Could Uric Acid Have a Role in Acute Renal Failure?

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Acute renal failure (ARF), induced by either toxins or ischemia, is associated with significant morbidity. The pathogenesis of ARF is complex and is characterized by renal vasoconstriction and oxidative stress in association with tubular and microvascular injury and interstitial inflammation. In many situations, ARF is associated with a rise in serum uric acid as a result of both increased generation and decreased excretion. Although it is widely recognized that markedly elevated levels of uric acid can cause ARF *via* supersaturation within the tubules with crystallization and intrarenal obstruction ("acute urate nephropathy"), the possibility that uric acid may affect renal outcomes at concentrations that do not lead to tubular obstruction have not been considered. This article reviews both the salutary and the adverse effects of uric acid on biologic processes and presents the hypothesis that hyperuricemia, particularly if chronic and marked, likely represents a true risk factor for ARF. Hyperuricemia also may account for the paradoxic lack of benefit of diuretics in the management of ARF. It is suggested that studies are needed to investigate the role of chronic hyperuricemia on renal outcomes after acute tubular injury.

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Acute renal failure (ARF) is observed most commonly after major surgeries; in patients with sepsis; in patients who receive chemotherapy for various malignancies; and after the administration of various nephrotoxins, such as contrast agents or antibiotics. The development of ARF has a significant effect on prognosis. For example, whereas the acute operative and postoperative mortality rate after cardiovascular surgery varies between 1 and 2%, this increases to 10 to 38% if renal insufficiency occurs and to >50% if dialysis is required (1,2). Therefore, identifying who is at risk for developing ARF and how to prevent it from happening are of paramount interest.

Uric Acid and ARF

Acute urate nephropathy is one type of ARF that is observed primarily in patients who have large tumor burdens and undergo chemotherapy that is associated with rapid death of tumor cells. In these patients, the rapid release of nucleotides results in increased uric acid generation by the liver with a rapid increase in serum levels often to levels of 12 mg/dl or greater. Increased renal excretion of uric acid results in supersaturation of the urine, crystallization of urate, and obstruction of the tubular lumina, resulting in local granulomatous inflammation that is associated with macrophage and T cell infiltration (3). Treatment is aimed at lowering uric acid levels with recombinant uricase, xanthine oxidase inhibitors, and/or dialysis and by alkalinization of the urine, which favors solubilization of the urate (4).

Although acute urate nephropathy usually is observed as a complication of the "tumor lysis syndrome," it also has been reported occasionally with rhabdomyolysis (5) and other conditions. It also possibly occurs in patients (particularly children) after cardiovascular surgery. For example, with cardiovascular surgery, serum uric acid levels rise intraoperatively and usually peak within 18 to 24 h after the operation (6). In one series, anuric renal failure was observed in three infants who had postoperative uric acid levels of >20 mg/dl (7). Another study reported that all three children who died had postoperative uric acid levels of 15 to 17 mg/dl (8).

The assumption in all of these studies is that uric acid contributes to ARF solely by forming intrarenal crystal–associated obstruction, and most nephrologists will ignore uric acid values if they are <10 to 12 mg/dl. However, even milder elevations of uric acid have been found to predict ARF in patients who receive cisplatin (9). Indeed, in a recent retrospective analysis of two large, randomized studies of patients with coronary artery bypass surgery (GUARDIAN [Guard during Ischemia against Necrosis; 11,590 patients] and EXPEDITION [Sodium-Proton Exchange Inhibition to Prevent Coronary Events in Acute Cardiac Conditions; 5761 patients]), the presence of either preoperative or postoperative serum uric acid level >7.5 mg/dl was associated with a two- to four-fold increased risk for ARF after controlling for age, gender, body mass index, baseline cardiac

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function, and baseline creatinine (B.K., I.T.-F., in preparation). The rise in serum uric acid may reflect simply increased generation from the ischemic injury as well as a falling GFR, reducing its excretion, and hence may be simply a marker of the severity of the insult. However, we present evidence that the rise in uric acid also may confer deleterious effects.

Potential Pathogenic Role of Uric Acid in ARF

There are several mechanisms by which uric acid may contribute to ARF (Table 1).

