The Vascular Basis for Acute Renal Failure in the Rat
Preglomerular and Postglomerular Vasoconstriction

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SUMMARY Myohemoglobinuric acute renal failure (ARF) was induced in dehydrated, salt-deficient, salt-loaded, and untreated rats by intramuscular injection of glycerol, and the renal vasculature was studied after 24 hours. Kidneys were prepared for examination by rapid freezing in vivo to -160°C and freeze substitution in -80°C alcohol, and by perfusion fixation with 1% glutaraldehyde in Ringer's solution at 120 mm Hg. Frozen kidneys were examined by light microscopy after paraffin and epoxy resin embedding. Techniques used in examining the perfusion-fixed kidneys were: (1) vascular injection with silicone rubber and clearing in glycerol, (2) electron microscopy, and (3) morphometric evaluation of lumen to wall area ratios of glomerular arterioles. Kidneys of all rats with ARF showed renal cortical arterial and glomerular arteriolar (afferent and efferent) vasoconstriction. The degree of constriction, estimated by lumen to wall ratios, correlated with the degree of azotemia ($r = -0.71; P < 0.001$). Differences between all ARF groups and respective controls were highly significant ($P < 0.001$). Vasoconstriction was maximal in the dehydrated group, intermediate in the untreated and Na-deficient rats, and lowest in the salt-loaded animals. Glomerular and peritubular capillaries were patent and free of endothelial swelling or thrombi. Glomerular basement membranes and epithelial foot processes showed no morphological alterations. The observations suggest that marked pre- and postglomerular vasoconstriction occurs in established myohemoglobinuric ARF, that it is related to azotemia, and that mechanical vascular obstruction does not play a major role in this experimental model.

THE PATHOGENESIS of oliguria in acute renal failure (ARF) is poorly understood. Tubular obstruction and backflow of glomerular filtrate have been considered as pathogenetic factors, but the balance of evidence suggests that primary failure of glomerular filtration also occurs. Functional studies have suggested that this may be mediated through decreases in renal cortical blood flow. The cause of the perfusion defect is thought to be preglomerular vasoconstriction but this has not been demonstrated. Experiments on postischemic kidneys have indirectly suggested that concurrent pre- and postglomerular vasoconstriction may occur early after restoration of blood flow. However, mechanical vascular obstruction may play a role in ARF, and it appears possible that endothelial swelling and intravascular coagulation are responsible for the development and maintenance of irreversible tubular injury. Whether such factors cause a hemodynamic abnormality is established ARF remains unknown. Decreased glomerular hydraulic conductivity, which is due to morphological abnormalities of glomerular epithelial foot processes in some models, has been suggested as a cause of filtration failure in ARF.

Many recent conflicting functional studies have reopened the question of whether a renal cortical perfusion defect occurs in experimental ARF. Unchanged renal cortical blood flows were found at the 24-hour stage in rat myohemoglobinuric ARF, the same model in which markedly decreased cortical perfusion previously was demonstrated. Blood flow was recorded as moderately decreased or normal in the early stages of uranyl nitrate poisoning in rats, and markedly decreased or normal in the late (48-hour) stage after identical doses of the nephrotoxin in dogs. In view of these inconsistencies, and to determine whether a significant renal cortical vascular defect (vasomotor or mechanical) occurs in established ARF, we have used more direct methods of approach to study the renal vasculature in the 24-hour rat myohemoglobinuric model. The results, obtained after rapid freezing of kidneys in vivo and intravascular perfusion fixation with morphometric analysis of glomerular arterioles, show that a marked combined preglomerular and postglomerular vasoconstriction occurs in the absence of other causes of vascular obstruction, and correlates with azotemia.

