Acute Tubular Necrosis Is a Syndrome of Physiologic and Pathologic Dissociation

Seymour Rosen* and Isaac E. Stillman†

*Department of Pathology, Beth Israel Deaconess Medical Center, and Harvard Medical School, Boston, Massachusetts; and †Department of Pathology and Renal Division, Department of Medicine, Beth Israel Deaconess Medical Center, and Harvard Medical School, Boston, Massachusetts

ABSTRACT

Acute tubular necrosis (ATN) is a syndrome of intrinsic renal failure secondary to ischemic or toxic insults. The histopathologic findings of ATN are inconstant. When present, they are limited to the tubulo-interstitium and often subtle despite profound dysfunction. Experimental models of ATN in healthy animals commonly use single insults that result in extensive injury, circumstances that do not parallel the human situation. Recently, there has been a shift to more clinically relevant models using an acute insult superimposed on predisposing factors. This review discusses the complex hemodynamic interrelationships of hypoxia, tubular injury, and altered glomerular filtration, suggesting new ways to understand the pathophysiology of ATN.

J Am Soc Nephrol 19: 871–875, 2008. doi: 10.1681/ASN.2007080913

The syndrome of acute renal failure (ARF) is common, particularly in hospitalized patients. Its two most frequent causes are prerenal failure, reflecting renal adaptation to volume depletion, without parenchymal injury, and what has been historically known as acute tubular necrosis (ATN). By this we mean a clinicopathologic syndrome of intrinsic acute renal injury that is secondary to ischemic or toxic insults. As we will see, necrosis is not a defining feature of this entity and the recent proposal to substitute the term "acute tubular injury" (ATI) reflects this reality. In this article, we will use the terms interchangeably. Furthermore, these two entities are related pathogenetically. We will present a case that exemplifies the most common histopathologic findings in ATN (limited tubular alterations) and highlights the paradox that typically characterizes this entity: profound renal failure without a morphologic equivalent (ATN without any "N"). An unusual case of overt tubular necrosis will be juxtaposed, as we focus on the complex interrelationships of hypoxia, altered intrarenal microcirculation, tubular injury, and diminished glomerular filtration rate (GFR) in an attempt to understand the dissociation between function and structure seen in ATN.

CASE REPORT

A 25-yr-old man presented with malaise 3 to 4 d following cocaine use. On admission, the patient was found to be volume-depleted and in oliguric ARF (SCr 3.2 mg/dl). Other laboratory values included a CPK of 304 (CK-MB and troponin in normal range) and a positive urine toxicology screen for cocaine. The patient was volume expanded without improvement and underwent biopsy on day 2 (SCr 7.4 mg/dl). Relevant biopsy findings were limited to some brush border diminishment and mild interstitial edema and mononuclear inflammation (Figure 1A). Casts, pigmented or otherwise, were inconspicuous. SCr peaked at 8.5 mg/dl and on day 4 he spontaneously converted to a nonoliguric state. The patient never required dialysis, was discharged (SCr 5.2 mg/dl), and did not return for follow-up.

RENAL INJURY OF ATN

Background

In the past, acute renal failure was often trauma related, and both World Wars were stimuli to identify and investigate this condition. Most studies were autopsy based and, thus, inherently limited. The modern era of investigation began with the widespread adoption of the renal biopsy and the study of non–trauma-related acute renal failure. Brun and Munk were one of the first to note the contrast between the limited pathologic changes seen on biopsy and the profound acute renal failure.[1] Autopsy studies also documented subtle changes, particularly involving the distal nephrons. Some correlations were found, such as an

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Isaac E. Stillman, Department of Pathology, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston, MA 02215. Phone: 617-667-4344; Fax: 617-667-7120; E-mail: istillma@bidmc.harvard.edu