Renal Vasoconstriction

Renal vasoconstriction is thought to have a pathogenic role in many types of ARF. In patients who undergo cardiovascular bypass, a 50% fall in renal blood flow commonly occurs despite maintenance of normal systemic BP, suggesting a renal vasoconstrictive response (10–12). In many but not all patients, renal blood flow continues to be depressed for several days after completion of the surgery (10–12). If the decrease in renal blood flow is significant, then injury to the S3 segment of the proximal tubule and the medullary thick ascending limb in the outer medulla may result (13). Ischemia to the outer medulla, coupled with the subsequent reperfusion phase, may injure tubular cells by depleting intracellular ATP; disrupting intracellular calcium homeostasis; generating free radicals; and causing cellular changes that destroy the integrity of the tight junction, apical-basolateral polarity, and cytoskeletal structure. The damaged renal tubular cells detach from the tubular basement membrane into the tubular lumen, where they result in the formation of cellular and then granular casts that may obstruct the tubular lumen. In addition, disruption of the tubular lining may lead to some backleak of filtrate, resulting in misguided filtration (14).

A variety of mechanisms for the vasoconstriction have been suggested, including the activation of the renin-angiotensin system, catecholamines release, oxidative stress, an inflammatory response characterized by expression of TNF-α and C-reactive protein (CRP), and the use of inotropic agents with vasoconstrictive activities. Uric acid also may have a role in renal vasoconstriction. Renal vasoconstriction occurs in rats with experimentally induced hyperuricemia and is characterized by a marked increase in resistance of the afferent (and, to a lesser extent, efferent) arterioles and a reduction in single-nephron GFR (15,16). The renal vasoconstriction can be prevented by lowering the uric acid with allopurinol (15,16).

Table 1. Mechanisms by which uric acid may contribute to ARF[a]

Renal vasoconstriction (*via* inhibition of NOS1, reduction in endothelial cell NO, and stimulation of the renin-angiotensin system)
Antiangiogenic properties (inhibition of endothelial cell proliferation and migration, stimulation of endothelial cell apoptosis)
Proinflammatory properties (stimulation of MCP-1 and CRP, activation of NF-κB and p38 MAPK)
Pro-oxidative properties (stimulation of oxidants and peroxynitrite-associated radicals)
Alteration of renal autoregulation

[a]ARF, acute renal failure; CRP, C-reactive protein; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein-1; NO, nitric oxide; NOS, NO synthase.

The mechanism for the uric acid–dependent decrease in renal blood flow seems to be loss of nitric oxide (NO), because the vasoconstriction can be reversed with L-arginine (17). Furthermore, uric acid strongly inhibits NO release from endothelial cells (18,19). This results in impaired vasodilation; indeed, classic acetylcholine-induced vasodilation of isolated aortic rings is inhibited stepwise by increasing concentrations of uric acid (20). We also have demonstrated a reduction in plasma nitrites (metabolites of NO) in hyperuricemic rats that can be rescued by allopurinol (18). In addition, hyperuricemic rats have a loss of neuronal NO synthase in macula densa cells (21).

Human studies also support a role for uric acid in endothelial dysfunction. Uric acid levels correlate with endothelial dysfunction as reflected by impaired brachial artery reactivity (which is a surrogate marker for impaired endothelial NO release) (22,23). Lowering uric acid improves endothelial function in patients with asymptomatic hyperuricemia (24), congestive heart failure (25), diabetes (26), and hypercholesterolemia (27). Uric acid also varies in a diurnal and opposite manner with NO levels in humans (28). All of these data suggest that uric acid is a potent regulator of endothelial NO levels.

The mechanism by which uric acid lowers NO seems to be multifactorial. In preliminary studies, we found that uric acid stimulates the production of oxidants *via* an increase in NADPH oxidase in both adipocytes and endothelial cells (D.H.K., Y.Y.S., unpublished observations, 2006), which can inactivate NO either directly or by uncoupling the endothelial NO synthase enzyme. Uric acid also stimulates L-arginase in endothelial cells (S. Zharikov, unpublished observations, 2006). Kang *et al.* (19) further showed that some of the depletion of NO is due to uric acid stimulation of CRP. Most interesting, uric acid may inactivate NO directly (29).

Recently Goligorsky's group has shown that preservation of endothelial NO levels can partially protect animals from ischemic ARF (30). Thus, the inhibition of NO by uric acid could provide a mechanism for augmenting renal vasoconstriction and ischemic injury.

Inflammation

Inflammatory pathways also are important in the pathogenesis of ARF. Chemotactic factors are expressed by ischemic or toxin-injured tubules that lead to the recruitment of inflammatory cells (neutrophils, monocytes, and T cells). In turn, inflammatory cells may augment renal injury in part by the release of oxidants and other vasoactive mediators (14,31). An increase in both oxidants and inflammatory mediators can be shown in patients after cardiovascular surgery (32,33). Uric acid also stimulates an inflammatory response. Uric acid increases pro-

duction of the chemotactic factor monocyte chemoattractant protein-1 (MCP-1) in vascular smooth muscle cells and CRP synthesis in human vascular endothelial and smooth muscle cells (19,34). Hyperuricemic rats have a significant increase in macrophage infiltration in their kidneys independent of crystal deposition (21). As mentioned previously, we also have found that uric acid stimulates NADPH oxidase in both endothelial cells and adipocytes (35). Indeed, the MCP-1 production that is observed in vascular smooth muscle cells in response to uric acid can be blocked with an NADPH oxidase inhibitor (34).

