Pathogenesis of Oliguria in Acute Renal Failure

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Nearly half a century has passed since Dr. A. N. Richards described his findings of continued glomerular filtration in a frog made anuric with HgCl$_2$ (1). Although his concept that nearly all of the glomerular filtrate passively moves across damaged tubular epithelial cells was given support by the microdissection studies of Dr. Jean Oliver et al. (2), the intervening years have not seen a consensus as to the factors responsible for the oliguria of acute renal failure.

Despite the facts that several pathophysiological events relating to the presence of oliguria have been identified and that each has received experimental support (3), a persisting controversy exists concerning the relative importance of tubular obstruction, passive backflow of filtrate, and failure of filtration due to such causes as preglomerular vasoconstriction, a decrease in glomerular plasma flow, or an alteration in the ultrafiltration coefficient of the glomerular capillary membranes. The situation becomes particularly complex in those experimental models in which more than one abnormality is found. Nonetheless, data accumulated over the past decade have led some to conclude that "...a primary abnormality in glomerular filtration plays a major role in all models to date, presumably reflecting significantly increased preglomerular vascular resistance" (4). As a result, it has been suggested that the syndrome of oliguric acute renal failure is most accurately referred to as "vasomotor nephropathy" (5). We believe, however, that the initial insult, whether it be due to ischemia, nephrotoxins, or a combination of both, sets into motion a series of events which are self-perpetuating. Such a sequence is illustrated in Figure 1. In this frame, one factor or another may assume predominance at any given time and obscure the contribution of others. Thus, we feel that it is advisable not to ascribe the oliguria to a single cause but rather to discuss it in terms of its generation and maintenance.

The development of this perspective has been aided by the application of an electronic servo-nulling pressure apparatus (6, 7) and by the identification by Dr. Klaus Thurau of a strain of Munich-Wistar rats possessing glomeruli on the surface of the kidney. This anatomy permits the direct measurement of glomerular capillary hydrostatic pressure and the assessment of changes in pre- and postglomerular vascular resistances. Use of the pressure apparatus also allows continuous monitoring of intratubular pressure during microinjection experiments to determine tubular permeability characteristics—a necessity when potentially diseased or damaged nephrons are considered. In addition, the recent availability of a noncannulating electromagnetic flow transducer of small enough size to measure blood flow in the rat kidney without interfering with normal kidney function allows for the first time accurate and instantaneous measurements of renal blood flow during a series of experimental observations (8). This method appears to be the one of choice for determining renal blood flow in the diseased kidney when the validity of other techniques such as the para-aminom hippuric acid clearance-extraction method may be suspect.

It is the purpose of this review to examine critically some of the micropuncture data which are supportive of each of the proposed pathophysiological mechanisms of oliguric acute renal failure. Included will be information recently obtained in our laboratory and a summary of what we believe to be a unifying hypothesis concerning the events responsible for the generation and the maintenance of the oliguria.

FILTRATION FAILURE

The most compelling data implicating alterations in preglomerular vascular resistance as the
FIGURE 1

Schema of interrelated events which may follow acute circulatory or toxic renal damage. Alterations in glomerular capillary pressure, permeability, and blood flow lead directly to a reduction in filtration and urine formation; obstruction of the tubules retards the flow of filtrate and promotes backleakage across damaged epithelium. The factors are not mutually exclusive nor are all necessarily present; moreover, they probably vary in importance between different models and from time to time in the same model. For details, see text.

major physiological abnormality in the reduction of filtration and the subsequent development of oliguria come from the studies of mercury- and glycerol-induced acute renal failure in rats by Oken and his colleagues. In their initial studies, Flanigan and Oken (9) employed relatively large doses of HgCl₂ (12 mg/kg, im). Periodically over the next 24 hours, they observed the appearance of the kidney in vivo, measured proximal intratubular pressures, and estimated intratubular flow rates. For the first 6 hours after mercury injection, the surface of the kidney appeared normal; then, the lumens of some tubules became narrow and the cells granular. By 24 hours, virtually all of the tubules were pale and coarsely granular and had extremely narrow or no lumens; there appeared to be little or no tubular flow. At no time, however, was any disturbance in peritubular capillary flow observed. Proximal intratubular pressure was normal the first 4–8 hours but decreased thereafter, with a greater than normal variability between nephrons. At 6 hours, single nephron glomerular filtration rate and absolute water reabsorption were diminished. These authors were not able to quantify water movement after 6 hours, but they arrived at qualitative estimates of intratubular flow rates by observing the behavior of small droplets injected into the tubules. The percent of nephrons with normal flow decreased progressively so that flow was minimal or absent at 24 hours.

