

NEPHROLOGY

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Radiocontrast Nephropathy

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Radiographic contrast media is the third most common cause of hospital-acquired acute renal failure (ARF), accounting for approximately 11% of cases. Almost half of these are secondary to cardiac catheterization (49%), with the remainder due to computed tomography (CT) (33%) and miscellaneous procedures.¹ The increasing number of procedures involving contrast administration places a larger portion of the population at risk of developing radiocontrast nephropathy (RCN). The incidence of RCN varies among different patient populations. While it appears to be as low as 3% to 5% for the general population,^{2,3} it may be as high as 40% in patients with preexisting chronic kidney disease (CKD) or diabetes mellitus.^{4,5} The importance of RCN resides in its consequences; in-hospital mortality may be as high as 7.1% to 14.3% in patients with RCN,⁶ compared to 1% to 5% in control subjects.^{2,4,7} Furthermore, one-year mortality rates also appear to be higher, in the range of 25% to 45% for patients with RCN compared to a range of 7% to 15% in control subjects.^{2,4,8,9} Those who develop RCN and require dialysis were reported to have a two-year mortality of ~80%.⁶ RCN is also associated with higher rates of cardiac, vascular, and systemic complications, increased length of hospital stay, and reduced procedural success.^{2,10,11} A recent study revealed that increases in serum creatinine (sCr) concentration after coronary interventions are more powerful predictors of mortality than increases in creatine kinase-MB (CK-MB).¹² This issue of *Nephrology Rounds* reviews the current state of knowledge regarding RCN, with particular emphasis on prophylactic strategies.

Definition, clinical features, and differential diagnosis

RCN is defined as “an acute decline in kidney function after the administration of intravascular contrast material, in the absence of other causes.”^{3,13} The most commonly used criteria to define RCN is an increase of $\geq 25\%$ or ≥ 0.5 mg/dL in sCr concentration, between 48 and 72 hours after the administration of contrast media.¹⁴⁻¹⁶

sCr concentration usually begins to increase within 24 hours after administration of contrast media and generally peaks between days 3 and 5, returning to baseline 7 to 10 days later.^{13,17,18} The ARF is non-oliguric in most cases. Nonspecific formed elements can appear in the urine, including renal tubular epithelial cells, pigmented granular casts, urate crystals, and debris. However, these urine findings do not correlate with severity.^{17,18} Urine osmolality tends to be < 350 mOsm/kg, the fractional excretion of sodium may vary widely,^{17,18} and mild-to-moderate proteinuria may be present.¹⁹ The differential diagnosis includes prerenal azotemia, other causes of acute tubular necrosis, acute interstitial nephritis, glomerulonephritis, post-renal azotemia, and atheroemboli.²⁰

Pathogenesis

Several hypotheses have been postulated to explain the nephrotoxicity of contrast media. The 2 most common mechanisms proposed for RCN are alterations in renal perfusion and direct toxicity of the contrast media.

- Under normal circumstances, the medullary partial pressure of oxygen is about half that of the renal cortex.²¹ The administration of contrast induces a biphasic hemo-

AS PRESENTED IN THE ROUNDS OF
THE NEPHROLOGY DIVISION OF
BRIGHAM AND WOMEN'S HOSPITAL
BOSTON, MASSACHUSETTS



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Table 1: Potential risk factors for radiocontrast nephropathy

Patient characteristics	
• Chronic kidney disease	• Hypotension
• Diabetes mellitus	• Age
• Heart failure	• Dehydration
• Myocardial infarction	• Proteinuria
• Kidney transplant	
Drugs	
• Angiotensin-converting enzyme inhibitors	
• Diuretics	
• Non-steroidal anti-inflammatory agents	
• Type and volume of contrast media	

dynamic response in the kidneys, with a transient vasodilatation followed by a prolonged vasoconstriction phase, probably leading to medullary ischemic injury and cellular necrosis.^{13,17,22}

- Contrast administration may also induce direct cytotoxicity as suggested by the histologic changes of cell injury and enzymuria.^{17,18} Experimental studies demonstrate that contrast media causes cytoplasmic vacuolization, interstitial edema, tubular degeneration, and disruption of intercellular tight-junctions.^{13,17} Increased production of oxygen-free radicals has been documented after contrast medium administration. Furthermore, radiocontrast agents reduce the activity of the antioxidant enzymes, catalase, and superoxide dismutase. The hypertonicity of contrast media may induce apoptosis.^{13,17,23}