Methods

ANIMALS

Female Sprague-Dawley rats were given the following diets: Thirty-one rats received standard laboratory chow and water ad libitum (untreated ARF and controls). Thirty rats on standard laboratory chow were deprived of water for 24 hours prior to the experiment (dehydrated ARF and controls). Control rats were studied at the end of the period of dehydration, whereas experimental rats had free access to water after induction of ARF. Twenty-five rats received the modified Hartroft sodium-deficient diet (Nutritional Biochemical Co., Cleveland) with water ad libitum for 3 weeks prior to the experiments (Na-deficient ARF and controls). Twenty-one rats receiving standard chow were given either 1% NaCl (eight rats) or 1% NaCl in 5% glucose (13 rats) as drinking water for 3 weeks prior to and during the experiments (salt-loaded ARF and controls). Individual rats were kept in metabolic cages before and during experiments, and then fluid intake and output was monitored. The weight of rats in the untreated, sodium-deficient, dehydrated,
salt-loaded groups averaged 266, 233, 231, and 293 g, respectively, immediately before the induction of ARF.

INDUCTION OF ARF

ARF was induced in 13 untreated, 21 dehydrated, 16 sodium-deficient, and 16 salt-loaded rats by the intramuscular injection of 50% glycerol (10 ml/kg) in divided doses into both thighs of animals.1 Eighteen untreated rats (nine, sodium-deficient and nine, dehydrated) and five salt-loaded animals did not receive glycerol injections and served as controls. Blood urea nitrogen (BUN) was measured in heparinized whole blood by an automated method.22

MORPHOLOGICAL AND VASCULAR STUDIES

Vascular studies were made under identical conditions in experimental rats 24 hours after glycerol injection and in control animals. The rats were anesthetized with pentobarbital (50 mg/kg, ip) and received no other medication. Blood (0.5 ml) was collected from the femoral vein of all rats under anesthesia. Rats that sustained any further blood loss during anesthesia were rejected from the vascular studies. Eighty-two rats were considered satisfactory for examination and were subjected to the following procedures.

FREEZE SUBSTITUTION

Left kidneys were freed gently from surrounding tissue and small boats of Parafilm placed underneath. Isopentane, cooled to -160°C with liquid nitrogen, was quickly poured onto the anterior surface of the kidneys to freeze them in vivo. Frozen kidneys were fractured from their pedicles, broken in half, and transferred to absolute alcohol at room temperature for 12 hours. Samples of renal cortex that had come into first contact with coolant then were embedded in paraffin and Epon 812 and small boats of Parafilm placed underneath. Isopentane, cooled to -160°C with liquid nitrogen, was quickly poured onto the anterior surface of the kidneys to freeze them in vivo. Frozen kidneys were fractured from their pedicles, broken in half, and transferred to absolute alcohol at room temperature for 12 hours. Samples of renal cortex that had come into first contact with coolant then were embedded in paraffin and Epon 812.

ELECTRON MICROSCOPY

This sections of Epon-embedded, perfusion-fixed renal cortex from five control and five ARF rats were cut with diamond knives, stained with uranyl acetate and lead citrate, and examined in a Philips 200 electron microscope.

MORPHOMETRY OF ARTERIOLES

A total of 1,794 glomerular arterioles in 2-μm-thick Epon sections of perfusion-fixed kidneys from rats of each group were photographed sequentially (400x on 35-mm film) and studied by a point-counting method33 described below. All arterioles within 60 μm of glomeruli, with the exception of interlobular vessels, were included. Afferent and efferent arterioles were traced to, and away from, glomeruli in 100 serial 2-μm sections from each of two ARF kidneys that had been embedded in Epon after freeze substitution and perfusion fixation.
lumen to wall, remains constant both in perfect cross sections or in obliquely cut sections. Thus, cross-sectional profiles of all arterioles with well defined lumina (including slightly oblique sections) were studied. Large sample sizes (mean number of samples = 39) were used to calculate mean lumen to wall ratios for individual rats, since it became obvious early in the study that glomerular arterioles are heterogeneous in their size range and show, within kidney, variation in vascular tone as measured by this technique (see distributions of lumen to wall ratios, in Figure 6). Differences between groups and within groups were studied after two-way analysis of variance.27