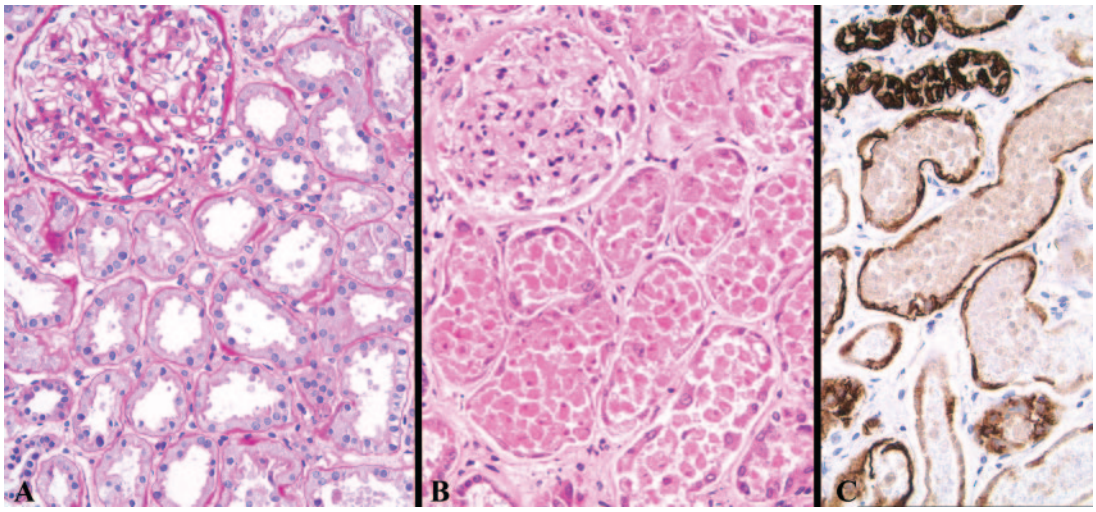

Figure 1. Renal findings in acute renal failure. (A) Renal biopsy in a case of ATN following cocaine. Cortical tubules are dilated, with some diminishment of their brush border, but no necrosis is noted (periodic acid-Schiff). (B) Renal autopsy findings of a different patient, 13 d following cardiac arrest. Proximal tubules are lined by flattened regenerating epithelium; their lumens contain necrotic cellular debris (hematoxylin and eosin). (C) Immunoperoxidase for cytokeratins (AE1/AE3; CAM 5.2) highlights the attenuated proximal tubular epithelium, which contrasts with the smaller intact distal tubules that show intense staining. A-C: original magnification, ×200.

inverse relationship between distal tubular necrosis and urine volume.[2]

A more recent biopsy study confirmed the limited nature of the findings and identified two tubular lesions significantly less severe in recovering *versus* sustained ATN: single cell necrosis and brush border loss.[3] The presence of nucleated cells within the vasa recta (possibly representing hematopoiesis or homing mesenchymal cells) has been regarded as a characteristic feature.[4] Ultrastructural studies confirmed only limited tubular injury, finding little necrosis and observing discrete cell loss mostly affecting the proximal tubule (pars recta), collecting duct and the medullary thick ascending limb (mTAL).[5] Biopsies of ATN in the transplant setting have shown similar findings; that is, very limited tubular necrosis, which often stands in sharp contrast to the marked and prolonged acute renal failure.[6] Another example of structural and functional dyssynchrony is seen in some cases (Type I) of acute humoral rejection. Given the minimal histologic alterations, it is not surprising that they are considered "ATN like."[7]

In summary, the histopathologic findings of ATN are inconstant. When present, they are essentially limited to the tubulo-interstitium, and often subtle and mild. Indeed, recent proposals to update the nomenclature reflect this. The term acute kidney injury (AKI) has been suggested in place of acute renal failure, reflecting the spectrum of declining GFR short of total "failure." Similarly, given the variable degree of necrosis in ATN, the replacement term acute tubular "injury" may indeed be more appropriate.