These authors concluded that, since glomerular filtration rate fell without an increase in intratubular pressure, tubular obstruction per se was not the responsible factor. Furthermore, they felt that the tubular obstruction by debris which was present in later phases resulted from the aggregation of particles when tubular flow was reduced and was not the cause of the diminished tubular flow. Since no experiments were done on rats whose mean arterial blood pressure was less than 85 mm Hg, the authors postulated that a primary decrease in glomerular filtration rate such as that which could be produced by preglomerular vascular constriction, postglomerular dilatation, or both, was the initial cause of anuria. Their results, which included the observation that reabsorption of saline droplets between oil columns decreased progressively with time and was almost nonexistent at 24 hours, led them to discount the possibility that anuria resulted from continuing filtration with total reabsorption of the filtrate through passive backflow.

Oken and his colleagues next turned to glycerol-induced acute renal failure in rats (10). They investigated this model extensively, since they believed that it was more closely related to the syndrome of acute renal failure in man, although the complexity of the model greatly complicates an understanding of its pathogenesis. Marked swelling of the injected muscles, destruction of muscle cells and red blood cells, and excretion of myoglobin and hemoglobin all occur. Undoubtedly, there are alterations in body fluid compartments, probably involving circulating blood volume; renal vasoconstriction even with normal blood pressure seems to be an a priori expectation. The sequence of events found by Oken and his associates was very similar to that described in the high-dose mercury poisoning experiments just discussed with the addition of an acute but transitory change in renal blood flow. Qualitative estimates of proximal flow rates obtained by observing the behavior of a small oil droplet injected into a nephron showed decreasing flow over a 24-hour period, especially in dehydrated rats. Single nephron glomerular filtration rate and absolute water reabsorption were diminished. At no time was there evidence of increased intratubular pressure; proximal intratubular pressure was reduced both early and later in the development of the syndrome even though pigment casts appeared in the tubules.

Again these authors came to similar conclusions, namely that a decreased rate of filtration and proximal flow resulted from failure of filtration due to vascular changes and that tubular obstruction and increased leakiness of the tubule were not
ACUTE RENAL FAILURE

-passive backflow of glomerular filtrate

The principal contemporary work that appears to support the passive backflow mechanism is the 1967 study by Bank and his colleagues (15). Rats injected with a low dose of mercuric chloride became anuric in about 24 hours following an earlier diuretic phase. The rats remained anuric for another 24 hours after which time urine output returned. The most striking data are color photomicrographs of the surface of a normal and a mercury-treated rat kidney following intravenous injection of lissamine green. The dye rapidly appeared in the peritubular capillaries of both kidneys, and the usual progression down the proximal tubule was seen in the normal kidney. In the mercury-treated rat kidney, in contrast, the color of the dye became progressively lighter as it flowed through coils of proximal convolutions and was barely visible in the terminal segments of the proximal tubule. It never appeared in distal convolutions. These observations suggested to the authors that the proximal epithelium had become abnormally permeable to lissamine green. Single nephron glomerular filtration rate determined from tubular fluid collected at various sites along the nephron appeared to support this point of view. Single nephron glomerular filtration rate was normal when it was determined on fluid collected from the early proximal tubule but was only 37% of this value when it was determined on fluid collected from the late proximal tubule and 26% of normal when it was determined on fluid collected from distal convolutions. The authors felt that these observations supported their supposition of extensive passive backflow or leakage of tubular fluid.

Several questions can be raised about this interpretation, however. The most extensive morphological changes following the administration of low doses of mercury like those used in these experiments, and in fact the only changes visible by light microscopy, are in the pars recta of the proximal tubule (16). Yet the observations of Bank et al. (15) suggest extensive permeability changes in the pars convoluta with little apparent inulin loss in the pars recta. It is possible that the apparent decrease in inulin flow along the tubule resulted from the selection of nephrons with heterogeneous single nephron glomerular filtration rates and does not truly represent transtubular inulin leakage. Inulin microinjections with very careful and continuous measurement of the intratubular pressure during the microinjection constitute a better method of

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1 It has very recently been suggested that glomerular permeability in rats given uranyl nitrate is significantly reduced before the onset of definite electron micrographic changes in the glomerulus (Blantz RC: Mechanism of acute renal failure after uranyl nitrate. J Clin Invest 55:621–635, 1975).
determining inulin leakage. Another apparent anomaly of the experiments of Bank et al. (15) is the fact that lissamine green did not appear in distal convolutions although fluid could be collected from them for inulin determinations. This observation is similar to that reported several years later by Steinhausen and his colleagues (17). They also followed lissamine green tubular flow in rats poisoned with mercury and observed that the dye became progressively paler the further along the proximal tubule it flowed. However, Steinhausen and his colleagues concluded that this effect was due at least in part to protein-binding of lissamine green, since suffusion of the renal surface with dilute acid caused the reappearance of the lissamine green. To study further the possibility of passive backflow, Steinhausen et al. microinjected inulin into proximal convolutions of rats treated with mercuric chloride. In one experiment all of the inulin was excreted in the urine from the ipsilateral kidney, indicating that there was no inulin leakage, but in the other five experiments there was very significant inulin excretion by the contralateral kidney. Rather surprisingly, however, in four of the five experiments, inulin excretion by the contralateral kidney vastly exceeded excretion by the kidney containing the microperfused tubule. This finding is hard to understand, since inulin lost from a permeable membrane. As a result, these experiments should not be considered conclusive.

