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The pathophysiology of obstructive acute renal failure

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Acute obstructive uropathy is a common entity occuring at all ages. It has been calculated that 166 patients per 100,000 population were hospitalized in the U.S. in 1985 with a presumptive diagnosis of obstructive uropathy[1]. Obstruction to the urinary tract remains a major cause of renal impairment world-wide, and will lead to end-stage renal failure if left untreated. Acute renal failure is a common presentation in patients with complete and sudden obstruction of the urinary tract. The acute changes in glomerular and tubular function that occur following ureteral obstruction have been examined in a variety of experimental animals and unlike many other forms of renal disease there are no major differences in the response of the kidney to obstruction in diverse species. There are rather limited data on renal functional alterations in humans with obstruction of the urinary tract, but the data available suggest that man behaves in a fashion similar to that of other species.

The alterations in renal function that occur as a result mechanical obstruction of the urinary tract are complex of and are not merely a consequence of impaired urine flow. There are major perturbations in renal hemodynamics with alterations in vasodilatory prostaglandins, vasoconstrictive substances, predominantly thromboxane A_2, and the renin-angiotensin system. In addition there are marked changes in tubular function with alterations in monovalent and divalent ion transport. To date, however, the pathophysiological processes which result from mechanical obstruction of the urinary tract and which lead to marked disturbances in renal function have not been completely elucidated.

Changes in ureteral function and glomerular hemodynamics following acute ureteral obstruction

Normal urine production and flow depend on 1) hydrostatic pressure that decreases progressively from Bowman's space to the bladder, and 2) ureteral peristalsis. Ureteral peristalsis generates the high intraluminal pressures necessary for the propulsion of a bolus of urine. Contraction of the circular muscle fibers of the ureter prevents this pressure from being transmitted to the kidney. Impedance to urine flow anywhere in the genitourinary tract causes a rise in pressure and volume of urine proximal to the obstruction. The contraction of the circular muscle fibers, coaptation, is lost and high intraluminal pressures are transmitted to the kidney. An increase in ureteral pressure results in increased intratubular pressure. The rise in intratubular pressure in tum decreases the net hydrostatic filtration pressure.

Following ureteral obstruction changes in the determinants of glomerular filtration rate (GFR) occur. The precise magnitude and relationship of these changes depend both on the hydration state of the animals and on whether the obstruction is bilateral or unilateral, i.e., whether there is a functioning contralateral kidney. Qualitatively, however, the changes are similar. GFR declines progressively following the onset of complete ureteral obstruction. This is initially a result of a net decrease in the hydraulic pressure gradient across glomerular capillaries, reflecting changes in proximal tubular pressure brought on by an obstruction-induced increase in ureteral pressure. Proximal tubular pressure appears to be the major factor responsible for the decline in GFR in the initial phase of ureteral obstruction. However, within 5 hours of ureteral obstruction proximal tubular pressure declines and GFR is reduced as a result of a fall in renal blood flow, a decrease in intraglomerular capillary pressure, and presumably a decline in the ultrafiltration coefficient (K_f) — probably related to a decrease in the glomerular surface area available for filtration[2].

There is a prostaglandin-dependent transient increase in effective renal plasma flow (ERPF) following ureteral obstruction[3,4], with vasodilatation of the afferent arteriole[2,5]. However, within five hours of the onset of the obstruction, renal blood flow begins to decline, reaching about 30 to 50 % of control values within 24 hours. Both micropuncture studies[6] and studies with microspheres[7] have shown that this vasoconstrictive response of the kidney as a consequence of unilateral ureteral obstruction results

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predominantly from an increase in resistance of afferent arterioles.

Following ureteral obstruction GFR decreases to a greater extent than ERPF[8, 9], resulting in a decreased filtration fraction in the post-obstructed kidney. This may reflect preferential constriction of the pre-glomerular blood vessels, as this would lower both blood flow and glomerular capillary pressure, thus resulting in a greater decrement in GFR than blood flow. Alternatively, it suggests that there is either diversion of blood to nonfiltering areas of the kidney or that there is an alteration in the ultrafiltration coefficient (K_f). This would result in a reduced area available for filtration per glomerulus. That the latter occurs is suggested by studies of Ichikawa et al.[10] in which K_f values from rats with ureteral obstruction were lower than those typically obtained in normal rats.