Results

GENERAL

Experimental rats from the untreated, dehydrated, and sodium-deficient groups had hemoglobinuria, variable oliguria, and azotemia (Table 1). Nine of 13 rats in the untreated group developed severe ARF with BUN greater than 50 mg/100 ml. They were not significantly oliguric and exhibited unpredictable weight gains or losses during the 24-hour ARF period. The other four animals, with BUN less than 50 mg/100 ml, had marked polyuria and weight loss [7.3% ± 0.9% (SEM) weight loss; P < 0.005]. Differences between ARF groups were significant (P < 0.001). BUN of Na-deficient ARF rats did not differ significantly from those of the untreated group and showed similar variability within each group (Table 1). Twelve rats with severe ARF had significant oliguria, and gained weight during the ARF period [3.8% ± 0.7% (SEM) weight gain; P < 0.001]. However, four rats with BUN less than 50 mg/100 ml were not oliguric and lost weight [4.4% ± 0.7% (SEM) weight loss; P < 0.01]. All 21 dehydrated ARF rats were severely azotemic and oliguric and gained weight during the ARF period [4.2% ± 0.7% (SEM) weight gain; P < 0.001]. Saline-loaded ARF rats, with two exceptions, had large urine volumes (not different from salt-loaded controls) and only moderate azotemia compared to all other ARF groups (Table 1), and showed unpredictable weight gains or losses. These rats are referred to as the “protected” ARF group. The two exceptions had oliguria, extreme weight gain and edema, and marked azotemia (BUN = 90 and 127 mg/100 ml, respectively) at the end of the 24-hour period. These two rats had renal vascular changes (see below) comparable to those found in severely azotemic ARF rats rather than in the “protected” group. Kidneys from all ARF animals revealed tubular epithelial swelling, degeneration and necrosis (Figs. 1 and 2), and pigmented casts (not shown). Tubules were fully patent in control kidneys, but were variably collapsed in ARF kidneys (Figs. 1 and 2), the degree of collapse roughly paralleling the degree of azotemia. Kidneys of saline-loaded protected rats showed tubular necrosis as in the other groups, but had greater numbers of open tubules and fewer casts in tubular lumina. Glomeruli and peritubular capillaries were within normal limits.

Table 1  Urine Volumes (24-hour), Blood Urea Nitrogen (BUN), and Lumen to Wall Ratios

<table>
<thead>
<tr>
<th></th>
<th>Urine volumes (ml/24 hr)</th>
<th>BUN (mg/100 ml)</th>
<th>Lumen/wall (mean ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control, untreated</td>
<td>9.8 ± 0.9* (23)</td>
<td>13.9 ± 0.9 (18)</td>
<td>0.57 ± 0.02 (5/183)</td>
</tr>
<tr>
<td>ARF, untreated</td>
<td>6.8 ± 2.7† (9)</td>
<td>88.9 ± 14.1 (13)</td>
<td>0.30 ± 0.02 (5/185)</td>
</tr>
<tr>
<td>BUN &gt; 50 mg/100 ml</td>
<td>46.5 ± 8.5 (4)</td>
<td>13.7 ± 1.5* (15)</td>
<td>0.77 ± 0.08 (5/180)</td>
</tr>
<tr>
<td>BUN &lt; 50 mg/100 ml</td>
<td>4.0 ± 0.49 (20)</td>
<td>19.2 ± 1.0 (9)</td>
<td>0.30 ± 0.02 (5/124)</td>
</tr>
<tr>
<td>Control, dehydrated</td>
<td>1.1 ± 0.5§ (21)</td>
<td>134.4 ± 4.9 (21)</td>
<td>0.71 ± 0.04 (5/175)</td>
</tr>
<tr>
<td>Control, Na-deficient</td>
<td>13.7 ± 1.5 (15)</td>
<td>14.1 ± 0.8 (9)</td>
<td>0.33 ± 0.04 (7/235)</td>
</tr>
<tr>
<td>BUN &gt; 50 mg/100 ml</td>
<td>1.5 ± 0.5§ (12)</td>
<td>86.0 ± 8.2 (16)</td>
<td>0.71 ± 0.03 (5/175)</td>
</tr>
<tr>
<td>BUN &lt; 50 mg/100 ml</td>
<td>18.8 ± 7.7 (4)</td>
<td>0.71 ± 0.03 (5/175)</td>
<td>0.30 ± 0.05 (9/370)</td>
</tr>
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</table>

