A Review of Contemporary Prevention Strategies for Radiocontrast Nephropathy: A Focus on Fenoldopam and N-Acetylcysteine

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The mechanism most likely responsible for the development of radiocontrast nephropathy (RCN) is contrast-induced renal tubular ischemia. At this time, intravenous hydration remains the mainstay for preventing RCN. The antihypertensive agent fenoldopam has been shown in a canine model, as well as in small, retrospective, prospective, and randomized human evaluations, to be effective for preventing RCN. In addition, studies have reported the ability of the free radical scavenger N-acetylcysteine (NAC) to prevent RCN. The clinical trial data for NAC, however, are not consistent regarding this effect, which, if present, appears to be modest and perhaps restricted to lower-risk clinical scenarios.
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Attempts to develop protocols for the prevention of radiocontrast nephropathy (RCN) have, with the exception of intravenous hydration, until recently met with failure. The development of effective prevention and treatment strategies has been an elusive goal. What continues to fuel the search for effective strategies is the large demographic of patients at risk for developing RCN, and a plethora of clinical data showing a strong and consistent relationship between the development of RCN and short- and long-term

mortality. Our improved understanding of the pathophysiology of RCN has focused on efforts to identify effective prophylactic therapies. The purpose of this discussion is to present a brief historical review of the attempts to prevent RCN. It is followed by a focus on two contemporary strategies involving the use of fenoldopam (Corlopam) and N-acetylcysteine (NAC).

The Mechanisms of Development of Radiocontrast Nephropathy

The mechanism most likely responsible for the development of RCN is contrast-induced renal tubular ischemia. It is known that radiocontrast induces a short-term increase in renal blood flow (RBF) that lasts up to about 30 minutes. It is followed by a more prolonged period of vasoconstriction of the renal artery and reduction of RBF.[1] Within the kidney, there is a steep oxygen gradient between the relatively richly perfused outer cortical segments and the deeper medullary segments. Baseline oxygen tension in the renal medulla is approximately 10–20 mm Hg, whereas the cortical oxygen tension is approximately 40–50 mm Hg.[2] Radiocontrast not only reduces total renal blood flow, but it also shunts residual blood flow from the underperfused medullary segments to the cortical segments.[3] This can produce either reversible ischemic tubular injury or irreversible tubular necrosis. The renal effect of this reduction in medullary perfusion is further exacerbated by the increase in metabolic demands placed on the renal tubules as they actively secrete dye from the circulation. As a result, the kidneys face a combination of increased metabolic demand and decreased perfusion. Ischemic injury would manifest itself clinically as a transient reduction in renal function, assessed by measuring serum creatinine, with a complete return to baseline levels within 10–14 days. Ischemic necrosis or acute tubular necrosis (ATN), resulting in a permanent loss of functional nephron units, would manifest itself as a lack of return to baseline serum creatinine. Approximately 10%–15% of patients who develop RCN will need dialysis therapy, and 30% of patients' serum creatinines do not return to baseline levels consistent with permanent loss of some renal functioning elements.[1]

Diabetic Patients With Renal Insufficiency Are at Highest Risk of Developing RCN

Patients at highest risk of developing RCN are those with renal dysfunction as manifested by a reduced glomerular filtration rate or proteinuria, particularly those with the diabetic form of nephropathy.[4] Intravascular volume depletion and congestive heart failure also predispose to the development of RCN. Diabetic nephropathy is a renovascular disorder with abnormalities of both renal macrocirculation and microcirculation; it therefore predisposes to contrast-induced ischemic injury. In addition to the ischemia model for RCN, other potential mechanisms include a direct toxic renal tubular effect or an increase in free-radical formation. Supporting a potential role for free radicals in the development of RCN is the ability of superoxide dismutase to reduce the contrast-induced increase in the urinary Tamm-Horsfall protein excretion.[5]

Early Attempts at Preventing RCN

Early attempts at preventing RCN focused on maintaining high urine volume around the time of contrast exposure. In the 1980s and early 1990s it was fairly routine for patients at risk to be prescribed a protocol of intravenous hydration, mannitol, and/or furosemide. To evaluate the effectiveness of this approach relative to intravenous hydration alone, Solomon and colleagues[6] randomized patients at risk to one of three arms: saline hydration alone, saline plus mannitol, and saline plus furosemide. The hydration-only group fared best, with 11% of patients developing RCN compared to 28% of patients who received saline plus mannitol and 40% of patients who received saline plus furosemide. This study had a dramatic effect at that time on the approach to the patient at risk for RCN by eliminating the routine use of mannitol and furosemide.