The role of the vasoconstrictors angiotensin II and thromboxane A_2 in the changes in renal hemodynamics

Two major vasoconstrictors, namely angiotensin II and thromboxane A_2, play a major role in the decrease in renal plasma flow per nephron and the decline in single nephron glomerular filtration rate (SNGFR) that is seen following ureteral obstruction[11]. As well as being potent vasoconstrictors, both angiotensin II[12] and thromboxane A_2[13] are able to contract mesangial cells in culture and thus can potentially reduce the glomerular capillary area available for filtration and therefore the ultrafiltration coefficient, K_f. If rats are pretreated with angiotensin converting enzyme inhibitors and thromboxane synthase inhibitors, the decline in renal function that is seen after release of ureteral obstruction is virtually prevented[14]. The initial afferent arteriolar dilatation following the onset of ureteral obstruction appears to be the predominant stimulus to renin secretion following ureteral obstruction, since the maximum renin release coincided with complete arteriolar dilatation[15, 16]. The increased renin release is almost completely abolished by pretreatment with the cyclo-oxygenase inhibitors indomethacin or meclofenamate[4, 15], suggesting that the formation of vasodilatory prostaglandins such as prostacyclin or prostaglandin E_2 represents a necessary step for the release of renin from juxtaglomerular cells[17]. In addition, the generation of renal cortical prostaglandins may act as a direct stimulus to the release of renin, since prostaglandins are able to release renin from renal cortical slices[18].

It is clear that following the onset of ureteral obstruction the hydronephrotic kidney exhibits an enhanced ability to generate thromboxane A_2[19-21]. This eicosanoid acts as a potent vasoconstrictor in the hydronephrotic kidney[22]. That the generation of this eisocanoid is pathophysiologically significant is suggested by the observations that inhibitors of thromboxane synthesis partially reverse the decline in renal function seen after obstruction[10, 23]. Prior administration of the thromboxane synthase inhibitor appears to convey more benefit than treatment after ureteral obstruction is established[14].

Interestingly, the generation of thromboxane in response to ureteral obstruction is conditioned by the diet the animals have been eating. Animals fed a low-protein diet do not generate as much thromboxane as animals fed a high-protein diet and exhibit less vasoconstriction in response to ureteral obstruction[10]. Furthermore, thromboxane synthase inhibitors are not effective in reversing the post-obstructive vasoconstriction in animals fed a low-protein diet.

The role of other vasoactive substances

Antidiuretic hormone (ADH) contributes to the renal vasoconstriction and the decrement in GFR observed in rats with bilateral ureteral obstruction[24]. We have shown[24] that pretreatment of the rats with a specific antagonist of the V_1 receptor resulted in a significant increase in GFR and ERPF and a significant decrease in mean arterial blood pressure after unilateral release of bilateral ureteral obstruction. Thus, the high levels of circulating ADH found in rats with bilateral ureteral obstruction may contribute to the decrease in GFR and ERPF observed in this setting.

Leukotrienes, potent mediators of inflammation, are synthesized by cells through the 5-lipooxygenase pathway. Glomeruli isolated from kidneys of rats with bilateral ureteral obstruction demonstrate increased synthesis of leukotriene B_4 when compared to «normal» glomeruli. Inhibition of the 5-lipooxygenase pathway *in vivo* ameliorated the decrease in GFR and in ERPF seen after unilateral release of bilateral ureteral obstruction[25].