ARF = acute renal failure.

Values given are mean for the group ± 1 standard error of the mean. Figures in parentheses correspond to the number of rats, and those for lumen/wall ratios, the number of rats and replications.

* Includes values from rats prior to glycerol injection.
† Paired t-test for polyuria on paired volume (before and after glycerol) not significant (P > 0.2).
§ Paired t-test for oliguria significant (P < 0.005). Differences between ARF groups and respective controls (BUN and lumen/wall ratios) were highly significant (P < 0.001). Differences between ARF groups were significant (P < 0.001) except between untreated and Na-deficient ARF (NS).
FIGURE 1  Light micrographs from tissue rapidly frozen in vivo to -160°C and substituted in -80°C alcohol (a-d, embedded in paraffin and stained with Verhoeff's elastic stain; e and f, embedded in Epon and stained with toluidine blue; a and b, scale bar = 0.1 mm; c-f, scale bar = 10 μm). a: Control kidney showing wide open interlobular arteries (arrows, elastica stained black), tubular lumina, and Bowman's spaces of glomeruli. 62×. b: Kidney from sodium-deficient rat with acute renal failure (ARF) showing narrowed interlobular arteries (arrows), collapsed tubules, and Bowman's spaces of glomeruli (compare with a). 62×. c: Widely patent interlobular artery and tubules from control rat kidney. 450×. d: Contracted interlobular artery and collapsed tubules from kidney of ARF rat of the dehydrated group. Note the marked wrinkling of arterial elastica and protrusion of endothelial cells into vessel lumen. Tubular cells show degenerative changes (compare with c). 450×. e: Kidney of control rat. Two widely open glomerular arterioles, containing erythrocytes, are present (arrows). Tubular lumina are patent and Bowman's spaces of glomeruli are open. Note preservation of the brush border of proximal tubules. 450×. f: Kidney of ARF rat of the dehydrated group. Glomerular arteriole (arrow) shows marked contraction in contrast to control kidneys. Tubular lumina are collapsed. Epithelial cells show degenerative changes and focal loss of nuclei. Bowman's space of glomerulus is collapsed (compare with e). 450×.
VASCULAR STUDIES

Freeze-substituted (Fig. 1) and perfusion-fixed (Fig. 2) ARF kidneys showed marked contraction of interlobular arteries and glomerular arterioles. Vessels from kidneys of all groups of controls were widely patent. (Compare: controls, Figs. 1a, c, e, and 2a, c; ARF, Figs. 1b, d, f, and 2b, d). Serial sections showed that contracted arterioles could be traced from the glomeruli either to interlobular arteries or to the peritubular capillary plexus. Thus, there was vasoconstriction of efferent as well as afferent arterioles. The following criteria were taken to be indicative of vasoconstriction: (1) irregular luminal narrowing; (2) bulging, rounded endothelial cells; (3) increase in wall thickness relative to lumen; (4) shortened and deformed medial cells; and (5) excessive waviness of the elastica. In freeze-substituted ARF kidneys, severely contracted arterioles were associated with collapse of the Bowman’s spaces in corresponding glomeruli (Fig. 1b and f).