Later Attempts at Preventing RCN

Aminophylline and Dopamine

More recently, studies have evaluated the ability of agents such as aminophylline and "renal-dose" dopamine (1-2.5 μg/kg/min) to prevent RCN.[7] These two compounds were felt to increase renal blood flow through different mechanisms and perhaps compensate for contrast-induced tubular hypoperfusion. Radiocontrast exposure increases the intrarenal levels of adenosine, where it acts as a very potent vasoconstrictor. Renal-dose dopamine was thought to increase renal perfusion by activating the renal dopamine receptor. In a randomized trial by Abizaid and colleagues[7] that compared aminophylline, low-dose dopamine, and saline hydration, there was no enhanced effect from these two agents. As a follow-up to this study, all patients who developed RCN on the three different treatments were then re-randomized to saline hydration or low-dose dopamine as treatments for RCN. Those patients who were given renal-dose dopamine fared much worse than

the patients who were given hydration alone. The implications of this trial are not only that aminophylline and dopamine are no more effective than saline hydration alone for the prevention of RCN, but that dopamine can actually exacerbate RCN, once it occurs.

What has become clear is that there is a wide variance in the plasma levels of dopamine achieved in patients who have received renal-dose dopamine. Although some patients may actually have plasma levels in the dopaminergic range, the variance is wide enough so that other patients will be in the β-range and be predisposed to develop cardiac arrhythmias, and others will be in the α-range, with associated vasoconstriction. This may partially explain why patients do not respond to low-dose dopamine and why renal function worsens further in some patients. This finding may have implications in other settings such as the intensive care unit, where it is common to use renal-dose dopamine to maintain or enhance renal function in trauma and other postoperative patients.

Forced Diuresis

The ability of forced diuresis to reduce the rate of contrast-induced nephropathy while euvolemia is maintained was assessed in the Prevention of Radiocontrast Induced Nephropathy Clinical Evaluation (PRINCE) trial.[8] The researchers found that there was no significant benefit from this protocol. The authors also made the observation that those patients who maintained the highest urine volumes were the least likely to develop RCN. It can be presumed that the group of patients with the highest urine volume had less tubular dysfunction rather than that the maintenance of high urine output represents a treatment for preventing RCN.

Low Osmolar Agents

The ability of low osmolar contrast agents to be less nephrotoxic remains controversial. One meta-analysis found a modest 20% reduction of RCN.[9] In the randomized PRINCE trial, however, the use of low osmolar agents was not protective.[8] A recent analysis of hydration protocols evaluated the differential effect of hydration with one-half normal saline solution versus normal saline solution in the incidence of RCN in patients undergoing coronary angiography and angioplasty.[10] A total of 1620 patients were randomized to either isotonic or half-isotonic saline infused at 1 mL/kg, starting the morning of the procedure. Isotonic saline was found to be superior to half-isotonic saline with a RCN incidence of 0.7% and 2.0%, respectively. The study authors concluded that using normal saline did provide an increment of enhanced effect in preventing RCN.

Fenoldopam and N-Acetylcysteine

More recently, much excitement has centered on the potential ability of fenoldopam and NAC to prevent RCN. Fenoldopam is a selective dopamine-1 (DA_1) receptor agonist which acts to increase renal blood flow and prevent the shunting of blood flow from the medulla to the cortex, thereby maintaining medullary oxygen tension. The DA_1 and DA_2 receptors exert paradoxic effects on renal perfusion and renal function (Table 1). Fenoldopam does not interact with the α-receptors or β-receptors.

Fenoldopam is indicated as an intravenous agent for the treatment of severe hypertension. As an antihypertensive agent, fenoldopam maintains renal blood flow while it lowers systemic blood pressure, in

Table 1
Activation and Renal Physiology of Dopaminergic Receptors

Agonist	DA_1 Fenoldopam	DA_2 Bromocriptine
Renal effects	↑ Renal blood flow	↓ Renal blood flow
	↑ Glomerular filtration rate	↓ Glomerular filtration rate
	↑ Natriuresis	↓ Natriuresis
	↑ Diuresis	↓ Diuresis
	Inhibits sodium/potassium exchange	Stimulates sodium/potassium exchange

DA, dopamine.

Adapted from Garwood S, Hines R. Perioperative renal preservation: dopexamine and fenoldopam—new agents to augment renal performance. *Semin Anesth.* 1998;17:308–318.