We have also examined the potential contribution of endothelium-derived relaxing factor (EDRF) to the changes in GFR and ERPF observed after unilateral release of bilateral ureteral obstruction[26]. Since the kidney is the major site of synthesis of arginine from citrulline for export to other organs and since arginine is the precursor in the generation of nitrous oxide (EDRF), we postulated that arginine may be a rate-limiting substrate for the synthesis of EDRF in rats with bilateral ureteral obstruction. We investigated the role of EDRF in post-obstructed kidneys by administering N^wnitro-1-arginine methyl ester (N^w-NAME), a competitive inhibitor of the synthesis of nitrous oxide from arginine. We also examined the effects of arginine administration immediately after the release of obstruction on GFR and ERPF. Arginine administration markedly increased GFR and ERPF in the post-obstructed kidney. On the other hand, administration of the competitive inhibitor of arginine after release of obstruction resulted in a marked decrease in GFR and ERPF. Rats with bilateral ureteral obstruction pretreated with the competitive inhibitor of arginine were anuric after release of the obstruction. The results of these studies suggest a decreased availability of the substrate for EDRF synthesis during bilateral ureteral obstruction. Alternatively, the results can be interpreted to

indicate that decreased EDRF activity during obstruction plays a role in the hemodynamic changes observed after release of bilateral ureteral obstruction of 24 hours duration.

Recent data sugest that platelet-activating factor (PAF) also has a vasodilatory role in obstructive nephropathy[27].

The role of leukocytes in hemodynamic changes

More than 15 years ago, chronic ureteral obstruction in rabbits was found to be associated with a proliferation of fibroblasts and an infiltration of mononuclear cells in the interstitium of the kidney[28,29]. More recently these developments have been linked to the increase in prostaglandin E_2 production by the chronically hydronephrotic rabbit kidney[30] and it has been postulated that the infiltration of the renal parenchyma by mononuclear cells may contribute to the augmented release of thromboxane A_2 and prostaglandin E_2 in response to bradykinin[31] or endotoxin[32]. Using a rat model of acute and reversible ureteral obstruction in which there is no necrosis and in which renal functional abnormalities are transient, we have more clearly defined the kinetics of the cellular infiltrate[33]; in addition the cell types making up the infiltrate have been determined. The leukocyte influx appears to be one of the earliest responses of the kidney to ureteral obstruction, occurring within four hours of obstruction, with the peak response occurring at 12 hours, after which a plateau is observed[33]. The leukocytes form distinctive rings around the tubules, particularly distal tubules. Of note, the infiltrate was observed not only in the cortex, but also in the medulla, which normally is almost completely devoid of resident leukocytes, presumably due to its hypertonic environment.

The mononuclear cell infiltrate observed in obstruction consists predominantly of macrophages. The second major leukocyte population consists of T-lymphocytes of the cytotoxic, suppressor cell subclass. Some degree of selectivity is implied by the fact that T-lymphocytes of the helper type do not constitute a significant portion of the infiltrate despite the fact that they predominate in the peripheral circulation[34]. B-lymphocytes do not appear in the renal interstitium. Neutrophils are also absent from this infiltrate, consistent with acute obstruction not being associated with tissue necrosis. After 24 hours of obstruction a neutrophil infiltrate is present[25].

The kinetics of the macrophage and leukocyte invasion correlate temporally with both the decline in GFR and the enhanced thromboxane production by the kidney that is seen in response to ureteral obstruction[33]. Since leukocytes are a known source of the vasoconstrictor thromboxane A_2 and possibly other vasoactive compounds these phenomena could be causally related. In support of this postulate is the finding that total body irradiation of rats prior to the onset of obstruction, so as to abolish the leukocyte infiltration observed in the kidney after 24 hours of obstruction, both reduced thromboxane B_2 excretion in the urine and significantly improved renal hemodynamics in the post-obstructed kidney[21]. By contrast, irradiation had no effect on renal morphology or function in normal rats. This implies that infiltrating leukocytes contribute to the decline in GFR and ERPF seen after obstruction, possibly via the production of vasoactive eicosanoids such as thromboxane A_2.

The elimination of the leukocyte infiltrate from the obstructed kidney, however, does not return the function of the post-obstructed kidney to normal. This is consistent with there being additional, leukocyte-independent, mechanisms operating in this model. Also it is of note that elimination of the infiltrating macrophages by prior irradiation did not reduce the thromboxane B_2 excretion in the urine to baseline levels. This is consistent with the notion that obstruction causes enhanced production of these vasoactive eicosanoids by structures intrinsic to the kidney such as glomerular epithelium or mesangium. Recently it has been demonstrated that glomeruli isolated from rats with ureteral obstruction have an enhanced ability to produce a variety of eicosanoids, including the vasoconstrictor thromboxane A_2, compared to glomeruli from nonobstructed kidneys[35]. Such leukocyte-independent sources of thromboxane A_2 also appear to be capable of modulating renal hemodynamics[36].