The question at issue is not whether there is a change in renal tubular permeability. Clearly, there must be major changes when there is necrosis of the tubular epithelium; this fact can be easily demonstrated. The question is the significance of a permeability change as a cause of anuria. Are there circumstances under which, in the presence of tubular necrosis, filtration continues and the balance of the driving forces—the physical factors—favors reabsorption? Tubular obstruction would tilt this balance of physical factors in that direction, and we believe it is likely that some passive backflow occurs under these conditions.

**INTRATUBULAR OBSTRUCTION**

Data suggesting a prominent role for tubular obstruction have been derived from micropuncture studies performed following temporary complete renal artery occlusion in the rat (18, 19). It is worth noting that many of the agents used to produce experimental acute renal failure do so not only by a direct nephrotoxic effect but also in association with an ischemic period of variable extent and duration. For this reason it is somewhat surprising that acute renal failure produced by ischemia has not received wider attention by those engaged in renal micropuncture studies. One complicating feature has been the reports by some that in the rat intrarenal circulation is not reestablished following variable periods of complete ischemia (20, 21). This so-called "no-reflow phenomenon" has been attributed to a markedly increased renal vascular resistance due to endothelial cell swelling (22). In this scheme, active sodium transport is inhibited during the period of ischemia, and intracellular sodium and water accumulate with swelling of the cells and a reduction in the diameter of the vascular lumens. Hypertonic solutions have been reported to decrease cell swelling through an osmotic effect and thus to reduce renal vascular resistance (22). This concept has received considerable discussion and has been applied in the study of the effects of ischemia on other vascular beds. For reasons to be mentioned later, we do not consider this phenomenon to be a major component of either the generation or the maintenance of oliguria.

Those who did find some degree of reflow were impressed by their inability to measure accurately either renal blood flow or glomerular filtration rate by the standard clearance methodology (23). This failure was attributed to the leakage of tubular fluid across damaged epithelial cells, a point of some importance in considering the events leading to oliguria. Data from several laboratories including our own (18, 19, 24) indicate that reflow generally occurs following 1 hour of temporary renal artery occlusion in the heparinized rat. We found that on release of the renal artery clamp renal blood flow measured by an electromagnetic flow transducer rapidly returned to approximately 50% of the control value. As blood flow returned, the previously collapsed tubules opened and then became distended. The return of glomerular filtration was confirmed by the appearance in the renal circulation and the proximal tubules of FD & C green injected intravenously. Dye remained in proximal tubules and was seen only rarely in distal convolutions, suggesting the presence of tubular obstruction. Obstruction was confirmed by the presence of markedly elevated proximal intratubular pressure. Glomerular capillary hydrostatic pres-
sure at this time was normal whether it was measured directly in Munich-Wistar rats or estimated from the sum of the intratubular stop-flow pressure and the arterial colloidal osmotic pressure. Although renal vascular resistance was increased as reflected by a decrease in renal blood flow at an unchanged perfusion pressure the resistance changes were such as to maintain glomerular capillary hydrostatic pressure. Tubular obstruction was thus responsible for the generation of the oliguria.

Other rats were studied 24 hours after the ischemic episode. Both proximal intratubular pressure and glomerular capillary hydrostatic pressure were now significantly reduced, indicating the secondary development of predominant preglomerular vasoconstriction. Although the decrease in proximal intratubular pressure did not suggest the continued presence of intratubular obstruction, there were several observations which did. Prominent among these was the presence of intratubular casts in histological sections. In addition, distal intratubular pressure remained elevated. As mentioned earlier, one would expect proximal intratubular pressure to be reduced even in the presence of obstruction when glomerular capillary hydrostatic pressure is low and damaged and necrotic tubular epithelium prevents the maintenance of large transtubular pressure gradients. The lack of tubular integrity was made apparent by the microinjection of dye at such a rate so as not to elevate the simultaneously recorded intratubular pressure. The dye was seen to form a "halo" around the injected tubule as it entered the peritubular circulation.

