Strategies to Prevent Radiocontrast Nephropathy

Steven G. Coca, DO
Mark A. Perazella, MD, FACP

Radiocontrast (RC) studies are widely employed for both diagnostic and therapeutic purposes. It is estimated that more than 10 million RC studies are performed in the United States each year.[1] At the same time, the prevalence of chronic kidney disease (CKD) has grown significantly, with approximately 18.3 million patients carrying this diagnosis, accounting for 12% of the population.[2] These data are important because underlying kidney disease is one of the major risk factors for developing radiocontrast-induced nephropathy (RCIN). RCIN is the third leading cause of acute renal failure (ARF) in hospitalized patients[3] and is associated with significant morbidity and mortality, even with minor degrees of ARF. The mortality rate described in association with RCIN-associated ARF is 34%.[4] As a result, there is considerable interest in preventing RCIN in patients who are at risk for this complication. This article briefly reviews the pathogenesis of RCIN, risk factors for developing RCIN, and strategies for preventing RCIN. Recommendations for prophylactic measures prior to administration of an RC agent to prevent development of RCIN are also provided.

TAKE HOME POINTS

- Radiocontrast nephropathy develops most commonly in patients with underlying kidney disease and diabetic nephropathy.
- Alternative, non–radiocontrast-based diagnostic tests (eg, ultrasound and magnetic resonance imaging with gadolinium) should be used when possible in patients at high risk for developing radiocontrast nephropathy.
- Strategies to prevent radiocontrast nephropathy should include administration of intravenous fluids before and after exposure to contrast, administration of oral N-acetylcysteine, and use of either low- or iso-osmolar contrast.

PATHOGENESIS OF RCIN

The pathogenesis of RCIN has been well studied in animals, but there are few human studies; therefore, the mechanism of RCIN in humans has been extrapolated from animal data. Acute tubular injury and necrosis are the end result of multiple damaging insults associated with RC administration (**Table 1**). Several animal models demonstrate that brief renal arteriolar vasodilation develops after RC administration, followed by prolonged, intense vasoconstriction with redistribution of intrarenal blood flow away from the renal medulla.[5] This untoward effect has been confirmed in humans who receive RC.[6] In animals, several mediators of vascular tone have been implicated as causative in the development of renal vasoconstriction, including adenosine,[7] endothelin,[8] angiotensin II,[9] and nitric oxide.[10] The high osmotic load associated with filtered RC is thought to promote vasoconstriction through induction of tubuloglomerular feedback at the juxtaglomerular apparatus.[11] Other potential mechanisms of renal vasoconstriction include direct endothelial cell injury and effects on vascular smooth muscle cells. Thus, one aspect of RCIN is caused by renal ischemia and ischemic acute tubular necrosis. Therapies and drugs have been developed to diminish renal vasoconstriction and abrogate the associated ischemic tubular injury.

In addition to ischemic kidney injury, direct renal tubular toxicity can develop following RC exposure. The high osmolality of RC agent may cause abnormal permeability in tubular epithelial cell membranes by inducing a redistribution of tight-junction proteins.[12] Pinocytosis of RC material occurs in proximal tubular cells and causes cellular swelling and vacuolization, which might explain why low- or iso-osmolar contrast is less nephrotoxic.

Dr. Coca is a fellow in nephrology, and Dr. Perazella is an associate professor of medicine, Section of Nephrology, Department of Medicine; director of the Renal Fellowship Program; and director of acute dialysis services. Both are at Yale University School of Medicine, New Haven, CT.

Table 1. Pathogenesis of RCIN-Associated ARF

Ischemic acute tubular necrosis
Vasoconstriction mediated by adenosine, endothelin, angiotensin II, and nitric oxide
Tubuloglomerular feedback (osmotic effects)
Direct endothelial damage
Smooth muscle injury
Direct tubular toxicity
Tubular cell dysfunction and swelling due to hyperosmolarity
Reduced tubular cell adenosine triphosphate
Increased intracellular calcium concentration
Oxidative stress and lipid peroxidation
Generation of reactive oxygen species
Apoptosis of tubular cells
Tubular cell injury from osmotic stress
Hypoxia of tubular cells

ARF = acute renal failure; RCIN = radiocontrast-induced nephropathy.

After RC exposure, tubular cell isolates have reduced adenosine triphosphate levels and increased intracellular calcium content (findings consistent with tubular injury).[13] Detection of enzymuria following RC exposure supports direct tubular injury as a mechanism of RCIN.

Exposure to RC media also causes renal injury through the action of oxygen free radicals and lipid peroxidation.[14] Again, the hyperosmolarity of RC may promote generation of reactive oxygen species (ROS) through induction of osmotic stress. Animal experiments have confirmed that RC infusion is associated with an increase in ROS generation.[14] Inhibition of ROS generation by drugs has preserved renal function in these experiments. Employment of the antioxidant N-acetylcysteine (NAC) to prevent RCIN is based in part on the role of ROS in the development of ARF.

Finally, apoptosis of renal tubular cells has been noted with RC exposure in both cell culture[12] and in vivo experiments.[15] In some studies, RC-associated hyperosmolarity rather than ischemia caused apoptosis in cultured cells.[12] This finding is not universal, as some studies demonstrate that ischemia induced by RC material is associated with apoptosis in tubular cells.[15] Thus, therapies directed at ischemia and use of low- or iso-osmolar contrast agents might reduce RCIN by avoiding the induction of apoptosis.

RISK FACTORS ASSOCIATED WITH RCIN

Although numerous RC studies are performed annually, only a small percentage of patients develop RCIN. This fact suggests that certain underlying patient risk factors and factors peculiar to RC agents are associated with development of RCIN and ARF.

