Contrast Medium–induced Nephrotoxicity: Which Pathway?1

Acute renal failure (ARF), the sudden and rapid deterioration in renal function that results in the failure of the kidney to excrete nitrogenous waste products and to maintain fluid and electrolyte homeostasis, can be the direct result of parenteral contrast medium administration, which is the third most common cause of hospital-acquired ARF (1,2). Contrast medium–induced ARF may range in severity from asymptomatic, nonoliguric transient renal dysfunction to oliguric (urine volume of less than 400 mL/d), severe ARF that necessitates dialysis.

Findings in recent reports in the cardiology literature indicate that the development of contrast medium–induced ARF after diagnostic coronary angiography and percutaneous intervention is associated with prolonged hospitalization, marked increases in morbidity, and early and late mortality. In 1826 consecutive patients who were undergoing percutaneous intervention, McCullough et al in 1997 (3) reported an incidence of contrast-induced ARF in 0.7% who did not require dialysis and in 14.5% who did.

Other than hydration, findings in most prior studies of measures to prevent contrast-induced ARF have been neutral, or researchers have found deleterious effects or, in the case of N-acetylcycteine, have reported mixed results (5–8).

It is difficult to prevent contrast-induced nephropathy when the cause is not understood. There are three relatively distinct mechanisms or pathways proposed for the pathophysiology in contrast-induced ARF: hemodynamic effects, direct contrast medium molecule tubular cell toxicity, and endogenous biochemical disturbances such as an increase in oxygen-free radicals and/or a decrease in antioxidant enzyme activity (Figure). On the other hand, an interaction of any two, all, or some other effects are also presumed as additional possibilities. The noteworthy investigation by Heinrich et al in the current issue of Radiology (9), and important results in recent clinical reports about potential antidotes, are the stimuli for this commentary.

Hemodynamic Effects

Of the three major pathways depicted in the Figure, the greatest amount of recent clinical attention has focused on the hemodynamic effects of contrast media. This is somewhat curious in view of a previous insight, almost 25 years ago, by Gilbert Mudge, MD, a leading expert in the field of contrast-induced ARF, who stated in a comprehensive review of this subject that “Despite repeated statements to the contrary, there is little evidence that ischemia is the mechanism by which urographic agents produce renal failure” (10). My academic interest has been to study the hemodynamic effects of and mechanisms of action of contrast media on renal function, and I favor this assessment.

Interest in the hemodynamic pathway was stimulated by three seminal animal investigations that included an assessment of the effects of hypertonic contrast media on renal blood flow. A decrease in renal blood flow following the direct intraarterial injection of contrast material into the renal vascular bed, which is unique in comparison with other vascular beds, was initially noted by Talner and Davidson in 1968 (11), Caldicott et al in 1970 (12), and Sherwood and Lavender in 1969 (13). The hemodynamic response with the direct intraarterial injection of contrast material is actually biphasic, with an initial increase followed by a decrease. Although the decrease in blood flow is only about 30% in comparison with baseline and is transient, lasting for only several minutes, this observation initiated the hypothesis that ischemia could be a likely candidate for the cause of contrast-induced renal toxicity. Subsequently, there have been numerous pharmacologic agents proposed to eliminate or minimize the contrast-induced decrease in blood flow: dopamine, endothelin antagonists, adenosine antagonists, calcium-channel blockers, and fenoldopam mesylate, none of which have proved to be clinically efficacious (14).

The biphasic changes in renal blood flow seen during direct injections of contrast material into the renal artery are far too transient and minimal to produce ischemic damage. Animal models of ischemic ARF require severe prolonged in-

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Osmotic agents such as mannitol have been shown to protect the kidney against ischemic injury in animals. Researchers in most studies in humans have failed to demonstrate the effectiveness of this agent in the prevention or treatment of ischemic ARF. If it is administered early in the course of ischemic renal failure, however, it can convert an oliguric state to a nonoliguric state (1). Investigators in animal studies who compared the hemodynamic effects of hypertonic saline or mannitol, matched for osmolality, with high-osmolality contrast materials have shown these responses to be indistinguishable (17,18). When these agents are matched for osmolality with contrast media and are injected directly into the renal artery, a biphasic blood flow response is also noted. In addition, hypertonic mannitol decreases the glomerular filtration rate in a manner similar to that of hypertonic contrast media, with this manner being a nonnephrotoxic nonspecific effect of all osmotic diuretics of small molecular size. The low-osmolality nonionic contrast media in widespread clinical use today show even lesser hemodynamic effects.