Risk factors

A mild, transient decline in kidney function may occur in virtually all patients undergoing contrast administration, but the development of RCN is associated with certain risk factors (Table 1). Approximately 7% of all patients referred for studies with intravascular administration of contrast have either diabetes mellitus or preexisting CKD.³

Pre-existing chronic kidney disease

Baseline CKD is the single most important risk factor for the development of RCN.^{17,24} This risk appears to be inversely proportional to the glomerular filtration rate (GFR), and the presence of proteinuria may further increase the risk.^{13,17} Even though a mild reduction in kidney function increases the risk of RCN,²⁵ the risk grows exponentially among patients with stage 3 CKD or higher, ie, a GFR that is <60 mL/min.^{16,26,27}

Diabetes mellitus

The second most important risk factor for the development of RCN appears to be diabetes mellitus, probably secondary to diabetes-related alterations in renal and vascular endothelial function, which affect

Table 2: Characteristics of various contrast agents

Type	Agent	Osmolality (mOsm/kg H ₂ O)	Iodine content (mg I/mL)	Ionization
• High-osmolar	ioxathalamate	2130	350	Ionic monomer
	Diatrizoate	2000	370	Ionic monomer
• Low-osmolar	lobitridol	915	350	Non-ionic monomer
	lopamidol	796	370	Non-ionic monomer
	lohexol	780	350	Non-ionic monomer
	lopromide	770	370	Non-ionic monomer
	loxaglate	600	320	Ionic dimer
• Iso-osmolar	lotrolan	320	~ 300	Non-ionic dimer
	lodixanol	290	320	Non-ionic dimer

their response to contrast agents.^{17,28} Diabetic patients with CKD may have as much as a 5-fold higher risk of RCN compared with their nondiabetic counterparts.^{2,6}

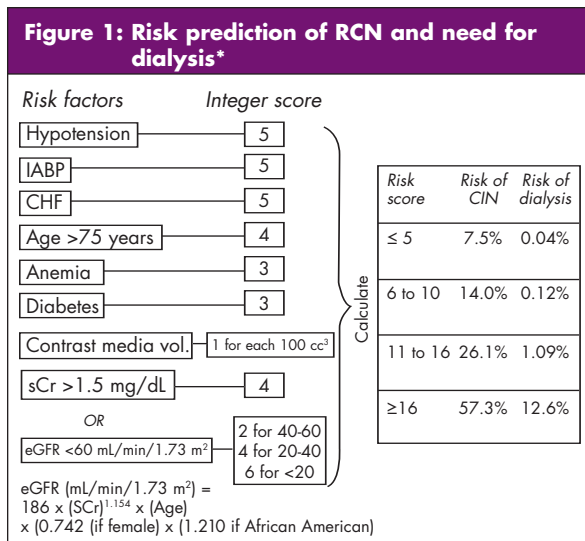
Heart disease

The presence of various cardiac conditions may predispose patients to develop RCN. Heart failure, myocardial infarction (MI), and cardiogenic shock are known to influence renal hemodynamics. One study reported that the presence of concomitant cardiac conditions placed these patients at a 3-fold higher risk of RCN than patients with normal cardiac function.²⁹

Radiocontrast material

Osmolality and ionic content: Table 2 summarizes the characteristics of common types of radiocontrast media. Both osmolality and ionic content vary between different contrast media. The incidence of ARF is approximately 3-fold higher with all high-osmolar contrast media than with low-osmolar media.^{30,29} The recent Nephrotoxicity in High-Risk Patients Study of Iso-Osmolar and Low-Osmolar Non-Ionic Contrast Media (NEPHRIC), demonstrated that RCN developed less frequently among patients who were randomized to receive iso-osmolar, dimeric, nonionic contrast media.³¹ However, the use of low-osmolar and iso-osmolar media is associated with an increase in healthcare expenditures,³² whereas the viscosity of dimeric media may impose technical difficulties.³³

Volume of contrast: Higher volumes of contrast are associated with a higher risk for RCN,⁴ although no clear threshold volume has been identified. A recent randomized trial noted that a volume of ≥140 mL, predicted the occurrence of RCN.³⁴ The severity of renal injury also appears to be related to the volume of contrast, as noted in a study in almost 2000 patients, in which none of the patients who received contrast volumes of <100 mL required dialysis.⁶