Microvascular Injury

ARF also is associated with injury to the microvasculature, resulting in endothelial cell loss and dysfunction (34,35). Studies in animal models of ischemia-induced renal injury have documented persistent reduction in blood flow up to 3 d after the insult, particularly in the peritubular capillaries (36,37). The importance of endothelial cell function was supported by the evidence that infusing endothelial cells in models of ARF could attenuate injury, possibly *via* their release of endothelial NO (30).

Uric acid also has been found to inhibit endothelial cell proliferation and migration (19) and to cause endothelial cell apoptosis (40). Therefore, the presence of markedly elevated uric acid might be expected not only to accelerate endothelial cell loss but also to retard the recovery process.

Altered Renal Autoregulation

In the setting of a decrease in renal perfusion pressure, the autoregulatory response of the kidney is critical as a means to maintain renal blood flow and prevent ischemia. In this regard, disease of the afferent arteriole has been shown to impair the renal autoregulatory response, likely as a consequence of collagen deposition within the vascular wall (15,16). Defective autoregulation (*e.g.*, from a diseased afferent arteriolar system) may explain why certain conditions, such as chronic renal disease, diabetes, and aging, are associated with increased risk for ARF.

In this regard, one of the major consequences of experimental hyperuricemia is the development of preglomerular arteriolar disease, which impairs the autoregulatory response (41,42). The arteriolopathy develops as a consequence of direct effects of uric acid to stimulate vascular smooth muscle cell proliferation as well as from indirect effects of uric acid to activate the renin-angiotensin system and to inhibit endothelial NO levels (21,41). Uric acid levels also are highly correlated with preglomerular arteriolar disease in humans (42).

Is There Experimental or Clinical Evidence That Lowering Uric Acid May Prevent or Reduce ARF?

There have been a number of studies in which xanthine oxidase inhibitors have been administered to patients who underwent cardiovascular surgery. In most of these studies, the allopurinol was posited to be acting by lowering xanthine oxidase–induced oxidants as opposed to lowering uric acid. It is interesting that most of the studies showed variable benefits on cardiovascular outcome, including improvement in postoperative mortality (43), arrhythmias and inotrope requirement (44), a reduction in perioperative myocardial infarction, and an improvement in cardiac index (43,45). However, none of these studies specifically examined the effect of this therapy on preventing ARF.

Care must be taken in interpreting animal studies that investigate the role of uric acid in ARF because of the difference in metabolism between humans and most other mammals. Uric acid is generated from xanthine by xanthine dehydrogenase or xanthine oxidase, the latter of which also generates a superoxide anion in the process. In most mammals, uric acid is degraded further by uricase to generate allantoin and an additional superoxide molecule (Figure 1). Most studies that have used xanthine oxidase inhibitors as a means to prevent ARF have been performed in rats or other animals that express uricase; therefore, interpretation of the studies is limited. It is interesting that allopurinol (a xanthine oxidase inhibitor) was protective in some models of ischemia reperfusion injury (46,47) but not in others (48).

Recently, we investigated the role of uric acid in the cisplatin model of renal injury (49). Rats were made mildly hyperuricemic with a uricase inhibitor and then were given cisplatin with or without uricase therapy. It is interesting that hyperuricemic rats that were given cisplatin had significantly more tubular injury and intrarenal inflammation in association with an increase in intrarenal MCP-1 expression than rats that were treated with cisplatin alone and also had a tendency for worse renal function. Uricase treatment resulted in significant improvement in the renal inflammatory changes and renal function compared with hyperuricemic rats with cisplatin-induced injury. The observation that uricase could provide benefit even though it releases oxidants in the degradation of uric acid strongly suggests that the uric acid was responsible for the worsening of the renal injury in the hyperuricemic rats.

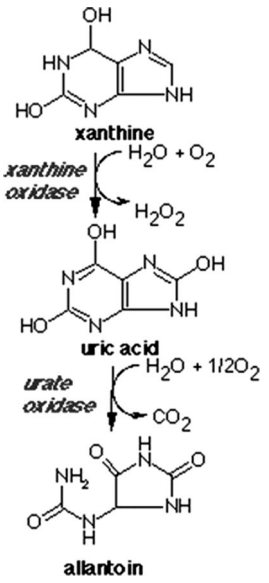

Figure 1. Pathway of urate generation and degradation.