A little appreciated fact is that the predominant hemodynamic response to all intravenously administered high- or low-osmolality contrast media is only a decrease in renal vascular resistance. This finding has been documented in both animal and human studies (6,18–20). Beyond these facts, however, arguments have been made that, given that these observations are valid, a decrease in the renal vascular resistance in the cortex without a parallel decrease in the vascular resistance in the medulla might lead to a “steal” of blood from the medulla, with subsequent hypoxia (21,22). In addition, vasodilatation increases the glomerular filtration rate and the delivery of sodium to the loop of Henle, and these increases result in a greater demand for oxygen consumption by the tubular cells (22). The hypothesis is that either a decrease in blood flow and/or oxygen tension can lead to necrosis of the medullary thick ascending limbs and subsequent renal failure. In contrast to the the steal hypothesis are findings in studies with microspheres in animals and humans after the administration of contrast material that showed no evidence of a redistribution of blood flow from the medulla to the cortex (23,24). Agmon et al in 1994 (25) actually showed an increase in medullary blood flow after contrast material administration in rats. Other investigations, however, have shown a decrease in medullary blood flow after contrast medium administration but have not proved this to be of a magnitude sustained enough to cause tubular cell damage with usual clinical doses (26,27).

In a clinical investigation, researchers provided additional compelling evidence that a direct hemodynamic pathophysiology is not primary. Fenoldopam mesylate, a specific dopamine-1 receptor agonist, is a unique vasodilator that selectively increases both renal cortical and outer medullary blood flow while it decreases systemic vascular resistance (28). This agent was shown to prevent the reduction in glomerular filtration rate that occurs in dogs after contrast material administration. Stone et al (7) in 2003 performed a large-scale multicenter prospective double-blind placebo-controlled randomized trial in 315 patients with baseline renal insufficiency to determine the safety and effectiveness of fenoldopam mesylate in the prevention of contrast-induced nephropathy in patients with chronic renal insufficiency. As far as is known to date, this is one of the few, if not the only, sufficiently powered clinical trials of a potential antidote. The results indicated that the specific dopamine-1 agonist fenoldopam mesylate is ineffective in preventing further renal function deterioration in patients with chronic renal insufficiency who receive contrast material. Premature study drug discontinuation occurred in some patients secondary to mild hypotension or tachycardia caused by the antidote itself. The authors concluded that the findings of their investigation suggested that disturbances in intrarenal hemodynamics may not represent the critical pathophysiology of contrast-induced ARF.

Renal ischemia that results from prerenal effects is the most common form of ARF in the hospital setting and includes any condition that induces hypovolemia, such as hemorrhage, dehydration, low cardiac output, and lowered systemic vascular resistance that can occur with general anesthesia (1,2,6). Most intravascular contrast media are osmotic diuretics and can, thus, induce or exacerbate hypovolemia secondary to their dehydrating effects. Interestingly, Fang et al in 1980 (29) found low fractional excretion of sodium during the oliguric phase of contrast-induced ARF, a more common characteristic of hypovolemic ARF than of direct renal injury. In addition, contrast media cause vasodilatation, usually mild and transient, but uncommonly lead to prolonged systemic hypotension (6,30). The indirect effect, therefore, of contrast media on renal hemodynamics is a reasonable hypothesis in regard to the pathophysiology involved and is rapidly reversible when restoration of renal blood flow and normal glomerular filtration rate occurs with hydration and/or administration of pharmacologic agents that correct hypotension.

Direct Contrast Medium Molecule Tubular Cell Toxicity

The study by Heinrich et al (9) that appears in the current issue of Radiology was rigorously performed, is timely, and has substantial results. Prior evidence for direct contrast medium toxicity to the renal tubular cell has been suggested by findings in studies in which the renal extraction of p-aminohippurate was assessed. A decline in p-aminohippurate indicates a reduction in tubular cell transport (secretory) of the proximal tubules of the cortical nephrons and can be an indicator of a toxic effect independent of the hemodynamic changes. The first such indication was suggested by Talner

![Diagram showing proposed pathways leading to contrast medium-induced nephrotoxicity](image-url)

Diagram shows proposed pathways leading to contrast medium-induced nephrotoxicity. These pathways include hemodynamic effects (direct and indirect), direct contrast medium (CM) molecule toxicity, and endogenous biochemical disturbance. Interrelationships and/or combinations of these effects are also possible. NO = nitric oxide.
and Davidson in 1968 (31). In their study in animals, they determined that a hypertonic contrast agent is capable of inducing a decrease in p-aminohippurate, exclusive of the effect of hypertonicity. Findings in that study were later corroborated by Dibona in 1978 (32). Pabico et al in 1989 (33) performed a study in dehydrated dogs in which dehydration was sufficient to reduce the glomerular filtration rate and effective renal plasma flow. They found that the parenteral administration of a hypertonic contrast agent further diminished the already compromised renal hemodynamic function, caused by dehydration, and impaired the renal tubular cell transport mechanism, as evidenced by a marked reduction in p-aminohippurate. The depressive effect on p-aminohippurate could not be attributed to the osmotic properties of the contrast medium itself.