Whether the beneficial effects of low-protein diets in decreasing thromboxane generation in response to ureteral obstruction result from an inhibiting effect on the leukocyte infiltrate or a modulation of renal cyclo-oxygenase activity is currently under investigation.

The infiltration of the kidney by leukocytes is a slowly reversible process requiring several days for leukocytes to revert to near normal levels once the obstruction has been released[21]. If the obstruction is not relieved, howewer, the infiltrate of macropages, with their known potential to induce fibroblast proliferation and scar formation, will persist[21]. It is likely that this immunological infiltrate may have long-term adverse consequences on renal function and structure. Indeed, it has been shown that in patients with ureteropelvic obstruction focal segmental glomerulosclerosis is a common histological finding in the obstructed kidney[37]. This glomerulosclerosis is found in areas closely associated with intense interstitial and peri-glomerular inflammation. Growth factors released by invading leukocytes may play a role in the development and progression of fibrotic and sclerotic changes that occur in the chronically obstructed kidney. It is, therefore, likely that the cellular infiltrate may contribute to the renal damage and to the progressive decrease in renal function observed with chronic urinary tract obstruction.

The signals responsible for recruiting macrophages into the obstructed kidney are not fully defined, but it would seem likely that the kidney releases chemoattractants in response to an increase in pressure or stretch. It has recently been demonstrated that the cortex of the obstructed kidney elaborates a unique chemoattractant that is spe-

cific for macrophages. This substance behaves biochemically as a lipid, but has not yet been fully characterized[38].

The pattern of change in glomerular macrophage number following ureteral obstruction is somewhat different. There is a relative depletion of resident leukocytes from the glomeruli associated with the leukocyte invasion of the interstitium. The destination of the glomerular leukocytes, which are resident mesangial macrophages[39], is unclear, but one possibility is that they are induced to migrate from the glomerulus to the insterstitium via the mesangial stalk in response to signals from the interstitium of the obstructed kidney. After release of the obstruction the glomerulus is repopulated with resident macrophages which accumulate to a level significantly greater than the level in control glomeruli[21]. The increase is comparable to the degree of macrophage infiltration observed in a model of moderate glomerulonephritis induced by nephrotoxic serum[40]. The pathophysyologic significance of this observation remains to be determined.

In the rat, following release of ureteral obstruction of short duration (less than 30 hours), recovery of GFR is complete 7-9 days later[41]. Although this would suggest that short term obstruction is completely reversible and that most of the early alterations in renal function are not due to structural changes, there is indirect evidence to suggest that restoration of GFR may not be a consequence of a homogeneous recovery in the SNGFR of all nephrons. Indeed, when SNGFR and the number of filtering nephrons were determined using a modification of Hansen's technique a decrease in the total number of filtering nephrons was found in the post-obstructed kidney, such that only 85 % of the nephrons in the post-obstructed kidney were filtering, compared to 100 % in the contralateral kidney. Thus, the normalization of whole kidney GFR occurs at the expense of hyperfiltration (increase in SNGFR) in the remaining functional nephrons, and there is a permanent decrement in the total number of functional nephrons[42]. It is interesting to speculate that this permanent loss of nephrons following release of only short periods of obstruction may be the result of the macrophage infiltration of the gloneruli that is seen following the release of the obstruction.

Alterations in tubular function following ureteral obstruction

Abnormalities in tubular function, common in urinary tract obstruction[43], result in changes in the renal transport of a variety of electrolytes and solutes as well as alterations in the regulatory control of water excretion. There is a decreased ability to concentrate the urine, and the reabsorption of sodium and other solutes such as phosphorus, magnesium and calcium ions is altered, as is the secretion of hydrogen and potassium. The mechanism for these alterations in function which results in the syndrome commonly referred to as «post-obstructive diuresis», remains unclear, but most of the evidence points to the distal nephron as the major site of altered salt and water transport. With protracted periods of obstruction there are morphological changes in the tubules. Thus, the resultant loss of function is not surprising. However, even with short periods of obstruction, when there is minimal histological change, the alterations in tubular function may be marked. This would suggest that following obstruction various modulators of tubular epithelial function are generated and act within the kidney. Since ureteral obstruction has now been shown to be associated with an interstitial infiltrate which predominantly rings distal tubular structures it is possible that leukocyte derived mediators may contribute to the post-obstructive alterations in renal tubular function. It is of note that in more classical forms of interstitial nephritis sodium and water wasting, phosphate wasting and impaired hydrogen ion secretion are well recognized features[44, 45].