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* Risk score prediction for patients undergoing cardiac catheterization. IABP = intra-aortic balloon pump; CHF = congestive heart failure; CIN = contrast-induced nephropathy; eGFR = estimated glomerular filtration rate with the MDRD formula.³⁵

Risk stratification

Apart from estimating the GFR and considering other risk factors, a recently developed risk score may help clinicians determine the risk for both RCN and the need for dialysis in patients undergoing percutaneous coronary intervention (Figure 1).³⁵

Methods to prevent RCN

Interventions aimed at preventing RCN are summarized below, and include fluid and drug administration (Table 3).

What seems to work

Fluid administration: The administration of intravenous fluids corrects clinical or subclinical dehydration and counterbalances the osmotic diuresis that follows contrast administration.^{18,36} Theoretically, fluid administration would decrease renin-angiotensin system activity, downregulate the tubuloglomerular feedback, augment diuresis and sodium excretion, dilute the contrast medium, and reduce endothelin and other intrarenal vasoconstriction mediators.³⁷

The role of fluid administration in the prevention of RCN was described in the early 1980s³⁸ and confirmed in patients with different risk profiles undergoing various procedures. However, the assumption of the benefit of fluid administration is either based on uncontrolled observational data or derived from randomized trials comparing fluid administration with other interventions.³⁹ However, the consensus among experts is unanimously in favor of fluid administration as the standard prophylaxis of RCN.

Most studies have used intravenous 0.45% saline. However, a recent randomized trial with 1,620 patients

Table 3: Interventions for the prevention of RCN in patients at risk

Beneficial	
• Fluid administration	
May be beneficial	
• N-acetylcysteine	• Theophylline
• Hemofiltration	• Bicarbonate infusion
Ineffective or harmful	
• Dopamine	• Fenoldopam
• Forced diuresis	• Hemodialysis

undergoing coronary angioplasty demonstrated that fluid administration with a 0.9% saline solution was superior to 0.45% saline with 5% glucose.⁴⁰

Contrast agents: As mentioned in the risk factor section, contrast volume reduction and low-osmolar or iso-osmolar, nonionic agents, may reduce the incidence of RCN.

What may work

Oral hydration: Intravenous fluids require hospital admission. Two randomized trials have evaluated the usefulness of oral fluid administration, with contradictory results.^{15,39}

Acetylcysteine: N-acetylcysteine (NAC) ameliorates the toxic effects of a variety of experimentally- or clinically-induced ischemia-reperfusion syndromes.^{41,42} It scavenges oxygen-free radicals and acts as a cofactor for enzymatic reactions that prevent the degradation of nitric oxide.⁴³ More than 20 randomized trials and >10 meta-analyses evaluating the use of NAC have been published. The latter are likely the consequence of the heterogeneous results of individual studies.⁴⁴⁻⁴⁹ The variability in results among meta-analyses may be explained by differences in their methodology and inclusion criteria. While many conclude that NAC reduces the incidence of RCN, caution in the interpretation of data is recommended. A large, randomized, controlled trial or a meta-analysis of individual-patient data would help to further characterize the effectiveness of NAC. Other features that need to be considered with regard to NAC use are the following:

- **Dosing:** Most studies use a dose of 600 mg by mouth twice daily, on the day before and on the day of the exposure to contrast media. A recent study evaluated the 600 versus the 1200 mg dose; the latter was perhaps more effective in the prevention of RCN.⁵⁰ Three trials have evaluated the use of intravenous NAC for emergency catheterizations, also with conflicting results. While 1 study using high-dose NAC (150 mg/kg) showed a renoprotective effect,⁵¹ 2 studies with lower-dose intravenous NAC demonstrated no benefit.^{52,53}
- **Presentation:** Some have noticed that most protective trials were done in countries outside the United

States (US), using a pill form of NAC, whereas in the US, it is available in liquid form. Whether pharmacokinetic properties influence the efficacy of NAC remains unclear.