Failure of Animal Models

Although human ATN has a multifactorial basis, for the purposes of research and conceptualization, etiological agents have been grouped into two major categories: ischemia and nephrotoxins.[8] Animal models have been developed using both ischemia (primarily warm ischemia with reperfusion) and drugs. However, the insults used have been, for the most part, too extreme, as evidenced by the extensive necrosis typically produced. Those models therefore have at best very limited clinical, pathophysiologic, and morphologic relevance to the human situation.[8]

Indeed, many of the nephrotoxins which are directly tubulotoxic in animal studies (such as cisplatin, gentamicin, and cephaloridine) produce minimal histologic changes in the human.[9] Furthermore, the distinction between ischemia and nephrotoxins is simplistic. Some nephrotoxins (cyclosporine and amphotericin) might be more accurately considered hypoxia-inducing agents, as they diminish renal perfusion, causing injury to zones (medullary ray and inner stripe) known to have limited oxygen availability.[10] Furthermore, the hypoxia-mediated renal injury induced by some nephrotoxins (amphotericin, heme pigments, and possibly radiocontrast agents) is likely also associated with direct tubulotoxicity.

Most cases of ATN occur in patients with predisposing comorbidities, in sharp contrast to the healthy animals used in most models of ATN. Consequently, intense insults, such as prolonged ischemia or mega-doses of nephrotoxins, are required to achieve reproducible experimental renal failure, which in turn is associated with tubular pathology that is far more extensive than is seen in humans. Unfortunately, such animal studies have become the reference point for analysis and interpretation of human ATN. For example, the model of renal artery obstruction with subsequent reflow (warm ischemia reperfusion) produces extensive necrosis of proximal tubules, lesions far beyond what is typical for humans.[11] Indeed, multiple clinical trials, based on success-

ful interventions in rats, have failed in humans.[9] Gentamicin is an example in which suprapharmacologic doses are necessary to cause tubular necrosis and renal failure in healthy animals.[10] Its distinctive lesion (intracellular laminar myelin type whorls) shows no correlation with renal toxicity in humans. However, when combined with additional insults (such as ischemia, volume depletion, obstruction, or organ necrosis), animals do develop renal failure with clinically relevant doses.[10] The combination of otherwise nontoxic doses of cisplatin and lipopolysaccharides results in severe renal failure and mortality in rats.[12] Myoglobin *per se* is relatively nonrenotoxic unless combined with other insults (volume depletion or prostaglandin synthesis inhibition). Under those circumstances, renal retention of the tubulotoxic agent may increase, and casts may form, leading to intrarenal obstruction, another possible mechanism for ATN.[13] Casts were inconspicuous in our biopsy, and the CPK was not markedly elevated, suggesting that this mechanism was not relevant in our case.

In summary, with the possible exception of calcineurin inhibitors, there is little correlation between the histology observed in many animal studies of ATN and the human situation.[10]

A New Approach

It seems clear that an appropriate model for ATN would be one of acute renal failure accompanied by limited changes by light microscopy, recapitulating the physiologic and pathologic dissociation. Indeed, recent studies in the isolated perfused rat kidney and in *in vivo* models of prostaglandin inhibitors and contrast nephropapthy seem to fit that goal, as in some protocols there is documented tissue hypoxia and adaptive responses in the setting of relatively intact tubular morphology. Upregulation of hypoxia inducible factors (HIF) with their multiple cell survival target genes have been localized to hypoxic cells. Experiments in isolated perfused kidneys[14] and *in vivo*[15] illustrate that failure to generate HIF and HIF-mediated responses is associated with lethal tubular injury. Rosenberger *et al.* have used high amplification HIF-1α immunohistochemistry to study human allograft ATN. Elevated HIF-1α expression was seen in immediate graft function, as opposed to the low levels noted in primary nonfunction.[16] Although counterintuitive, these findings likely reflect higher renal oxygen tensions that are a function of diminished tubular oxygen demand secondary to reduced GFR. Taken together, these studies document acute renal failure with only limited morphologic alterations and suggest novel therapeutic approaches using drugs that upregulate HIF and target genes, such as erythropoietin.[17] These strategies have been shown to both promote cell survival in isolated perfused kidneys[18] and ameliorate renal failure after warm-ischemia reflow.[19]