Cytokine induced changes in tubular function

A variety of immune cell derived cytokines have been shown to affect the rate of ion transport in non-renal cells, raising the possibility that renal epithelia may also be subject to regulation by such factors. Interleukin 1 (Il-1) is capable of stimulating amiloride-sensitive sodium entry in a B cell line[46] and tumor necrosis factor (TNF) induces a decrease in the electrical potential across skeletal muscle plasma membrane within 5 minutes of initial exposure[47]. In addition TNF also increases glucose transport into the muscle cell line L6, probably via an increase in the number of plasma membrane transporters[48]. Both Il-1 and TNF are macrophage-derived products. Supernatants obtained from activated mouse peritoneal macrophages stimulate the sodium-dependent uptake of glucose and aspartate in primary cultures of proximal tubular cells. Sodium-independent transport processes were not affected by the macrophage supernatant, suggesting that the factor was primarily acting by modulating sodium transport. Purification of the macrophage supernatant subsequently showed that the active component was Il-1[49]. At least twelve hours of exposure to Il-1 is required to directly increase sodium entry into proximal tubular cells, and both RNA and protein synthesis are required for the effect.

Interleukin 1 also exerts a considerable, although somewhat different effect on distal nephron function, causing a marked natriuresis and diuresis when infused into rats[50, 51]. Micropuncture data have confirmed that his a direct tubular effect, with a threefold increase in sodium excretion being observed within one hour of Il-1 infusion without a change in GFR, ERPF or systemic blood pressure[52]. Absolute delivery to the late proximal and mid-distal tubule is unaltered by Il-1 whereas sodium delivery to the papillary collecting duct is increased. This would suggest that Il-1 is acting on the late distal tubule and collecting duct. The diuretic action of Il-1 appears to occur through

the stimulation of the cyclo-oxygenase pathway, since the effect is abolished by indomethacin[50]. In addition, Il-1 infusions induce a prompt rise in renal prostaglandin E_2 (PGE_2) excretion, and Il-1 increases PGE_2 synthesis by papillary collecting duct cells in culture[53], but not by proximal tubular cells[54]. PGE_2, which is the major arachidonate metabolite synthesized by the collecting duct[55], may act directly on the cortical collecting tubule[56] and papillary collecting duct[57,58] to inhibit sodium and water transport. In addition the vasodilatory action of PGE_2 could reduce medullary tonicity and contribute to the diuresis.

Since cytokines appear to have different effects at different sites along the nephron the localization of any infiltrate, as well as the substances it produces, will determine the overall biologic effect. In view of the localization of the cellular infiltrate in obstructed kidneys around the distal tubule[21], it is tempting to speculate that cytokines released from these cells (and in particular Il-1) may contribute to the alterations in tubular function seen in response to ureteral obstruction.

The role of Na,K-ATPase in altered sodium reabsorption

The mechanisms underlying the decreased reabsorption of sodium are due at least in part to altered activity of Na,K-ATPase in the nephron. Wilson et al.[59] found reduced Na,K-ATPase activity in cortical and medullary homogenates of rat kidney one to seven days after relief of either unilateral or bilateral ureteral obstruction and correlated this change with alterations in sodium reabsorption and post-obstructive diuresis. Williams, Fanestil and Blackard[60] also reported a reduction in Na,K-ATPase after ureteral obstruction in the dog. Sabatini and Kurtzman[61], using tubular segments, described decreased Na,K-ATPase activity in several nephron segments after 24 hours of unilateral ureteral obstruction.