Kidney Disease and Diabetes Mellitus

The most important patient risk factor for RCIN is underlying kidney disease,[16] either newly developed ARF or CKD. Most published studies show that as renal function declines, the risk of developing RCIN increases. In addition, the degree of preexisting kidney disease often determines the severity of RCIN. Various serum creatinine cut-offs have been employed to define the at-risk patient (serum creatinine concentration > 1.4 mg/dL). Other indicators of high risk for coexistent kidney disease include proteinuria, hematuria, and hypertension. Calculation of the glomerular filtration rate (GFR) using estimation formulas (modified Modification in Diet in Renal Disease or Cockcroft-Gault) is probably the best predictor of underlying kidney disease. A reasonable estimated GFR cut-off that portends risk for RCIN is below 60 mL/min or stage 3 kidney disease using the Kidney Disease Outcomes Quality Initiative CKD classification system.[17] Underlying diabetes mellitus is another important risk factor for RCIN.[18] Studies have shown that patients with diabetes without underlying kidney disease maintain a risk of ARF following RC exposure that is similar to that in patients with underlying kidney disease. Coexisting diabetes and kidney disease further raises risk beyond that in either disease state alone.[16,19] Patients with diabetic nephropathy appear to have the greatest risk of developing RCIN.

Intravascular Volume Depletion

Intravascular volume depletion, whether true (eg, vomiting, diarrhea, diuretics) or effective (congestive heart failure, cirrhosis, nephrosis), is a risk factor for RCIN. Sluggish urine flow increases RC concentration and increases its contact time with the tubular cells. Hypercalcemia and drugs that reduce renal artery blood flow (eg, nonsteroidal anti-inflammatory drugs, calcineurin inhibitors, and several vasopressors) increase risk for developing ARF when RC exposure occurs. Underlying multiple myeloma, when complicated by kidney disease, enhances the risk for RCIN. Nephrotoxic medications, such as aminoglycosides and amphotericin B, also increase risk of RCIN.

Other Risk Factors

Other risk factors for RCIN that are not specific to underlying patient characteristics include administration of large volumes of RC or repeated RC administration and use of high-osmolar, iodinated RC material.

Prophylaxis with furosemide, even when it does not cause intravascular volume depletion, is also associated with higher likelihood of developing RCIN.

STRATEGIES TO PREVENT RCIN

Several strategies have been employed to prevent the development of RCIN, most of which are based on therapies directed at the ischemic injury and tubular toxic and oxidative stress associated with RC exposure. While many therapies are nephroprotective in animals, not all have been shown to have similar benefits in humans.

Intravascular Volume Repletion

Intuitively, correcting subtle, subclinical volume depletion should be renoprotective in patients who undergo RC studies. Additionally, volume repletion with intravenous (IV) fluids increases urine flow rates, which could potentially dilute urinary concentration of the contrast and wash away obstructing tubular debris.

An initial study that examined 0.45% saline infusions as prophylaxis for RC studies demonstrated benefit for 12 hours before and after infusions.[20] Adding mannitol to this hydration regimen did not further reduce the occurrence of RCIN, whereas adding furosemide increased the occurrence of RCIN.[20] Subsequently, a study showed a statistically significant reduction in RCIN with 0.9% IV saline (0.7% developed RCIN) versus 0.45% IV saline (2% developed RCIN) in patients undergoing coronary angiography with a low-osmolar, nonionic RC agent (volume > 200 mL of RC); the patients received hydration for a total of 24 hours at a rate of 1 mL/kg/h.[21] Unlimited oral hydration was inferior to 0.9% IV saline at 1 mL/kg/h started 12 hours prior to and continued for 12 hours after RC exposure.[22] In this study involving patients undergoing coronary angiography with low-osmolar contrast, 3.7% of patients who received 0.9% IV saline developed RCIN as compared with 34.6% in the oral hydration group. In another study of patients receiving low-osmolar contrast, 0.9% IV saline infusion 12 hours prior to RC exposure was compared with a 300-mL bolus of 0.9% IV saline.[23] The 12-hour preinfusion group faired better than the bolus group (only 5.3% developed RCIN compared with 15%).

Recently, IV sodium bicarbonate was compared with 0.9% IV saline in CKD patients undergoing coronary angiography and digital subtraction angiography with low-osmolar, noniodinated contrast.[24] Both groups received a 3 mL/kg bolus over 1 hour prior to RC exposure, and hydration was continued for 6 hours during and following exposure. Only 1.7% of patients infused with sodium bicarbonate developed RCIN as compared with 13.6% of those who received 0.9% IV saline. The marked reduction in RCIN led to halting of the study, and subsequent patients were given sodium bicarbonate and enrolled in a registry; of 191 patients enrolled, only 3 developed RCIN (1.6%). The low rate of RCIN in the bicarbonate group was obtained without coadministration of NAC.

In multiple studies, IV fluids have reduced RCIN development as compared with no IV fluid administration. As such, administering IV fluids is considered the standard of care in the prophylaxis of high-risk patients undergoing RC procedures. Although the differences among patients and hydration regimens examined in these studies make it impossible to directly compare therapeutic efficacy, it is reasonable to conclude that all patients should receive preinfusion of IV fluids at least 6 to 12 hours prior to RC exposure when possible. IV sodium bicarbonate appears more effective than 0.9% IV saline. Since it is inexpensive and safe, we recommend using this infusion fluid for high-risk patients. Confirmation of its potentially beneficial effects is required.

Vasodilators

Dopamine. Dopamine is a renal vasodilator and diuretic that increases urine output in patients with acute and chronic renal failure. Heterogeneous results have been obtained in studies employing dopamine as a prophylactic agent against RCIN.[25–28] Although small benefits were obtained in some of these studies, concern was raised when diabetic patients treated with dopamine paradoxically had an increased risk of RCIN compared with controls.[28] In addition, dopamine therapy has other adverse effects, including intestinal ischemia and cardiac arrhythmias. Therefore, dopamine is not used clinically for the prevention of RCIN.