Under these circumstances, the relative importance of augmented preglomerular vascular resistance in the maintenance of the oliguric state was not clear. Therefore, several maneuvers were made in an attempt to decrease renal vascular resistance and restore glomerular capillary hydrostatic pressure toward normal. Neither the infusion of a potent competitive antagonist of angiotensin II (1-Sar-8-Ala-angiotensin II) nor the administration of an alpha-adrenergic blocking agent (phenoxybenzamine) significantly altered renal blood flow or renal vascular resistance. When rats were volume expanded with isotonic saline or isonicotic rat plasma, however, renal blood flow promptly returned to normal values. This return was not associated with any increase in urine flow. Both glomerular capillary hydrostatic pressure and proximal intratubular pressure rose in response to volume expansion, the latter to levels significantly above the control value. This observation clearly indicates the presence of continued tubular obstruction as the predominant factor in the maintenance of oliguria. With regard to the relationship between cell swelling and oliguria, data exist which indicate that tubular epithelial cell swelling disappears promptly after the circulation is restored (25). Restoration of renal vascular resistance to normal values by volume expansion with isosmotic fluid does not support the cell swelling theory.

It should be pointed out that if conclusions were to be drawn from our pressure data alone it would appear that preglomerular vasoconstriction was the major factor in the maintenance of the oliguria. When the pressure data are considered in relation to the events occurring in the early postischemic phase along with the morphological evidence and the response to acute volume expansion, it is clear that intratubular obstruction is a major factor in both the generation and the maintenance of the oliguria in ischemia-induced acute renal failure.

The reasons for the development of increased renal vascular resistance are not known but may be related to the presence of a vasoconstrictor, the absence of a vasodilator, or a combination of both. Prostaglandin concentrations are known to increase in renal venous blood following temporary renal ischemia (26). Angiotensin itself stimulates the release of prostaglandins which tend to limit the vasoconstrictor response of the renal vasculature (27). Administration of angiotensin in the absence of prostaglandins, as with pretreatment with indomethacin, results in a proportionately greater increase in renal vascular resistance (28). We found that neither chronic salt loading nor infusion of 1-Sar-8-Ala-angiotensin II in the postischemic period was able to decrease renal vascular resistance. Although these observations do not support a role for the renin-angiotensin system in the production of the vasoconstriction, it is possible that intrarenal renin was not reduced completely and that the antagonist was not reaching critical effector sites. Moreover, the changes seen may be the result of other vasoconstrictors.

Of potential significance with regard to the increase in renal vascular resistance is the relationship between other forms of obstruction to tubular flow and the delayed onset of preglomerular vasoconstriction (29). Flamenbaum et al. (30) have speculated that a feedback mechanism between impairment of tubular flow and intraglomerular filtration pressure exists in rats studied 1 day after being injected with 4.7 mg/kg of HgCl₂ subcutaneously. We have found (29) that 24 hours following unilateral ureteral ligation both renal blood flow and estimated glomerular capillary hydrostatic...
pressure are significantly below control values—a response similar to that seen in our studies of acute renal failure but without the complicating features of ischemia and tubular necrosis. In addition, when individual nephrons are obstructed with oil and studied 24 hours later, estimated glomerular capillary hydrostatic pressure is reduced to a similar extent although adjacent, unobstructed nephrons have normal glomerular capillary hydrostatic pressures. Thus, there appears to be a delayed response to tubular obstruction which is operative on an individual nephron basis and which results in constriction of afferent arterioles. An important but unproved corollary to this proposal is that the return of renal vascular resistance to normal levels will occur following relief of intratubular obstruction and reestablishment of tubular flow. For this return to occur the tubular epithelium must regain its integrity. As intratubular pressure rises, tubular fluid flow increases and the stimulus to afferent arteriolar vasoconstriction lessens; these changes are followed by an elevation in glomerular capillary hydrostatic pressure and a return of glomerular filtration rate and renal blood flow to normal values.

Thus, our micropuncture studies of postischemic acute renal failure have clearly demonstrated the presence of tubular obstruction, passive backflow of filtrate, and preglomerular vasoconstriction (Fig. 1). Sequential studies have indicated that tubular obstruction is responsible for the generation of the oliguria and continues to be of prime importance in its maintenance. Analysis of the prolonged effects of ureteral ligation and obstruction to individual nephrons supplies a link between the obstruction to tubular flow and the development of preglomerular vasoconstriction. Although pathophysiological alterations occur within the renal vasculature, we prefer not to use the term “vasomotor nephropathy” in describing this model, since the term tends to obscure the contribution of other factors in both the generation and the maintenance of the oliguria. Instead, we prefer to follow the classification of Oliver et al. (2) which describes the lesion in terms of its etiological and morphological features as either ischemic or nephrotoxic acute renal failure, recognizing that there is considerable overlap between the two.

References

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