The implications of this trial are not only that aminophylline and dopamine are no more effective than saline hydration alone for the prevention of RCN, but that dopamine can actually exacerbate RCN, once it occurs.

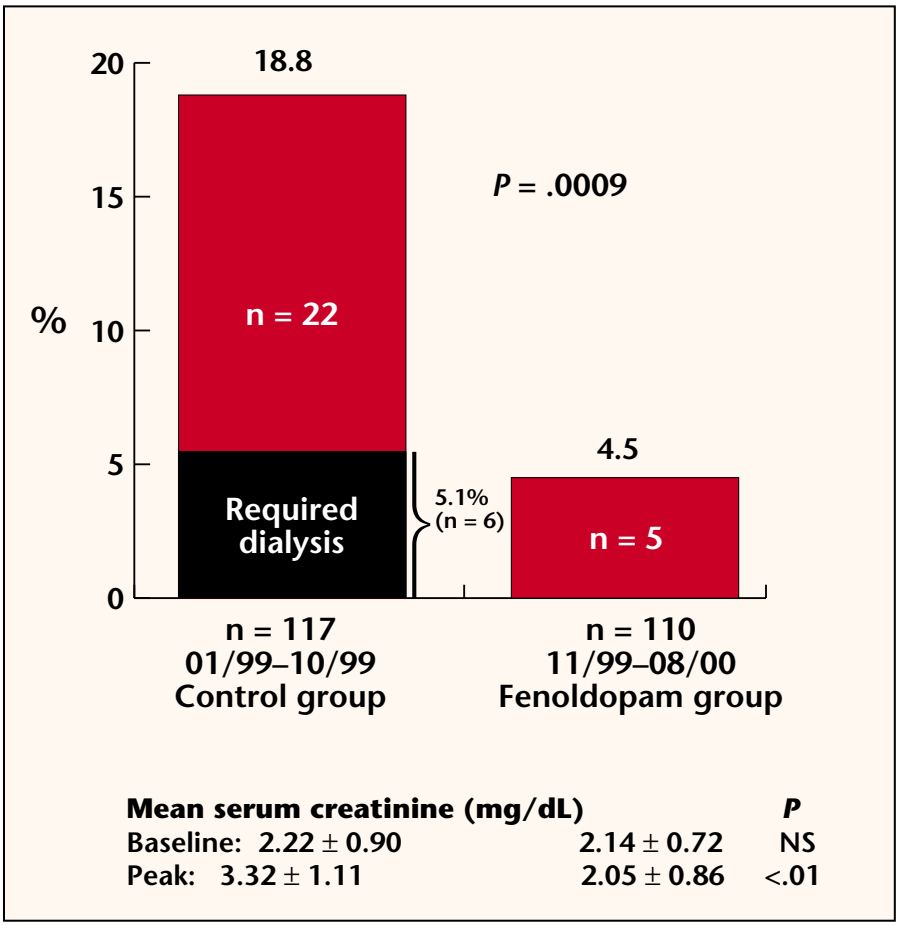

Figure 1. *Incidence of RCN and mean baseline and peak serum creatinine in PCI patients with baseline renal dysfunction: historical controls vs patients who received fenoldopam treatment. Reproduced from Kini and Sharma.*[15]

contradistinction to other vasodilators.[11] This is a characteristic of an ideal antihypertensive agent, particularly in a patient with any type of compromised renal function. In normotensive patients, the use of fenoldopam is associated with very modest reductions in blood pressure in the infusion ranges commonly used for prevention of RCN (0.05 μg/kg/min to 0.4 μg/kg/min).[12]

The ability of fenoldopam to prevent RCN has been confirmed in a canine animal model, retrospective and prospective nonrandomized trials, and in a pilot multicenter, randomized, double-blind clinical trial. In a study by Bakris and associates,[13] anesthetized, volume-depleted dogs were exposed to radiocontrast after baseline measures were taken of renal blood flow (RBF) and glomerular filtration rates (GFR). Following contrast exposure, the study authors measured a 50% reduction in both RBF and GFR. When RBF and GFR returned to baseline, these same dogs were given infusions of fenoldopam followed by contrast exposure. Repeat measures of RBF and GFR at this time revealed no reductions in blood flow or renal function.