We have examined the potential mechanisms underlying the decrease in Na,K-ATPase activity[62]. We found that the Na,K-ATPase activity was markedly reduced in basolateral membrane vesicles prepared from the cortex of the obstructed kidney of rats with unilateral ureteral obstruction of 24 hours duration when compared to basolateral membrane vesicles obtained from the contralateral kidneys of the same rats or to basolateral membrane vesicles from kidneys of sham-operated animals. However, such differences disappeared three days after release of unilateral ureteral obstruction. This restoration of Na,K-ATPase activity in basolateral membranes, three days after release of obstruction, differs from results published previously using whole kidney homogenates. The reason for these differences is not immediately apparent but may relate to the methodology used.

When basolateral membrane vesicles were incubated with sodium dodecyl sulfate to permeabilize the vesicles, no differences in the degree of enzyme latency were detected between the basolateral membrane vesicles from obstructed kidneys and those from sham-operated rats. Immunoblotting techniques and analysis via antibodies to the alpa-subunit of Na,K-ATPase revealed equal amounts of enzyme in the basolateral membrane vesicles from contralateral kidneys, obstructed kidneys, and kidneys from sham-operated rats. When incubated with liposomes under conditions conducive to fusion and lipid exchange, basolateral membrane vesicles from obstructed kidneys demonstrated Na,K-ATPase activity reconstituted almost to normal levels. Such an increase in enzyme activity did not occur in basolateral membranes from contralateral kidneys or in membranes from kidneys of sham-operated rats incubated under similar conditions. Thus, the reduction in renal Na,K-ATPase activity due to ureteral obstruction is not related to reduced quantity of the enzyme or to its sequestration in impermeable vesicles, but to changes in the lipid environment of the basolateral membrane.

It should be noted that lipid changes occur in the kidney after 24 hours of obstruction. Tannenbaum et al.[63] noted an increase in triglycerides and a decrease in phospholipid content after 24 hours of ureteral occlusion in the rat. There was also increased incorporation of ^{14}C-oleic or ^{14}C-arachidonic acid into triglycerides in both cortex and medulla. Morrissey et al.[64] also reported decreases in phospholipids and cholesterol in renal tubular membranes. Some of these lipid changes may underlie the decrease in Na,K-ATPase observed in obstruction.

The concentrating defect of urinary tract obstruction

Impaired ability to concentrate the urine is evident after relief of obstruction in rats with either unilateral or bilateral ureteral obstruction[65,66]. Vasopressin administration does not reverse the defect[67,68]. A fall in the solute content of the papillary interstitium may be a major factor. One definite contributing factor is a relative increase in blood flow to papillary structures. Although GFR of deep nephrons can be reduced by 50-60 % during obstruction, inner medullary plasma flow either does not change from control levels or increases slightly. The hyperosmolality of the medulla is generated by the greater reabsorption of solutes than water from the thick ascending limb of Henle's loop. Thick ascending limbs of animals with ureteral obstruction when perfused *in vitro* demonstrate decreased sodium chloride reabsorption[67]. A decrement in the medullary tonicity decreases water efflux from the descending limb of Henle's loop and increases the amount of fluid delivered to the bend of the loop after relief of obstruction. This, in turn, may decrease the sodium chloride gradient necessary for the passive efflux of sodium chloride from the thin ascending limb of the loop. In addition, a decrease in medullary solute content will decrease the diffusion of water out of the collecting duct.

The hydroosmotic response to vasopressin is decreased in the cortical collecting duct[67,68]. When this segment

of the nephron was perfused *in vitro*, after dissection from kidneys with ureteral obstruction, the hydroosmotic response to both vasopressin and cyclic AMP was markedly decreased. Changes in the levels of G proteins and a decrease in cyclic AMP generation after ADH seem to underlie part of the defective responsiveness of the cortical collecting duct to vasopressin. However, post-cyclic AMP events also appear to have a role in the altered response to antidiuretic hormone. Thus, the concentrating defect in obstruction is presumably due to a variety of factors: a decrease in the number of juxtamedullary nephrons; a decreased removal of solute from the thick ascending limb of Henle's loop in functional juxtamedullary nephrons; washout of solute from the medulla due to increased medullary flow; and a decreased hydroosmotic response of the cortical collecting duct to antidiuretic hormone.

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