Humes et al in 1987 (34) reported a possible direct deleterious effect of sodium diatrizoate on renal tubular cells; they used suspensions enriched in rabbit proximal tubular cell segments incubated with sodium diatrizoate. A variety of well-established metabolic parameters used to quantitate the extent of cell injury were measured. Sodium diatrizoate produced marked declines in tubular cell potassium (K+), adenosine triphosphate, and total adenine nucleotide contents; marked decreases in tubular cell basal and uncoupled respiratory rates; and a marked increase in tubular cell calcium content, an increase that is indicative of cell injury. A period of 22 minutes 30 seconds of hypoxia also caused deleterious changes in each of these quantitative indexes of cell viability, and diatrizoate potentiated the degree of hypoxia-induced cell injury. The effects could not be explained on the basis of the toxicity of the contrast agent, since equimolar concentrations of mannitol had no detrimental effects on the cell viability parameters. It was concluded that a possible direct toxic effect of the contrast material on plasma membrane permeability and transport processes was a likely cause.

The current investigation in Radiology reinforces and expands on the importance of direct tubular cell toxicity on the pathophysiology of contrast-induced ARF (9). The authors have shown convincing evidence of a direct cellular toxicity of contrast agents independent of either hemodynamic mechanisms or osmolality. This refocuses attention on the contrast medium molecule itself and on direct cellular mechanisms for elucidation of the pathophysiology of contrast-induced ARF and, thus, on the potential for a solution. The model also suggests development of an assay for preclinical testing of newly developed contrast media molecules and potential strategies for engineering safer agents.

The finding of differential effects of contrast media molecules with incubation for 24 hours supports our speculation that situations that lead to a prolongation of contrast media dwell time in the tubular lumen can be a major factor in renal toxicity. Specific circumstances where there is a delay in the excretion of contrast media molecules from the tubular lumen would occur in prerenal clinical conditions, such as hypovolemia secondary to dehydration (that can be exacerbated by the osmotic diuretic effects of contrast media) and with the osmotic diuresis that can occur with diabetes mellitus (1). The effects also may be exacerbated by an increased concentration of the contrast medium molecules in the renal tubular lumen, as would occur in dehydration.

**Oxygen-Free Radicals**

The third pathway that is proposed is an increase in oxygen-free radicals or a decrease in antioxidant enzyme activity triggered by contrast medium administration (35–37). In some ways, this could be a sequel of the direct tubular cell toxicity pathway if the endogenous biochemical disturbances are simply the product of tubular cell damage rather than the primary cause of the resultant tubular cell damage.

Free radicals are atoms or molecules that contain one or more unpaired electrons. In vivo, oxygen molecules are changed into water molecules after successive reduction reactions. Intermediate species are called “reactive oxygen species.” The catabolism of adenosine by xanthine oxidase leads to the formation of one of the reactive oxygen species that has been demonstrated by Katholi et al (38) in vivo and in vitro with contrast material administration. At high concentrations, free radicals have highly deleterious effects on all cellular constituents and cause oxidative stress and protein damage. It has been suggested that reactive oxygen species are important in the renal damage caused by contrast agents (35,36,39). In laboratory animals, contrast agents increase lipid peroxidation (40), and superoxide dismutase, a scavenger of reactive oxygen species, preserves renal function (35).

For many years, N-acetylcysteine has been known to promote detoxification and act as a reactive oxygen species scavenger. On the basis of the assumption that the reactive oxygen species could be involved in the pathophysiology of contrast-induced ARF, researchers in clinical studies have assessed the potential prophylactic effects of the oral or intravenous administration of N-acetylcysteine. The initial positive results by Tepel et al (37) precipitated numerous subsequent assessments of the potential value of N-acetylcysteine in the prevention of contrast-induced nephrotoxicity. The subsequent clinical investigations have been mixed, however, and all lack a sufficiently powered prospective randomized placebo-controlled end point. In the most recent meta-analysis of 16 prospective controlled clinical trials with a total of 1538 patients, Kshirsagar et al (8) in 2004 showed neither a confirmation of validity nor a recommendation for the routine use of N-acetylcysteine. Thus, there is yet no clinical substantiation that the liberation of oxygen-free radicals is the mechanism for contrast-induced ARF.

The current article by Heinrich et al in Radiology provides a renewed focus on the direct tubular cell toxicity pathway of contrast medium–induced ARF and, in my opinion, a promising pathway to solve a growing clinical crisis. In the meantime, we know that close attention to patient hydration before and after the administration of contrast material, attention to the risk factors of preexisting renal insufficiency and diabetes, and active communication with referring clinicians are effective strategies for prevention.

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**References**

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