Fenoldopam. Fenoldopam is a selective agonist of the dopamine-1 receptor. It provides physiologic benefits in the kidney (renal artery and afferent arteriole vasodilation, inhibition of proximal tubular sodium reabsorption resulting in natriuresis) without many of the adverse side effects of dopamine. Fenoldopam increases blood flow to both the cortex and medulla, which may be important as RC material reduces medullary blood flow to a greater extent.[29]

Animal studies demonstrated that the reduction in blood flow and GFR that occurs with RC administration can be completely ameliorated by fenoldopam.[29] Small, uncontrolled studies of fenoldopam for the prevention of RCIN were promising, with increases in renal plasma flow and trends toward a reduction in the incidence of RCIN.[30–32] These early data resulted in selective use of

fenoldopam, primarily by cardiologists, in high-risk patients. However, 2 randomized controlled trials have shown no benefit of this expensive agent (~$700/vial).[33,34] In the largest study, 315 patients with creatinine clearance of less than 60 mL/min were randomly assigned to fenoldopam or placebo plus 0.45% IV saline at 1.5 mL/kg/h for 2 to 12 hours prior to RC administration.[34] The agent was continued for 12 hours following cardiac catheterization. The primary endpoint (defined as a ≥ 25% increase in serum creatinine level at 96 hours postprocedure) occurred in 33.6% of patients who received fenoldopam and 30.1% of those who received placebo.[34] Additionally, there were no significant differences in 30-day mortality, need for dialysis, or rehospitalization. Given the negative results of the 2 recent randomized controlled trials, fenoldopam has no role in preventing RCIN.

Antioxidants

N-acetylcysteine. NAC is a thiol-containing antioxidant that has traditionally been used to treat pulmonary diseases and acetaminophen-induced hepatotoxicity. NAC may ameliorate RCIN by its vasodilatory properties,[35] by a direct protective effect on the kidney to ischemic injury,[36] or by scavenging oxygen free radicals.[37] A landmark study in 2000 reported efficacy in preventing RCIN with NAC.[38] Eighty-three patients with CKD (mean baseline serum creatinine concentration, 2.4 mg/dL) who underwent computed tomography scanning with a nonionic, low-osmolality contrast agent were randomly assigned to receive NAC 600 mg orally twice daily and 0.45% IV saline at 1 mL/kg/h 12 hours before and after RC administration or placebo with the same hydration regimen. RCIN incidence (defined by a 0.5 mg/dL increase in serum creatinine at 48 hours) was 21% in the placebo group versus 2% in the NAC group. The results of this study led to the use of the Tepel protocol nationwide for preventing RCIN.

However, controversy and questions still existed after this study. In the Tepel study,[38] only 75 mL of an IV contrast agent were administered twice the day before and twice the day of the procedure. It remains unclear whether NAC is effective with larger doses of contrast, if these results are applicable only to patients undergoing coronary angiography, if the dosing regimen is appropriate (ie, for more emergent contrast procedures), and if the agent is effective for patients with more severe renal failure.

Since Tepel's publication, there have been at least 17 published randomized controlled trials examining NAC's role in RCIN prophylaxis,[33,39–54] with some trials finding benefit and others failing to do so. Several recently published meta-analyses that sought to resolve this issue and have also yielded mixed results.[55–60] Three meta-analyses have concluded that treatment with NAC is beneficial for reducing the primary endpoint of RCIN development,[55,56,59] 2 others found nonstatistically significant trends toward benefit,[58,60] and one reported that because of significant heterogeneity among the reviewed trials, the RCIN incidence is too inconsistent to yield a conclusion on efficacy.[57] The overall rate of dialysis-requiring RCIN is too low among all of the meta-analyses to determine whether NAC is effective at preventing this more severe form of RCIN. Subgroup analysis from 2 of these reports revealed that in patients with more advanced kidney disease (serum creatinine concentration > 1.9 or 2.0 mg/dL, respectively), NAC did not confer significant protection from RCIN.[59,60] Also of interest, one analysis found that NAC seemed to benefit patients who received more than 140 mL of RC (relative risk, 0.38 [95% confidence interval, 0.21–0.68]; $P = 0.001$),[59] whereas another analysis found no benefit of NAC prophylaxis in the subgroup that received the same amount of RC.[60]

Finally, in a study that examined the efficacy of IV NAC,[61] the IV NAC group experienced a reduction in the overall endpoint of RCIN; however, the control group was treated differently. In essence, the NAC group received a larger saline load, which is likely the most important factor in reducing the risk of RCIN.[21]

On the whole, data suggest that there is some prophylactic benefit with NAC added to standard saline therapy. The heterogeneity of results of the individual clinical trials and the meta-analyses prevent the experts from conclusively recommending NAC. However, given its excellent side effect profile, ease of administration, and inexpensiveness (~$16 total for 4 doses), it is prudent to continue to administer oral NAC until larger, randomized controlled trials provide a definitive answer.

Vasoconstrictor Antagonists

Theophylline. RC material causes local release of adenosine, a potent renal vasoconstrictor. In animal models, theophylline, an adenosine antagonist, has been shown to abrogate RCIN by preventing reduced renal blood flow. Early clinical studies of theophylline showed very modest benefits in some measures of renal function, but no clear advantages over saline alone were noted.[27,62–64] Two recent studies suggest that theophylline may have a clinically significant protective effect. In a study of 70 patients with a relatively preserved GFR (85 mL/min), administration of theophylline 200 mg twice daily for 24 hours before and 48 hours after coronary angiography, in addition to saline, reduced the rate

of RCIN (defined by a 25% reduction in GFR measured by nuclear renal scan) from 31% to 3% ($P = 0.004$).[65] The high rate of RCIN in the placebo group, despite the apparently adequate GFR at baseline, was probably due to the patient's preexisting diabetes mellitus, which if proteinuria is present, is an independent risk factor for developing RCIN. In the second study, 100 patients with mean serum creatinine concentrations of 1.3 mg/dL or more received 200 mg IV theophylline 30 minutes prior to coronary angiography; the incidence of RCIN was reduced from 20% to 4% ($P = 0.0138$).[66] Although these 2 studies have mildly revived interest in theophylline, before its use can be recommended, larger studies must be performed to determine whether theophylline is truly beneficial, what its role will be in addition to the current standard of care (ie, saline plus NAC), and the appropriate dose as well as route of administration.

Radiocontrast Agents

High-osmolar, iodinated and low-osmolar, noniodinated RC. The first-generation contrast agents are extremely hyperosmolar (500–1800 mOsm/kg) and are iodinated. Second-generation contrast agents are noniodinated and much less hyperosmolar (600–850 mOsm/kg) but still greatly exceed the osmolarity of plasma. It is hypothesized that greater degrees of hyperosmolarity produce greater osmotic diuresis and, thus, more activation of tubuloglomerular feedback, thereby decreasing GFR.