Dynamic Changes in Intrarenal Microcirculation

Changes in renal microcirculation and oxygenation are likely to occur following use of prostaglandin inhibitors, radiocontrast administration, or strenuous exercise, such as marathon running. Compensatory mechanisms in healthy individuals maintain renal function. With increasing intensity of renal insults, and importantly, as they are multiplied, tubular injury develops, as has been documented by urinary detection of biomarkers such as cytokines (IL-6, IL-8, IL-18),[20,21] NGAL,[22] NAG, and KIM-1.[23] Interestingly, IL-6 RNA was upregulated in renal allograft donor biopsies after cold ischemia and reperfusion and was correlated with longer cold ischemia times.[24]

Numerous studies over the past two decades have focused on the limited oxygen availability (pO_2) of the medulla, in both animals and humans.[25] This "hypoxic condition" is a function of both the renal microanatomy that enables urinary concentration and the energy demands of tubular reabsorption. Multiple mechanisms, such as prostaglandins, nitric oxide, adenosine enable the preservation of pO_2 by balancing regional oxygen supply with transport activity. When the insults are limited, these adaptive responses preserve tubular function and integrity, as in prerenal failure. When they are overwhelmed, as in ATN, tubular dysfunction, as reflected by diminished urine concentrating capacity and sodium reabsorption, ensues.

Furthermore, activation of tubuloglomerular feedback may alter glomerular hemodynamics and reduce filtration rate to an extent out of proportion to tubulointerstitial injury, hence reducing tubular transport and improving medullary oxygenation, a process Thurau and Boylan cleverly called acute renal success.[26] Recently developed noninvasive techniques may help document the evolution of these changes over time. BOLD (blood oxygen level detection) MRI studies based on the magnetic resonance of deoxyhemoglobin have demonstrated limited oxygen availability in the human medulla as well as the expected increase in pO_2 when transport activity is inhibited by loop diuretics.[27] BOLD MRI confirms diminished medullary pO_2 in animal models of contrast nephropathy.[28] Interestingly, renal sodium MRI can detect early loss of tubular function (diminished sodium concentration gradient) in this model when there is still very limited tubular injury.[29]

The recent introduction of extended sepsis models more analogous to the human situation (with the use of fluid resuscitation, antibiotics, and inotropes), and the finding of primary toll-like receptors for Gram-negative toxins, such as TLR4 and their effector proteins, such as MyD88, have also led to a deeper understanding of acute renal failure in sepsis.[30] The minimal morphologic lesions present underscore their clinical relevance. Indeed, studies of autopsies in patients with sepsis have found apoptotic changes primarily limited to the gastrointestinal tract and the spleen.[30] There seems to be agreement, certainly in animals and likely in humans, that both systemic and renal blood flow dynamics are severely altered in sepsis.[30]

Vasomotor Hypoxic Nephropathy

As we have seen, the pathophysiologic basis for acute renal failure likely relates to alterations in renal blood flow and oxygenation. In our case, acute renal failure

was secondary to the action of cocaine, known to induce marked vasoconstriction.[31] Blood flow, sufficient to prevent necrosis, but not enough to maintain GFR, is the likely explanation for the parenchymal preservation. This is likely accomplished by "corticomedullary blood redistribution," and tubuloglomerular feedback (diminishing filtration), leading to acute renal success, and preserving medullary pO_2. Comparison of our case with another, showing the unusual finding of extensive tubular necrosis is useful in exploring their differing pathophysiologies.

Case 2 was a 71-yr-old man with a hospital course complicated by cardiopulmonary arrest with postresuscitation hemodynamic instability, respiratory compromise, and oliguric renal failure, requiring ventilation and dialysis until his death 13 d later. Postmortem examination of the kidneys revealed marked necrosis of proximal tubules with regenerative changes. Distal tubules appeared spared (Figure 1, B and C). This case parallels the warm ischemia reflow animal model (cardiac arrest followed by reperfusion) and indeed showed widespread tubular necrosis and regeneration at autopsy, findings almost never seen in clinical ATN.