SILICONE RUBBER INJECTIONS

“Complete” injections with silicone rubber showed uniform filling of the renal vasculature in control (Fig. 3a), but not ARF rats. In the latter, small “filling defects” were observed in the cortex (Fig. 3b), where the viscous injection mass (15–25 centipoise) often stopped at the level of severely narrowed preglomerular arterioles. Evaluation of these vessels was difficult in completely injected specimens because there was some filling of peritubular capillaries.

Figure 2 Light micrographs from tissue fixed by perfusion at 120 mm Hg with 1% glutaraldehyde, embedded in Epon, and stained with toluidine blue. Black material in vessels is silicone rubber, shrunken by alcohol dehydration (a and b, scale bar = 10 μm; c and d, scale bar = 10 μm). a: Kidney of control rat, showing open tubular lumina, and widely patent interlobular artery (arrow) and vein. 450x. b: Kidney of rat with acute renal failure (ARF) showing markedly contracted interlobular artery (arrow); it has thickened walls, wrinkled elastica, and bulging endothelial cells. Tubules show collapse and degeneration of epithelium. Dark droplets represent reabsorbed myoglobin and hemoglobin (compare with a). 450x. c: Kidney of control rat, showing widely open glomerular arteriole (arrow). There are many dark staining renin granules in the medial smooth muscle cells. G = glomerulus. 925x. d: Kidney of ARF rat, markedly contracted glomerular arteriole (arrow). As in c dark granules in the media represent renin droplets (compare with c). 925x.
(Fig. 3b). In incompletely injected preparations, narrowing of interlobular arterial and afferent arteriolar lumina could be demonstrated in all ARF kidneys (Figs. 3d, 4b, and 4c) but not in controls (Figs. 3c and 4a). Narrowing of efferent arterioles also could be demonstrated (Fig. 4b). The degree of narrowing varied between different rats and within the same kidney, but roughly paralleled the severity of ARF (see also Morphometry of Arterioles). Arterioles and arteriolar
lumina often were narrowed irregularly, giving the casts a "beaded" or "hourglass" appearance (Fig. 4b and c) similar to that of arterioles contracted by vasoactive agents. These vascular changes were present in kidneys from saline-loaded "protected" rats also, but were less severe in degree than in the dehydrated, sodium-deficient, and untreated ARF groups. Images of glomeruli from control and ARF rats did not differ significantly.

**MORPHOMETRY OF ARTERIOLES**

Sample arterioles in various stages of contraction and their lumen to wall ratios are shown in Figure 5a-f. The results are shown in Table 1 and Figure 6. Among control animals, mean lumen to wall ratios were significantly lower in untreated than in salt-deficient, salt-loaded, or dehydrated groups which did not differ among themselves. The values for the ARF groups were decreased significantly, the degree of vasoconstriction being greatest in the dehydrated ARF group and lowest in the untreated and salt-loaded ARF groups as compared to their respective controls (Table 1). When the ARF groups were compared among themselves with reference to the untreated controls, vasoconstriction was least in the salt-loaded group, maximal in the dehydrated rats, and intermediate in the untreated and sodium-deficient rats. Differences between the latter two groups were not significant (Table 1). Mean lumen to wall ratios in ARF rats correlated well with the severity of disease, as estimated by BUN, lower ratios being associated with higher BUN (Fig. 7). Histograms showing percent distribution of arterioles in arbitrarily divided lumen to wall ratio classes (0.0-0.25, 0.26-0.50, 0.51-0.75, 0.76-1.00, 1.01-1.75) are shown in Figure 6-1 to 6-V.

**ELECTRON MICROSCOPY**

Glomerular and peritubular capillaries from ARF rats had patent lumina and no endothelial swelling or degeneration (Fig. 8a and b) even from areas that were not filled with silicone rubber. There was no evidence of significant simplification, flattening, or "fusion" of visceral epithelial foot processes in glomeruli (Fig. 8a). Studies of contracted (Fig. 9b) as opposed to noncontracted (Fig. 9a) arterioles revealed nuclear membrane convolution and "pinches" in smooth muscle cells in addition to other features of contraction.