Several studies and a meta-analysis have reported a decreased incidence of RCIN with low-osmolar agents as compared with high-osmolar agents in patients with preexisting renal insufficiency.[67–69] However, in patients without risk factors for developing RCIN, there is no obvious clinical benefit in using low-osmolar agents, as the rate of RCIN is very low with both types of agents in these patients.[70] Examination of the largest study published (1196 patients) reveals that the employment of high-osmolar contrast was associated with a risk of RCIN that was 3.3 times greater than that in the low-osmolar contrast group.[19] The use of low-osmolar contrast was beneficial only in patients with kidney disease (baseline creatinine concentration > 1.4 mg/dL), and benefits were greatest in those who had concomitant diabetes mellitus, with RCIN being reduced from 27% to 11.8%. There was no benefit in patients with normal creatinine levels, with diabetes alone, or those who received contrast intravenously rather than intra-arterially. Notably, all of the trials examining NAC as an intervention have been performed in the setting of low-osmolarity RC administration for both treatment and control groups.

Iso-osmolar, noniodinated RC. Iodixanol is the only available iso-osmolar (290 mOsm/kg), nonionic contrast agent. While the lower osmolarity may produce less osmotic diuresis, experimental data suggest that the higher viscosity of iodixanol may result in stasis in renal tubules,[71] produce greater reductions in renal blood flow,[72] and result in a greater degree of medullary hypoxia[73] than low-osmolar agents. In several small human studies, iodixanol provided no clinical benefit in the reduction of RCIN in comparison with low-osmolar agents in patients with normal renal function[74,75] or mild/moderate[76] or severe kidney disease.[77] However, Chalmers and Jackson[78] were able to show a small reduction in the incidence of RCIN from 10% to 3.7% in patients with significant baseline kidney disease (mean creatinine concentration, 3.0–3.3 mg/dL). The amount of contrast volume correlated with the change in serum creatinine concentration with both contrast agents. No patients in either group required dialysis.

Finally, a randomized, double-blind, prospective, multicenter trial compared the nephrotoxicity of iodixanol (iso-osmolar nonionic) with iohexol (low-osmolar, nonionic) in diabetic patients undergoing coronary or aortofemoral angiography with underlying mild/moderate kidney disease.[79] In this study, baseline serum creatinine concentration was between 1.5 and 3.5 mg/dL, with a mean baseline creatinine clearance of approximately 50 mL/min. The mean volume of contrast given was 162 mL in both groups, and both groups received approximately 1 L of IV fluids periprocedure. Only 4 patients in the iodixanol group and 7 patients in the iohexol group received NAC. The peak increase in serum creatinine after 3 days was significantly lower in the iodixanol group compared with the iohexol group (0.13 mg/dL versus 0.55 mg/dL; $P = 0.001$). RCIN incidence (defined as an increase in serum creatinine concentration of 0.5 mg/dL) was only 3% in the iodixanol group and 26% in the iohexol group (odds ratio, 0.09; $P = 0.002$). Finally, 15% of patients in the iohexol group but none in the iodixanol group had an increase in serum creatinine concentration of at least 1.0 mg/dL.

In conclusion, the overall data suggest that using low-osmolarity agents reduces nephrotoxicity in high-risk patients, with iso-osmolar agents conferring further reductions in risk. However, whether iso-osmolar agents will still confer a clinically significant benefit in the setting of the rather inexpensive, safe, and widely used prophylactic strategies, such as bicarbonate and NAC administration, is yet to be determined.

Radiocontrast Removal

Hemodialysis. Contrast media are removed mainly by the kidneys via glomerular filtration and therefore

retained in patients with kidney disease. It has been hypothesized that elimination of contrast media by hemodialysis performed directly after RC procedures may prevent the development of RCIN. Three small studies randomized CKD patients undergoing angiography to prophylactic hemodialysis or standard saline infusion.[80–82] None of the studies showed a reduction in the incidence of RCIN at 48 hours; in fact, there was a nonsignificant trend towards an increased incidence of RCIN in dialyzed patients.

Given the small sample size, the study may have lacked sufficient power to allow statistical differences to manifest between the 2 therapies. Additionally, the lack of benefit may be related to a very rapid onset of renal injury after administration of contrast media (within 20 minutes).[83,84] The earliest time that hemodialysis was initiated following contrast was 30 minutes, with a delay as long as 280 minutes. It is also possible that the hemodialysis treatment per se was nephrotoxic and might have offset the beneficial effect of the removal of contrast media. Nephrotoxicity associated with dialysis has been linked with the activation of inflammatory reactions from exposure of blood to the dialysis membrane.[85] Induction of hypovolemia and hypotension associated with ultrafiltration and the presence of blood in the extracorporeal circulation may have promoted further renal ischemia and acute tubular necrosis. In conclusion, there is not sufficient evidence to indicate that hemodialysis is as effective as nonhemodialysis measures in preventing RCIN among patients with preexisting renal insufficiency; therefore, it cannot be recommended at this time.

Hemofiltration. Hemofiltration is a continuous form of renal replacement therapy that is generally associated with hemodynamic stability.[86] Marenzi et al[87] studied the effectiveness and safety of administering prophylactic hemofiltration to 114 patients with significant underlying kidney disease (serum creatinine concentrations, > 2 mg/dL; mean serum creatinine concentration, 3 mg/dL; mean calculated creatinine clearance, 26 mL/min). Coronary angiography was performed with iso-osmotic nonionic contrast. Fifty-eight patients were randomly assigned to hemofiltration initiated 4 to 8 hours prior to coronary intervention and continued for 18 to 24 hours after the procedure. Fifty-six patients were randomly assigned to isotonic fluid replacement at a rate of 1 mL/kg/h initiated and discontinued with the same timing pre- and postprocedure as the intervention group. Hemofiltration reduced the incidence of RCIN (defined as a 25% rise in serum creatinine) from 50% to 5% ($P < 0.001$); however, the relevance of this endpoint is questionable as creatinine was removed during the hemofiltration procedure, and GFR was not formally assessed. Examination of the other endpoints does reveal uniform benefits in the hemofiltration group. Need for renal replacement therapy was reduced from 25% to 3% ($P < 0.001$), the incidence of pulmonary edema was reduced from 11% to 0% ($P = 0.02$), in-hospital mortality was reduced from 14% to 2% ($P = 0.02$), and 1-year mortality was reduced from 30% to 10% in the hemofiltration group.