In a prospective, nonrandomized series of trials by Madyoon, patients undergoing coronary and peripheral vascular interventions received fenoldopam prior to contrast exposure; the study authors then compared the incidence of RCN to valid historical controls. Patients had a mean serum creatinine of 2.3 mg/dL and were exposed to an average of 144 cc of contrast. A nearly 60% reduction in the incidence of RCN was noted compared to that for historical controls.[14] In a more recent series, Kini and Sharma[15] compared the incidence of RCN in consecutive patients at risk, in 1999, before the use of fenoldopam, and in 2000, when this agent was routinely used. They found a 75% reduction

Main Points

- The most likely mechanism responsible for the development of radiocontrast nephropathy (RCN) is contrast-induced renal tubular ischemia.
- As an antihypertensive agent, fenoldopam maintains renal blood flow while it lowers systemic blood pressure, in contradistinction to other vasodilators.
- The ability of fenoldopam to prevent RCN has been confirmed in an animal model, in retrospective and prospective nonrandomized trials, and in a multicenter, randomized, double-blind clinical trial.
- Until further data is obtained, it would be prudent to include the use of fenoldopam in patients at higher risk for the development of RCN in addition to intravenous hydration and perhaps N-acetylcysteine.

in RCN with the use of fenoldopam (Figure 1).

In a multicenter, randomized clinical trial by Tumlin and colleagues,[16] 44 patients with chronic renal insufficiency who were undergoing coronary angiography and CT scanning with serum creatinines between 2.0–5.0 mg/dL were randomized to either one-half saline hydration or hydration plus fenoldopam. The trial was powered to assess the ability of fenoldopam to prevent the contrast-media–associated reduction of renal blood flow. The striking results of this trial were that fenoldopam prevented the contrast-induced reduction of renal blood flow. In addition, there was a 45% reduction of RCN representing a strong trend towards a treatment effect. In the group of patients receiving one-half normal saline alone, there was a significant increase in serum creatinine from the baseline value to the 72-hours' postexposure measure. In the patients receiving fenoldopam, there was no significant rise in serum creatinine from the baseline value. The results of the prospective, randomized, placebo-controlled trial of fenoldopam mesylate for the prevention of radiocontrast nephropathy (CONTRAST trial) will provide additional insights into the ability of fenoldopam and NAC to prevent RCN.[17]

Since the report by Tepel and associates,[18] much has been made of the ability of the free radical scavenger NAC to prevent RCN. This small, single-center, randomized trial compared the use of oral NAC, given with intravenous hydration before and after 75 cc bolus of contrast for CT scanning, to hydration alone. The study authors reported a 21% incidence of RCN in the control group compared with a 2% incidence in the NAC group. However, there was no significant difference in serum creatinine levels from baseline to the 48-hour end point in the control group, and only a small but significant decrease in the NAC group.

Since the report by Tepel and associates, much has been made of the ability of the free radical scavenger N-acetyl cysteine (NAC) to prevent RCN.

Since the publication of these results, other trials have been completed, which have not shown a consistent positive effect from NAC. In a trial by Briguori and colleagues,[19] 183 patients were randomized to receive either NAC plus hydration or hydration alone. There was no incremental benefit in the use of NAC in this study. On further analysis of the data, patients exposed to more than 140 cc of contrast had a trend towards worse outcomes with NAC, whereas patients exposed to less than 140 cc contrast were protected from perturbation of renal function. It would be anticipated that if an effective agent were identified to prevent RCN, its effect would be amplified with higher risk states—including exposure to higher doses of radiocontrast—rather than the opposite effect.

The Acetylcysteine to Prevent Angiography-Related Renal Tissue Injury (APART) trial was a single-center, randomized trial in which the observation again was made that in a lower-risk patient population (mean baseline serum creatinine of 1.6 mg/dL), the effect of NAC was relatively modest.[20] At 48 hours following contrast exposure, the serum creatinine was 1.88 mg/dL in the control group and 1.53 mg/dL in the NAC group. In addition, a single-center, randomized trial by Caputo and associates[21] showed no significant benefit with the use of NAC.

Conclusions

At this time, it is fair to conclude that intravenous hydration remains the mainstay for preventing RCN. Fenoldopam has been shown in a canine model, as well as in retrospective, prospective, and randomized human evaluations to have potential benefit in preventing RCN. Although the ability of NAC to prevent RCN has been observed, clinical trial data are not consistent regarding this effect, which, if present, seems to be modest and perhaps restricted to lower-risk clinical scenarios. We await the results of the CONTRAST trial which should provide further information on the effect of fenoldopam in preventing RCN. ■

The striking results of this trial were that fenoldopam prevented the contrast-induced reduction of renal blood flow.

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