**Discussion**

The results indicate: (1) that preglomerular and postglomerular vasoconstriction occur in kidneys during the established phase of rat myohemoglobinuric ARF; (2) that mechanical (organic) vascular obstruction does not occur at this stage of disease; and (3) that the degree of vasoconstriction is related to the severity of azotemia.

**TECHNICAL CONSIDERATIONS**

The validity of our results is suggested by the following: (1) Rapid freezing in vivo was used to control the results obtained by perfusion fixation. Sampling was restricted to tissue that first had come into contact with coolant. (2) Although lumen to wall ratios showed some variability within each kidney, there was uniformity of mean ratios

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**FIGURE 4** Light micrographs of kidneys processed as in Figure 3. Incompletely injected with silicone rubber (scale bar = 0.1 mm). a: Kidney of control rat showing interlobular arteries, afferent arterioles, glomeruli, and one efferent arteriole. 100x. b and c: Kidneys of untreated rats with acute renal failure (ARF) showing irregular narrowing of the caliber of interlobular arteries and afferent arterioles. Efferent arteriole in b shows segmental constriction. 100x.
among control rats and, with few exceptions, among ARF rats with similar severity of disease (Fig. 7). (3) Differences between control and experimental rats were consistent and reproducible. (4) The consistent observation of open tubules in control kidneys and collapsed tubules in similarly studied experimental kidneys suggests that the "functional" state of the tissue was preserved by both fixation methods.33, 34

Barbiturate anesthesia decreases renal blood flow in
Figure 6  Histograms showing the distribution of glomerular arterioles from perfusion fixed kidneys in arbitrarily divided lumen to wall (L/W) ratio classes in the control and various acute renal failure (ARF) groups (see text); 0-0.25 represents the most contracted class.  y = percent of arterioles in each group;  x = lumen to wall ratio. Controls shown represent untreated controls. Dehydrated, sodium-deficient, and salt-loaded controls exhibited a shift toward the 0.76–1 lumen to wall ratio class (not illustrated). Number of arterioles in the various groups were: control, 183; untreated ARF, 185; dehydrated ARF, 243; Na-deficient ARF, 283; and salt-loaded ARF, 370.
normal dogs; surgery may result in similar alterations. In our study, all rats were subjected to identical procedures and, thus, to the experimental error. Nevertheless, it is possible that these extraneous stimuli provoke more vasoconstriction in ARF kidneys than in controls. Alternatively, the renal vasculature may respond abnormally to the altered internal milieu in ARF, even in the absence of specific constrictor mechanisms. In any case, the vascular response was a function of disease, since lumen to wall ratios correlated with BUN. Study of vascular hypersensitivity requires noninvasive techniques of investigation, but these do not appear possible at present. As blood pressures were not monitored, the occurrence of hypotension in occasional rats was not ruled out. However, myohemoglobinuric ARF rats in which normal blood pressures had been recorded during the experiments showed marked reduction in renal cortical blood flow and therefore increased vascular resistance. This, taken in conjunction with our consistent observation of renal cortical vasoconstriction in ARF rats, in the absence of mechanical obstruction, indicates that blood pressure alterations are not major determinants of the vascular abnormality.