It is unclear why this intervention provided such benefits. Certainly, this group was at higher risk for RCIN compared with other study groups given their advanced degree of kidney disease and the large volume of contrast used (~250 mL in each group). These benefits may have been related to an improvement in volume status, the use of bicarbonate-buffered replacement fluid, or the removal of the contrast agent. However, the maximal clearance of contrast achieved by hemofiltration would only be approximately 40%. In addition, it is questionable whether this involved procedure should be applied empirically to all patients prior to a coronary procedure in order to prevent applying it to some patients postprocedure. Given this uncertainty and lack of more clinical data, the costs and invasiveness of the procedure, and the need for an intensive care unit bed, hemofiltration cannot be recommended for preventing RCIN at this time.

Unanswered Questions

Despite numerous clinical trials over the past several years, several unanswered questions remain regarding the most effective strategy for prophylaxis against RCIN. The optimal hydration strategy is likely isotonic saline, yet the majority of randomized controlled trials utilized hypotonic saline (0.45% IV saline) in their hydration protocol. Furthermore, the most appropriate isotonic solution may be one that contains bicarbonate rather than chloride, but further trials to confirm Merten et al's results[24] must be conducted to eliminate any skepticism about the benefits of bicarbonate. In addition, the effects of bicarbonate plus NAC must be elucidated, and if this combination is extremely effective, it should be determined if there are any additional benefits of highly expensive iso-osmolar contrast.

Finally, one large question looms. While these agents reduce "RCIN," is the arbitrary endpoint of an increase in creatinine concentration by 0.5 mg/dL or 25% at 48 hours postcontrast administration clinically meaningful? Most of the NAC trials do not examine the effects on hard endpoints (ie, need for dialysis or death). Only one study has been able to show a reduction in length of hospital stay,[48] and no trial to date, with the exception of

Table 2. Risks of Short-Term and Long-Term Mortality Associated with RCIN

	In-Hospital Mortality			1-Year Mortality			5-Year Mortality		
	No ARF (%)	RCIN (%)	RCIN + HD (%)	No ARF (%)	RCIN (%)	RCIN + HD (%)	No ARF (%)	RCIN (%)	RCIN + HD (%)
McCullough et al[89]	1.1	7.1	35.7	—	—	—	—	—	—
Levy et al[4]	7	34	62	—	—	—	—	—	—
Gruberg et al[90]	4.9	14.9	22.6	19.4	35.4	45.2	—	—	—
Rihal et al[91]	1.4	22	30	2.3	12.1	—	14.5	44.6	—

ARF = acute renal failure; HD = hemodialysis; RCIN = radiocontrast-induced nephropathy.

the hemofiltration study, has been able to show a reduction in hard endpoints. In fact, a recent study found that while NAC was effective in reducing RCIN, the endpoints of death, nonfatal myocardial infarction, and need for dialysis both during hospitalization and at 9 months were not altered by NAC administration.[88]

RCIN is not trivial: several reports have shown that patients who develop RCIN have an increased in-hospital mortality,[4,89–91] which is even greater in those who require dialysis from RCIN (**Table 2**).[4,89] The development of RCIN may be a prognostic "marker" that unveils the individual's underlying poor health status. Both 1-year[91,92] and 5-year[91] mortality are markedly increased in patients who develop RCIN. Reduced GFR is associated with cardiovascular events;[92] however, because even severe RCIN is often transitory,[90] it is difficult to imagine that short-lived reversible renal failure would itself be driving the marked increase in long-term death. Studies examining postcardiac surgery ARF found that even after adjustment for other independently associated factors, patients who suffered episodes of ARF that completely resolved by the time of discharge had an elevated long-term risk of death (hazard ratio, 1.66), similar to those whose renal failure was persistent (hazard ratio, 1.72).[93] These data also support the hypothesis that ARF in this setting is likely a marker that portends a poor prognosis. While potentially averting dialysis-requiring ARF is clearly beneficial, it is less clear if avoiding an increase in serum creatinine concentration will improve overall patient health and survival.

RECOMMENDATIONS FOR PROPHYLAXIS OF RCIN

Based on data generated in humans, we recommend the following strategies to prevent the development of ARF following RC administration:

- Define the underlying risk profile of the patient being considered for exposure to RC.
- In high-risk patients (stage 3 or higher CKD, incipient or overt diabetic nephropathy), investigate the possibility of employing alternative diagnostic tests (eg, magnetic resonance imaging or angiography with gadolinium,[94] ultrasonography).
- Administer IV isotonic sodium bicarbonate or saline solution for 12 hours prior to RC exposure and for 12 hours after exposure. In emergencies that do not allow preinfusion, isotonic saline can be given as a bolus (3 mL/kg over 1 hour) prior to RC exposure and continued for 12 hours at a rate of 1 mL/kg/h. IV fluids should be adjusted based on the patient's underlying intravascular volume status. Volume status should be monitored while IV fluids are administered.
- Administer oral NAC (600 mg twice daily) on the day prior to the procedure and on the day of RC exposure. IV NAC may be employed in emergent situations that do not allow oral therapy as described above.
- Use an iso-osmolar RC agent in very high-risk patients (stage 4 CKD, diabetic nephropathy). The volume of contrast that is administered should also be limited as much as possible.
- In low-risk patients, the use of low-ionic or non-ionic contrast is an unnecessary expense. **HP**

REFERENCES

1. Neugut AI, Ghatak AT, Miller RL. Anaphylaxis in the United States: an investigation into its epidemiology. Arch Intern Med 2001;161:15–21.
2. Burt VL, Whelton P, Roccella EJ, et al. Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988–1991. Hypertension 1995;25:305–13.
3. Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. Am J Kidney Dis 2002;39:930–6.
4. Levy EM, Viscoli CM, Horwitz RI. The effect of acute renal failure on mortality. A cohort analysis. JAMA