- Interference with assay: Some physicians hypothesize that NAC may interfere with the sCr assay. Two studies aimed at evaluating this issue had contradictory results.^{54,55}
- Costs: Although inexpensive, we are not aware of cost-benefit analyses evaluating the use of NAC.
- Clinical significance: A recent randomized trial found that NAC reduced RCN, but not the 9-month incidence of death, MI, need for dialysis or repeat hospitalization for cardiac causes.⁵⁶

Natriuretic peptides: Natriuretic peptides increase renal blood flow, but studies with atrial natriuretic peptide have failed to demonstrate a protective effect.⁵⁷ Other studies are currently evaluating brain natriuretic peptide and its effect on risk for RCN.

Theophylline: Theophylline is an adenosine antagonist that has been evaluated as a prophylactic drug for RCN because adenosine decreases when radiocontrast is administered. Adenosine regulates the intracellular calcium concentration, which appears to mediate the prolonged vasoconstrictor phase that follows contrast administration.¹⁷ A recent meta-analysis concluded that prophylactic administration of theophylline or aminophylline appears to protect against RCN.⁵⁸

Calcium channel blockers (CCBs): CCBs can prevent adenosine-induced vasoconstriction and the decrease in nitric oxide synthesis that follows contrast media administration in humans.⁵⁹ While a small RCT showed some benefit with CCBs,⁶⁰ a larger study with nitrendipine found no difference in comparison with placebo.⁶¹ There is an ongoing trial in 290 patients, in which amlodipine is being given 7 days before, and continued 2 days after, radiocontrast media exposure.⁵⁹

Renal replacement therapy: Hemodialysis removes contrast media effectively.⁶² Two studies in patients with CKD failed to demonstrate an influence of hemodialysis on the incidence of RCN.^{62,63} The results of a large randomized trial comparing fluid administration with NAC and dialysis are still pending.⁶⁴

Other methods of renal replacement therapy have been successful. Marenzi et al randomized 114 patients with CKD (sCr >2 mg/dL) to hemofiltration or saline hydration, both before and after the administration of contrast media. The incidence of RCN was 5% in the hemofiltration group, versus 50% in the control group. In-hospital complications and mortality, as well as

cumulative 1-year mortality, were also reduced in the hemofiltration group.⁹

Contrast agents: Gadolinium was shown to be safe in patients with CKD in 2 small studies,^{65,66} and was used successfully for coronary angiography in 3 case reports. However, most types of gadolinium lack enough density to allow the image quality necessary for interventional catheterizations.⁶⁷⁻⁶⁹

Other interventions: Hydration with sodium bicarbonate in comparison with saline reduced the incidence of RCN in 1 recent randomized trial.⁷⁰ Other investigations using ascorbic acid or statins have shown promising results.^{71,72} These studies need to be reproduced in future trials.

What doesn't work

Forced diuresis with furosemide or mannitol, as well as dopamine administration were found to be either harmful or conferred no benefit.^{14,73,74} Despite initial optimism, it was demonstrated that fenoldopam did not reduce the incidence of RCN in 3 randomized trials.⁷⁵⁻⁷⁷

Treatment of RCN

There is no standard treatment for RCN. Management is supportive while waiting for the recovery of kidney function 7 to 10 days after exposure to radiocontrast material.^{18,78} If patients become oliguric and are volume replete, fluid repletion should be discontinued and diuretics may be required. If they are non-oliguric, it seems reasonable to maintain euvolemic status. Potentially nephrotoxic drugs, such as angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and non-steroidal anti-inflammatory agents, should be discontinued. The effect of dopamine to treat RCN was deleterious in 1 study of 72 patients.⁷³

Conclusions

RCN is a common cause of ARF and is associated with significant morbidity and mortality. Its incidence varies among different population groups, but patients with diabetes and CKD are at particularly increased risk.

Future research should lead to the development of a standard definition of RCN in order to compare the results of studies. Consideration should be given to estimating the risk of RCN in all patients expected to undergo contrast administration. Those at risk should be given intravenous fluid administration. There may be some benefit from the use of oral NAC or, for patients undergoing emergency procedures, high-dose intravenous NAC, but these are not substitutes for

intravenous fluid administration. The use of lower osmolality agents, as well as bicarbonate infusions, should be considered.⁷⁹

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Dr. Alonso has no disclosures to announce in association with this issue. Dr. Sarnak has received grant support from Amgen Inc.

This publication is made possible by an educational grant from

Amgen Inc.

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