Does Uric Acid Have a Good Side in ARF?

Although all of the studies mentioned here suggest that uric acid may have vasoconstrictive, proinflammatory, pro-oxidative, and antiangiogenic properties that could promote the development of ARF, uric acid also is known to be an antioxidant and is considered the most abundant antioxidant in human plasma (50). In particular, uric acid has been found to react with superoxide anion and peroxynitrite (51) and also helps to maintain levels of extracellular superoxide dismutase by preventing its oxidative degradation (52). Furthermore, uric acid has been found to help preserve endothelial NO levels in response to peroxynitrite (53) (which is in contrast to the reduction in NO that is observed when uric acid is incubated with endothelial cells alone).

It is possible that in conditions of severe oxidative stress, a rise in uric acid might provide some antioxidant benefit. We have observed some evidence for this in the ischemia-reperfusion model in which we gave a single dose of a uricase inhibitor 4 h before inducing the renal ischemia. In this model, we observed a mild rise in uric acid at the time of ischemia (3.4 ± 0.4 *versus* 1.1 ± 0.4 mg/dl; $P < 0.01$; $n = 6$ rats each), and this was associated with slightly better blood urea nitrogen levels at 48 h (24 ± 6 *versus* 35 ± 11 mg/dl; $P < 0.05$) but not creatinine (0.56 ± 0.09 *versus* 0.70 ± 0.17 mg/dl; NS) and with no difference in histology.

Although these studies suggest that under certain conditions a rise in uric acid may be beneficial, we believe that hyperuricemia if marked (>7.0 mg/dl) and persistent is unlikely to be beneficial. In this regard, we recently demonstrated that the reaction of uric acid with peroxynitrite is not necessarily benign, because it generates alkylating intermediates as well as several carbon-based radicals (54). Santos *et al.* (55) also reported that the reaction of uric acid with peroxynitrite can generate aminocarbonyl radicals. Perhaps more important, we recently demonstrated that uric acid preferentially will react directly with NO over peroxynitrite, and this reaction will be blocked only by glutathione (or N-acetyl cysteine; G.H., submitted). Hence, with the depletion of intracellular glutathione under conditions of oxidative stress, such as occur with ARF, the ability of uric acid to react with and reduce endothelial NO levels will be enhanced.

Diuretics and ARF

Diuretics have been used commonly in the management of ARF to aid in the management of extracellular volume and because of their theoretical benefit of flushing casts through the tubular lumina and reducing tubular oxygen consumption. However, surprising, there is little evidence that they protect against ARF, and some studies suggest that they may prolong recovery of renal function (56,57).

If diuretics have negative effects in ARF, then it may relate to effects on renal perfusion. Although many patients have elevated extracellular volume with third-spacing after cardiovascular surgery, this often is associated with relative "underfilling" of the arterial circulation. Diuretics may reduce blood volume further and thereby reduce renal perfusion, which could result in either prerenal azotemia or ARF. However, diuretics also stimulate reabsorption of uric acid in the proximal tubule, both by direct effects of diuretics on the renal transporters (58) and by causing a reduction in renal perfusion, which secondarily stimulates proximal sodium and urate reabsorption (59). It is tempting to propose that the theoretical benefit of diuretics to reduce renal oxygen consumption and improve tubular urinary flow may be offset by the effects of diuretics on effective blood volume and serum uric acid.

Conclusion

In this article, we propose that serum uric acid not only may be a marker but also may contribute pathogenetically to the renal vasoconstriction as well as to the endothelial dysfunction, inflammatory response, oxidative stress, and disturbances in autoregulation that occur with ARF. Although uric acid also has some antioxidant effects that may be beneficial, we believe that the net effect of hyperuricemia, particularly if it is marked or persistent, will be to affect renal outcomes adversely. Further studies to investigate the role of uric acid in ARF are needed.

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Disclosures

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Uric acid has received recent attention concerning various manifestations of renal disease, including acute renal failure as emphasized by this paper. Forman *et al.* could find no independent effect, however, between the serum uric acid and the risk of incident hypertension among older men in this month's issue of *JASN* (pp. 287–292). In addition to uric acid, other reactive oxygen species are important mediators of acute injury in experimental and now clinical acute renal failure. See the review of oxidants in kidney disease by Shah *et al*. in this month's issue of *JASN* (pp. 16–28).