1996;275:1489–94.
5. Heyman SN, Reichman J, Brezis M. Pathophysiology of radiocontrast nephropathy: a role for medullary hypoxia. Invest Radiol 1999;34:685–91.
6. Tumlin JA, Wang A, Murray PT, Mathur VS. Fenoldopam mesylate blocks reductions in renal plasma flow after radiocontrast dye infusion: a pilot trial in the prevention of contrast nephropathy. Am Heart J 2002;143894–903.
7. Arend LJ, Bakris GL, Burnett JC Jr, et al. Role for intrarenal adenosine in the renal hemodynamic response to contrast media. J Lab Clin Med 1987;110:406–11.
8. Heyman SN, Clark BA, Kaiser N, et al. Radiocontrast agents induce endothelin release in vivo and in vitro. J Am Soc Nephrol 1992;3:58–65.
9. Larson TS, Hudson K, Mertz JI, et al. Renal vasoconstrictive response to contrast medium. The role of sodium balance and the renin-angiotensin system. J Lab Clin Med 1983;101:385–91.
10. Heyman SN, Goldfarb M, Carmeli F, et al. Effect of radiocontrast agents on intrarenal nitric oxide (NO) and NO synthase activity. Exp Nephrol 1998;6:557–62.
11. Russo D, Minutolo R, Cianciaruso B, et al. Early effects of contrast media on renal hemodynamics and tubular function in chronic renal failure. J Am Soc Nephrol 1995;6:1451–8.
12. Hizoh I, Strater J, Schick CS, et al. Radiocontrast-induced DNA fragmentation of renal tubular cells in vitro: role of hypertonicity. Nephrol Dial Transplant 1998;13:911–8.
13. Humes HD, Hunt DA, White MD. Direct toxic effect of the radiocontrast agent diatrizoate on renal proximal tubule cells. Am J Physiol 1987;252(2 Pt 2):F246–55.
14. Bakris GL, Lass N, Gaber AO, et al. Radiocontrast medium-induced declines in renal function: a role for oxygen free radicals. Am J Physiol 1990;258(1 Pt 2): F115–20.
15. Beeri R, Symon Z, Brezis M, et al. Rapid DNA fragmentation from hypoxia along the thick ascending limb of rat kidneys. Kidney Int 1995;47:1806–10.
16. Parfrey PS, Griffiths SM, Barrett BJ, et al. Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both. A prospective controlled study. N Engl J Med 1989;320:143–9.
17. Davidson CJ, Hlatky M, Morris KG, et al. Cardiovascular and renal toxicity of a nonionic radiographic contrast agent after cardiac catheterization. A prospective trial. Ann Intern Med 1989;110:119–24.
18. Weisberg LS, Kurnik PB, Kurnik BR. Risk of radiocontrast nephropathy in patients with and without diabetes mellitus. Kidney Int 1994;45:259–65.
19. Rudnick MR, Goldfarb S, Wexler L, et al. Nephrotoxicity of ionic and nonionic contrast media in 1196 patients: a randomized controlled trial. The Iohexol Cooperative Study. Kidney Int 1995;47:254–61.
20. Solomon RC, Werner C, Mann D, et al. Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. N Engl J Med 1994;331:1416–20.
21. Mueller C, Buerkle G, Buettner HJ, et al. Prevention of contrast media-associated nephropathy: randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. Arch Intern Med 2002;162:329–36.
22. Trivedi HS, Moore H, Nasr S, et al. A randomized prospective trial to assess the role of saline hydration on the development of contrast nephrotoxicity. Nephron Clin Pract 2003;93:C29–34.
23. Bader BD, Berger ED, Heede MB, et al. What is the best hydration regimen to prevent contrast media-induced nephrotoxicity? Clin Nephrol 2004;62:1–7.
24. Merten GJ, Burgess WP, Gray LV, et al. Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. JAMA 2004;291: 2328–34.
25. Hans SS, Hans BA, Dhillon R, et al. Effect of dopamine on renal function after arteriography in patients with pre-existing renal insufficiency. Am Surg 1998;64:432–6.
26. Hall KA, Wong RW, Hunter GC, et al. Contrast-induced nephrotoxicity: the effects of vasodilator therapy. J Surg Res 1992;53:317–20.
27. Abizaid AS, Clark CE, Mintz GS, et al. Effects of dopamine and aminophylline on contrast-induced acute renal failure after coronary angioplasty in patients with preexisting renal insufficiency. Am J Cardiol 1999;83:260–3, A5.
28. Weisberg LS, Kurnik PB, Kurnik BR. Dopamine and renal blood flow in radiocontrast-induced nephropathy in humans. Ren Fail 1993;15:61–8.
29. Bakris GL, Lass NA, Glock D. Renal hemodynamics in radiocontrast medium-induced renal dysfunction: A role for dopamine-1 receptors. Kidney Int 1999;56:206–10.
30. Chamsuddin AA, Kowalik KJ, Bjarnason H, et al. Using a dopamine type 1A receptor agonist in high-risk patients to ameliorate contrast-associated nephropathy [published erratum appears in AJR Am J Roentgenol 2002;179:1645]. AJR Am J Roentgenol 2002;179:591–6.
31. Kini AS, Mitre CA, Kamran M, et al. Changing trends in incidence and predictors of radiographic contrast nephropathy after percutaneous coronary intervention with use of fenoldopam. Am J Cardiol 2002;89:999–1002.
32. Madyoon H. Clinical experience with the use of fenoldopam for prevention of radiocontrast nephropathy in high-risk patients. Rev Cardiovasc Med 2001;2 Suppl 1: S26–S30.
33. Allaqaband S, Tumuluri R, Malik AM, et al. Prospective randomized study of N-acetylcysteine, fenoldopam, and saline for prevention of radiocontrast-induced nephropathy. Catheter Cardiovasc Interv 2002;57:279–83.
34. Stone GW, McCullough PA, Tumlin JA, et al. Fenoldopam mesylate for the prevention of contrast-induced nephropathy: a randomized controlled trial. JAMA 2003;290:2284–91.
35. Jones AL, Bangash IH, Bouchier IA, Hayes PC. Portal and systemic haemodynamic action of N-acetylcysteine in patients with stable cirrhosis. Gut 1994;35:1290–3.