Inasmuch as tubular necrosis is not a necessary prerequisite for ATN, what these two cases share is an important element of hemodynamic dysregulation. This spectrum of changes is detailed in Table 1. How then can we explain the difference in morphologic patterns? Parenchymal preservation results when intrarenal blood flow dysregulation is associated with sufficient pO_2. Renal failure results when that flow does not maintain glomerular filtration and tubular function. However, in almost all cases, efferent arteriolar perfusion is sufficient to maintain tubular integrity, as demonstrated in our biopsy, and the reduction in GFR may serve to preserve tubular integrity by decreasing tubular transport work and oxygen consumption. In the contrasting autopsy case, there likely was a period of no renal perfusion, a scenario that is not typical of ATN. This extreme insult, as used in many animal models, led to a similar pattern of widespread tubular necrosis.

Furthermore, it appears that tubular segments respond differently to hypoxia. Proximal tubules normally reside in a high pO_2 region and have a more constant workload and therefore oxygen requirement. Their injury, at least in warm ischemia reflow, seems to be more related to diminished pO_2 than increased demand. This is the type of injury evident in the extensive necrosis present at autopsy and only minimally present in our biopsy case. Distal tubules, in contrast, reside in a hypoxic environment and their workload is more variable, a function of the GFR and proximal solute reabsorption. mTAL injury thus reflects an imbalance between regional pO_2 and tubular oxygen demand and can occur both initially, and during recovery from ATN, as filtration rate increases. Adaptive responses as discussed above may limit these changes, a process that may account for the tubular preservation seen in our biopsy.

ATN may therefore be understood as a (mal)adaptive response of the kidney-trading away GFR for the preservation of medullary pO_2 and tubular integrity. If so, the effect of therapeutic agents in ATN may be more of a function of their ability to restore normal intrarenal hemodynamics and tubular integrity. Indeed, restoration of GFR alone, resulting in increased tubular oxygen demand, may be counterproductive unless accompanied by reconstitution of the peritubular microcirculation/oxygenation.

Important questions remain as to how this aberration of flow develops and is maintained. Vascular tone is a function of endothelial and smooth muscle cell interaction. Endothelial cells release many vasoactive factors, some potent vasodilators (such as nitric oxide, prostaglandin E_2, and prostacyclin) and others vasoconstrictors (such as endothelin, prostanoids, and components of the renin-angiotensin system). Some agents, such as endothelin, angiotensin-II, and adenosine, have diverse effects on cortical vasoconstriction and medullary microcirculation vasodilation, depending on the type and density of their various receptors. Reactive oxygen species signaling may be relevant to the control of vascular dynamics. Elaborated by the mTAL and governing HIF-1 activation, reactive oxygen species are crucially poised to regulate or dysregulate vascular function and integrity.[32] Cytokines have also been suggested as early markers for ATN and are known to have a profound effect on vascular tone, both inducing the expression of cytokine receptors and other mediators of vasoconstriction as well the expression of enzymes such as inducible NO synthase and cyclooxygenase-2.[33]

In summary, the physiologic derangements of ATN are far more striking than the morphologic changes that accompany them. Noninvasive techniques and recently developed experimental models have begun to unravel this paradox.

Table 1. Hypothetical schema of hemodynamic dysregulation in acute kidney injury

Hemodynamic State	Compensated	Dysregulation	Total Cessation of Blood Flow
Clinical scenario	Prerenal azotemia	Acute tubular necrosis	Vascular catastrophe
Tubular injury	0	Rare-↑, focal	↑ ↑ ↑
Biomarkers	0-limited	↑-↑ ↑	↑ ↑ ↑
GFR	↓-↓ ↓	↓-↓ ↓ ↓	↓ ↓ ↓-0
Clinical frequency	Common	Less common	Rare

↑, increase; ↓, decrease.

ACKNOWLEDGMENTS

The authors thank John Conrey who graciously supplied information on the biopsy case and Von Samedi who performed the postmortem examination on the contrasting case as well as Samuel Heyman and Christian Rosenberger for reviewing this manuscript and collaborating on many related studies, and Mayer Brezis who helped form the foundation for these ideas. Finally, we all owe Franklin Epstein special recognition as a pioneer in this field, and gratitude for being our mentor.

DISCLOSURES

None.

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