CONTRACTION OF ARTERIES AND ARTERIOLES

The images of renal cortical resistance vessels in both perfusion-fixed and rapidly frozen ARF kidneys fulfill the criteria for vasoconstriction described previously. Although superficial and deep glomeruli were not differentiated in the quantitative studies (both being included in one group), analysis of specimens that received silicone rubber casts, (2) serial sections of glomerular arterioles, and (3) the distribution patterns of lumen to wall ratios in ARF groups. Figure 6 shows that 69% of arterioles from dehydrated ARF kidneys were of the 0-0.25 lumen to wall ratio class (this being the “most contracted” group), compared to only 7% in untreated controls and 4.4% in dehydrated controls (not illustrated). Thus, more than half of glomerular arterioles in the dehydrated ARF group were severely contracted relative to controls, indicating simultaneous involvement of afferent and efferent arterioles. Although postglomerular constriction was not quantified relative to preglomerular involvement, serial sections and silicone rubber casts of ARF kidneys suggested that both groups of vessels were equally narrowed.

GLOMERULAR AND PERITUBULAR CAPILLARIES

Glomerular and peritubular capillaries were free of thrombosis and endothelial swelling 24 hours after injection of glycerol; this suggests that these factors do not play a significant role in clinical disease at this stage of ARF. However, the possibility of vascular lesions occurring early in the course was not ruled out. Glomerular fibrin deposition, obstruction due to hemoglobin sludge, swelling of glomerular cells, and vascular spasm occur 0-4 hours after glycerol injection and may be related to the development of tubular lesions. Likewise, endothelial and peritubular cell swelling may account for the “no reflow phenomenon” and lead to ischemic renal injury and failure immediately after total renal artery occlusion. “Fusion” of glomerular epithelial foot processes has been considered as a possible cause for reduced glomerular filtration in ARF. Glomerular epithelial changes were not observed in our present experiments. The techniques used in the present study do not permit us to rule out other factors that might lead to decreased hydraulic conductivity of the glomeruli. On the other hand, contracted arterioles were associated with collapsed tubular lumina and Bowman’s spaces in corresponding glomeruli of experimental kidneys.
FIGURE 8  Electron micrographs of dehydrated acute renal failure (ARF) kidneys fixed by perfusion at 120 mm Hg with 1% glutaraldehyde, embedded in Epon, and stained with uranyl acetate and lead citrate. a: Glomerular capillaries (CAP) showing patent lumina and normal-appearing endothelium and epithelium (EP). MES = mesangium. Scale bar = 1 μm. 4,000×. b: Peritubular capillary (CAP) and necrotic tubular epithelium (TUB). Capillary endothelium (END) does not appear swollen (arrows). Scale bar = 1 μm. 10,000×.
This supports the notion that hemodynamic factors are related to glomerular filtration in myohemoglobinuric ARF.

**PATHOGENESIS OF VASOCONSTRICTION**

The pathogenesis of renal cortical vasoconstriction in ARF remains unknown. In our experiments dehydration, but not sodium deficiency, increased the severity of clinical disease and arteriolar constriction over that seen in untreated rats; salt-loading afforded protection. Although dehydration (and sodium deficiency) and chronic salt-loading are known to induce enhancement and suppression of renal renin activity, respectively, our results do not permit us to make definitive statements regarding the influence of this factor on clinical disease and renal cortical vasoconstriction. The results may well be explained by the general systemic effects of these treatments rather than by changes in intrinsic renal factors. Recent evidence suggests that the renin-angiotensin axis is unrelated to renal function in myohemoglobinuric ARF and that other factors may be involved. On the other hand, tubular obstruction appears to be causally related to the development of increased vascular resistance in other models. The techniques used in our present experiments may offer an approach to the study of the effects of these factors on preglomerular and postglomerular vessels in ARF. Finally, the relative roles played by tubular and vascular factors in the genesis of oliguria in this model of ARF need to be determined, as has been done for unilateral renal ischemia.

**Acknowledgments**

It is a pleasure to acknowledge the statistical assistance provided by Drs. H.M. Venkatachalam and B. Rosner and the secretarial work performed by Vonda Samuels. Dr. Ramzi S. Cotran provided help and encouragement throughout this study.

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The vascular basis for acute renal failure in the rat. Preglomerular and postglomerular vasoconstriction.

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doi: 10.1161/01.RES.38.4.267

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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