36. DiMari J, Megyesi J, Udvarhelyi N, et al. N-acetyl cysteine ameliorates ischemic renal failure. Am J Physiol 1997; 272(3 Pt 2):F292–8.
37. Brunet J, Boily MJ, Cordeau S, Des Rosiers C. Effects of N-acetylcysteine in the rat heart reperfused after low-flow ischemia: evidence for a direct scavenging of hydroxyl radicals and a nitric oxide-dependent increase in coronary flow. Free Radic Biol Med 1995;19:627–38.
38. Tepel M, van der Giet M, Schwarzfeld C, et al. Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. N Engl J Med 2000;343:180–4.
39. Adamian MG, Moussa I, Mehran R, et al. The role of mucomyst administration prior to percutaneous interventions on renal function in patients with chronic renal failure [abstract]. J Am Coll Cardiol 2002;39:1A.
40. Briguori C, Manganelli F, Scarpato P, et al. Acetylcysteine and contrast agent–associated nephrotoxicity. J Am Coll Cardiol 2002;40:298–303.
41. Diaz-Sandoval LJ, Kosowsky BD, Losordo DW. Acetylcysteine to prevent angiography-related renal tissue injury (the APART trial). Am J Cardiol 2002;89:356–8.
42. Durham JD, Caputo C, Dokko J, et al. A randomized controlled trial of N-acetylcysteine to prevent contrast nephropathy in cardiac angiography. Kidney Int 2002; 62:2202–97.
43. Kahlon JP, Moser L, Rosman H, et al. Effectiveness of N-acetylcysteine for the prevention of radiocontrast-induced nephropathy: is the jury still out [abstract]? Circulation 2002;106:II–691.
44. Shyu KG, Cheng JJ, Kuan P. Acetylcysteine protects against acute renal damage in patients with abnormal renal function undergoing a coronary procedure. J Am Coll Cardiol 2002;40:1383–8.
45. Vallero A, Cesano G, Pozzato M, et al. [Contrast nephropathy in cardiac procedures: no advantages with prophylactic use of N-acetylcysteine (NAC).] [Article in Italian.] G Ital Nefrol 2002;19:529–33.
46. Boccalandro F, Amhad M, Smalling RW, Sdringola S. Oral acetylcysteine does not protect renal function from moderate to high doses of intravenous radiographic contrast. Catheter Cardiovasc Interv 2003;58:336–41.
47. Goldenberg I, Jonas M, Matetzki S, et al. Contrast-associated nephropathy and clinical outcome of patients with chronic renal insufficiency undergoing cardiac catheterization: lack of additive benefit of acetylcysteine to saline hydration [abstract]. J Am Coll Cardiol 2003;41: 537A.
48. Kay J, Chow WH, Chan TM, et al. Acetylcysteine for prevention of acute deterioration of renal function following elective coronary angiography and intervention: a randomized controlled trial. JAMA 2003;289:553–8.
49. Loutrianakis E, Stella D, Hussain A, et al. Randomized comparison of fenoldopam and N-acetylcysteine to saline in the prevention of radio-contrast induced nephropathy [abstract]. J Am Coll Cardiol 2003;41:327A.
50. Oldemeyer J, Cichowski E, Wurdeman R, et al. Prophylactic acetylcysteine is not effective in preventing contrast-induced nephropathy following coronary angiography [abstract]. J Am Coll Cardiol 2003;41:328A.
51. Nogareda G, Ricci D, Im P, et al. Oral N-acetylcysteine administered immediately prior to routine percutaneous coronary procedures ameliorates contrast-induced nephrotoxicity [abstract]. J Am Coll Cardiol 2003;41:62A.
52. El Mahmoud R, Le Feuvre C, Le Quan Sang KH, et al. [Absence of nephro-protective effect of acetylcysteine in patients with chronic renal failure investigated by coronary angiography.] [Article in French.] Arch Mal Coeur Vaiss 2003;96:1157–61.
53. Azmus AD, Gottschall C, Manica A, et al. Effectiveness of acetylcysteine in prevention of contrast nephropathy. J Invasive Cardiol 2005;17:80–4.
54. Ochoa A, Pellizzon G, Addala S, et al. Abbreviated dosing of N-acetylcysteine prevents contrast-induced nephropathy after elective and urgent coronary angiography and intervention. J Interv Cardiol 2004;17:159–65.
55. Birck R, Krzossok S, Markowetz F, et al. Acetylcysteine for prevention of contrast nephropathy: meta-analysis. Lancet 2003;362:598–603.
56. Isenbarger DW, Kent SM, O'Malley PG. Meta-analysis of randomized clinical trials on the usefulness of acetylcysteine for prevention of contrast nephropathy. Am J Cardiol 2003;92:1454–8.
57. Kshirsagar AV, Poole C, Mottl A, et al. N-acetylcysteine for the prevention of radiocontrast induced nephropathy: a meta-analysis of prospective controlled trials. J Am Soc Nephrol 2004;15:761–9.
58. Pannu N, Manns B, Lee H, Tonelli M. Systematic review of the impact of N-acetylcysteine on contrast nephropathy. Kidney Int 2004;65:1366–74.
59. Alonso A, Lau J, Jaber BL, et al. Prevention of radiocontrast nephropathy with N-acetylcysteine in patients with chronic kidney disease: a meta-analysis of randomized, controlled trials. Am J Kidney Dis 2004;43:1–9.
60. Nallamothu BK, Shojania KG, Saint S, et al. Is acetylcysteine effective in preventing contrast-related nephropathy? A meta-analysis. Am J Med 2004;117:938–47.
61. Baker CS, Wragg A, Kumar S, et al. A rapid protocol for the prevention of contrast-induced renal dysfunction: the RAPPID study. J Am Coll Cardiol 2003;41:2114–8.
62. Erley CM, Duda SH, Rehfuss D, et al. Prevention of radiocontrast-media-induced nephropathy in patients with pre-existing renal insufficiency by hydration in combination with the adenosine antagonist theophylline. Nephrol Dial Transplant 1999;14:1146–9.
63. Erley CM, Duda SH, Schlepckow S, et al. Adenosine antagonist theophylline prevents the reduction in glomerular filtration rate after contrast media application. Kidney Int 1994;45:1425–31.
64. Katholi RE, Taylor GJ, McCann WP, et al. Nephrotoxicity from contrast media: attenuation with theophylline. Radiology 1995;195:17–22.
65. Kapoor A, Kumar S, Gulati S, et al. The role of theophylline in contrast-induced nephropathy: a case-control

