatinine increased in each of the recipient dogs from an initial mean value of 1.0 ± 0.1 to a mean value of 2.0 ± 0.4 mg/100 ml on the sixth posttransplant day. The range of individual values was +0.3 to +2.85 mg/100 ml. Because of the relatively large rise in serum creatinine in one dog, the standard error of the increase in serum creatinine was relatively large, and thus paired t-testing of the increase in serum creatinine did not show a statistically significant change (0.1 < P < 0.2). On the average, the transplanted kidney increased in weight by 140% (range, 110–210%). We assume that the increase in transplant kidney weight was due almost entirely to the effects of renal allograft rejection since the technique of transplantation itself does not substantially affect kidney weight. This was shown in a separate experiment in which we autotransplanted one of the dog’s kidneys into the iliac fossa and then removed the contralateral kidney. We found that, 6 days post-autotransplantation, the autotransplant kidney was only 10% heavier than its mate kidney removed at the time of autotransplantation. In this dog, the serum creatinine was 0.7 mg/dl at the time of autotransplantation and 0.85 mg/dl by the sixth day post-autotransplantation. The fact that the serum creatinine did not change importantly indicates that absence of swelling of the autotransplanted kidney was not due to infarction of a major portion of that kidney, since this would have resulted in a much higher rise in serum creatinine.

**Discussion**

This study was undertaken to assess whether the acute parenchymal swelling associated with renal allograft rejection results in stretching of the renal vasculature. Previous microangiographic studies of transplant rejection have not evaluated this question (Almgard et al., 1966, 1967; Clark et al., 1977; Gardner et al., 1968). We compared the length and width of glomerular afferent arterioles (AL and AW, respectively) in normal dog kidneys to those of their contralateral mate kidneys after they had been allowed to undergo 6 days of unmodified rejection. We chose to measure the length and width of the glomerular afferent arteriole because this segment of the vasculature is easily defined and because the glomerular afferent arteriole is a principal resistor in the renal vascular circuit (Abe et al., 1970). We also measured, in both control and transplant kidneys, the shortest distance between the glomerulus and its feeding artery (GD) and the width of the glomerulus (GW).

We found that, on the average, AL was about one-third longer and, at its midpoint, about one-eighth narrower in the swollen rejecting kidneys than in the normal kidneys. Furthermore, we determined that the increase in AL was due almost entirely to stretching (i.e., an increase in true length) of the glomerular afferent arteriole. This determination rests on the observation that, on the average, most glomerular afferent arterioles are...
nearly straight as shown by the fact that mean GD approximates mean AL. Thus, as discussed in detail in Results, uncoiling of the glomerular afferent arteriole (which results in an increase in length of the glomerular afferent arteriole visible to the camera but does not stretch the glomerular afferent arteriole) could not contribute importantly to the measured increase in AL.

To the extent that uncoiling of the glomerular afferent arteriole occurred in the transplant kidney, the present study overestimated the degree of stretching. It seems unlikely, however, that the estimated increase in transplant kidney AL is an overestimate of the degree of afferent arteriolar stretching which actually occurred because the effect of uncoiling on the measurement of AL was probably more than offset by overestimation of control kidney AL. An overestimation of control kidney AL occurred because glomeruli with short afferent arterioles are underrepresented in the measurement of AL in the control kidneys, for reasons discussed in Results. Thus, since control kidney AL is overestimated, this resulted in a falsely low value for the ratio (AL, transplant kidney/AL, control kidney), and this ratio was used as the measure of the degree of transplant kidney afferent arteriolar stretching.

We also found that the transplant kidney afferent arterioles were significantly narrowed compared to those of the control kidney. The finding of the highly significant difference in AW between control and transplant kidneys is especially remarkable because, of all the measurements, AW was measured with the least accuracy. This was unavoidable because AW measurements involve relatively short distances and thus the blurred margins of the projected image, even with optimum focusing, were a substantial part of the total length measured. Despite this source of variability in the measurement, a highly significant difference between transplant and control kidney AW was clearly demonstrated.

We also found that glomeruli were slightly reduced in size in the transplanted kidney, compared to the control kidney. It is unlikely that this finding is due to lesser filling of the transplant kidney glomeruli since only those glomeruli which appeared to be completely filled from side to side (by demonstrating smoothly rounded margins of the glomerulus) were chosen for measurement. It also seems unlikely that the smaller size of the glomeruli in the transplant kidneys is due to glomerular compression since we have found that intrarenal pressure, as assessed by renal subcapsular pressure measurement (Hebert and Arbus 1971) and wedge renal venous pressure measurement, is normal or near normal (unpublished observations). Thus, the most likely reason for the smaller glomeruli in the transplant kidneys is the presence of lower glomerular capillary hydrostatic pressure. This could be the result of an increase in afferent arteriolar resistance because of afferent arteriolar stretching and narrowing.

The present study cannot assess the extent to which afferent arteriolar stretching contributes to the impaired renal function seen in swollen renal allografts since only the afferent arteriole was examined and its diameter measured only at the midpoint. However, if the true average degree of afferent arteriolar stretching and narrowing were 1.32 and 0.88, respectively, resistance to flow through the afferent arteriole would approximately double. Clearly such a change in afferent arteriolar resistance could affect renal function substantially, regardless of adjustments elsewhere in the renal vascular bed.

In summary, as the renal cortex swells in acute allograft rejection, glomeruli are pulled away from their feeding arteries, their afferent arterioles become stretched and narrowed, and the glomeruli become smaller. These anatomic findings indicate that resistance to flow through the afferent arteriole is increased, resulting in a fall in glomerular hydrostatic pressure and, presumably, filtration rate. Thus acute, compliance-mediated expansion of renal parenchymal volume accounts, at least in part, for the impaired function of the swollen renal allograft undergoing acute rejection.

Acknowledgments

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\[ \frac{R_i}{R_o} = \frac{L}{L_{aw}} \] where 

\[ R = \text{resistance, } L = \text{length, and } r_s = \text{radius of vascular segment all under control conditions.} \]

However, if \( L = 1.32 \text{ mm} \) and \( r_s = 0.88 \text{ mm} \), then

\[ \frac{R_i}{R_o} = \frac{L}{L_{aw}} (0.88) \cdot \frac{1}{(2.17)} \]
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