study. Nephrol Dial Transplant 2002;17:1936–41.
66. Huber W, Schipek C, Ilgmann K, et al. Effectiveness of theophylline prophylaxis of renal impairment after coronary angiography in patients with chronic renal insufficiency. Am J Cardiol 2003;91:1157–62.
67. Katholi RE, Taylor GJ, Woods WT, et al. Nephrotoxicity of nonionic low-osmolality versus ionic high-osmolality contrast media: a prospective double-blind randomized comparison in human beings. Radiology 1993;186:183–7.
68. Taliercio CP, Vlietstra RE, Ilstrup DM, et al. A randomized comparison of the nephrotoxicity of iopamidol and diatrizoate in high risk patients undergoing cardiac angiography. J Am Coll Cardiol 1991;17:384–90.
69. Lautin EM, Freeman NJ, Schoenfeld AH, et al. Radiocontrast-associated renal dysfunction: a comparison of lower-osmolality and conventional high-osmolality contrast media [published erratum appears in AJR Am J Roentgenol 1991;157:895]. AJR Am J Roentgenol 1991; 157:59–65.
70. Barrett BJ, Carlisle EJ. Metaanalysis of the relative nephrotoxicity of high- and low-osmolality iodinated contrast media. Radiology 1993;188:171–8.
71. Ueda J, Nygren A, Hansell P, Erikson U. Influence of contrast media on single nephron glomerular filtration rate in rat kidney. A comparison between diatrizoate, iohexol, ioxaglate, and iotrolan. Acta Radiol 1992;33:596–9.
72. Deray G, Bagnis C, Jacquiaud C, et al. Renal effects of low and isoosmolar contrast media on renal hemodynamic in a normal and ischemic dog kidney. Invest Radiol 1999; 34:1–4.
73. Lancelot E, Idee JM, Lacledere C, et al. Effects of two dimeric iodinated contrast media on renal medullary blood perfusion and oxygenation in dogs. Invest Radiol 2002;37:368–75.
74. Grynne BH, Nossen JO, Bolstad B, Borch KW. Main results of the first comparative clinical studies on Visipaque. Acta Radiol Suppl 1995;399:265–70.
75. Murakami R, Tajima H, Kumazaki T, Yamamoto K. Effect of iodixanol on renal function immediately after abdominal angiography. Clinical comparison with iomeprol and ioxaglate. Acta Radiol 1998;39:368–71.
76. Carraro M, Malalan F, Antonione R, et al. Effects of a dimeric vs a monomeric nonionic contrast medium on renal function in patients with mild to moderate renal insufficiency: a double-blind, randomized clinical trial. Eur Radiol 1998;8:144–7.
77. Jakobsen JA, Berg KJ, Kjaersgaard P, et al. Angiography with nonionic X-ray contrast media in severe chronic renal failure: renal function and contrast retention. Nephron 1996;73:549–56.
78. Chalmers N, Jackson RW. Comparison of iodixanol and iohexol in renal impairment. Br J Radiol 1999;72:701–3.
79. Aspelin P, Aubry P, Fransson SG, et al. Nephrotoxic effects in high-risk patients undergoing angiography. N Engl J Med 2003;348:491–9.
80. Lehnert T, Keller E, Gondolf K, et al. Effect of haemodialysis after contrast medium administration in patients with renal insufficiency. Nephrol Dial Transplant 1998;13: 358–62.
81. Vogt B, Ferrari P, Schonholzer C, et al. Prophylactic hemodialysis after radiocontrast media in patients with renal insufficiency is potentially harmful. Am J Med 2001; 111:692–8.
82. Berger ED, Bader BD, Bosker J, et al. [Contrast media-induced kidney failure cannot be prevented by hemodialysis.] [Article in German.] Dtsch Med Wochenschr 2001;126:162–6.
83. Heyman SN, Brezis M, Epstein FH, et al. Early renal medullary hypoxic injury from radiocontrast and indomethacin. Kidney Int 1991;40:632–42.
84. Russo D, Minutolo R, Cianciaruso B, et al. Early effects of contrast media on renal hemodynamics and tubular function in chronic renal failure. J Am Soc Nephrol 1995;6:1451–8.
85. Herbelin A, Nguyen AT, Zingraff J, et al. Influence of uremia and hemodialysis on circulating interleukin-1 and tumor necrosis factor alpha. Kidney Int 1990;37:116–25.
86. Forni LG, Hilton PJ. Continuous hemofiltration in the treatment of acute renal failure. N Engl J Med 1997; 336:1303–9.
87. Marenzi G, Marana I, Lauri G, et al. The prevention of radiocontrast-agent-induced nephropathy by hemofiltration. N Engl J Med 2003;349:1333–40.
88. Miner SE, Dzavik V, Nguyen-Ho P, et al. N-acetylcysteine reduces contrast-associated nephropathy but not clinical events during long-term follow-up. Am Heart J 2004;148:690–5.
89. McCullough PA, Wolyn R, Rocher LL, et al. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. Am J Med 1997;103: 368–75.
90. Gruberg L, Mintz GS, Mehran R, et al. The prognostic implications of further renal function deterioration within 48 h of interventional coronary procedures in patients with pre-existent chronic renal insufficiency. J Am Coll Cardiol 2000;36:1542–8.
91. Rihal CS, Textor SC, Grill DE, et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. Circulation 2002;105: 2259–64.
92. Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296–305.
93. Loef BG, Epema AH, Smilde TD, et al. Immediate postoperative renal function deterioration in cardiac surgical patients predicts in-hospital mortality and long-term survival. J Am Soc Nephrol 2005;16:195–200.
94. Remy-Jardin M, Dequiedt P, Ertzbischoff O, et al. Safety and effectiveness of gadolinium-enhanced multi-detector row spiral CT angiography of the chest: preliminary results in 37 patients with contraindications to iodinated contrast agents. Radiology 2005;235:819–26.