Radiocontrast-Induced Acute Renal Failure: Allocations and Outcomes

Roxana Mehran, MD, FACC, FACP, Dale T. Ashby, MD

Lenox Hill Heart and Vascular Institute, Cardiovascular Research Foundation, New York, NY

Radiocontrast-induced nephropathy causes significant morbidity and mortality with increase in hospital length of stay and costs. It can be largely prevented by identifying the patients at risk before the procedure. Once the at-risk patient is identified, ways to prevent the development of acute renal failure are: avoiding volume depletion, aggressive saline hydration with the aim of keeping the urine output over 150 mL/hour, and the use of low-osmolality contrast agents, with as little volume used as possible. There is theoretical potential for the dopamine DA_1 agonist fenoldopam as a preventive agent, and this is currently being tested in randomized trials. [Rev Cardiovasc Med. *2001;2(suppl 1):S9–S13*].

Radio-opaque contrast agents are widely used in percutaneous coronary and peripheral angiography and interventions (PCI), computerized tomography, and other radiocontrast-requiring procedures. Radio-opaque contrast agents are vital for these procedures, but there are adverse effects associated with their use. Predictable short-lived adverse effects are nausea, vomiting, allergic reactions and bradycardia, hypotension, and depression of ventricular systolic function. One of the most important adverse effects of contrast agents is that of contrast-induced nephropathy, which can cause substantial morbidity and mortality during hospitalization and can lead to chronic end-stage renal disease.

Contrast nephropathy can be defined as a greater than 0.5 mg/dL increase in serum creatinine within 48 hours of contrast exposure in the absence of other causes.[1] The time course of contrast-induced renal insufficiency is predictable. It occurs within 24 to 48 hours of exposure, with a typical peak creatinine after 3 to 5 days and a return to baseline or near baseline in 1 to 3 weeks.[2] The in-hospital mortality rate in patients developing renal impairment is directly related to the level of increase in serum creatinine concentration, ranging from 3.8% with an increase in creatinine from 0.5 to 0.9 mg/dL, to 64% when the creatinine concentration is greater than 3.0 mg/dL.[2] In patients having coronary and periph-

eral angiography and interventions, where the hospital stay is often short, the development of contrast nephropathy greatly increases the length of stay and health costs related to the admission.

Risk Factors for Contrast Nephropathy

The likelihood of contrast nephropathy occurring is closely related to a number of risk factors (Table 1). The three most important risk factors are pre-existing renal impairment, the presence of diabetes mellitus and the volume of contrast agent used.

In a study of 1826 consecutive patients undergoing PCI, the incidence of acute renal failure (ARF) without the need for dialysis occurred in 14.5% of patients, and ARF requiring dialysis occurred in 0.7% of patients.[4] The in-hospital mortality rate was 35.7% for inpatients with diabetes and ARF, compared to 1.1% in patients with no diabetes and normal renal function (Figure 1). The predictors for ARF were the presence of baseline chronic renal impairment, diabetes mellitus, and contrast volume. In a prospective, controlled study of 220 patients undergoing radiographic procedures with intravascular contrast material, Parfrey and colleagues showed that the largest risk group for the development of contrast nephropathy were diabetics with pre-existing renal insufficiency.[5] Clinically important ARF attributable to contrast did not occur in nondiabetic patients with pre-existing renal insufficiency or in diabetics with normal renal function.

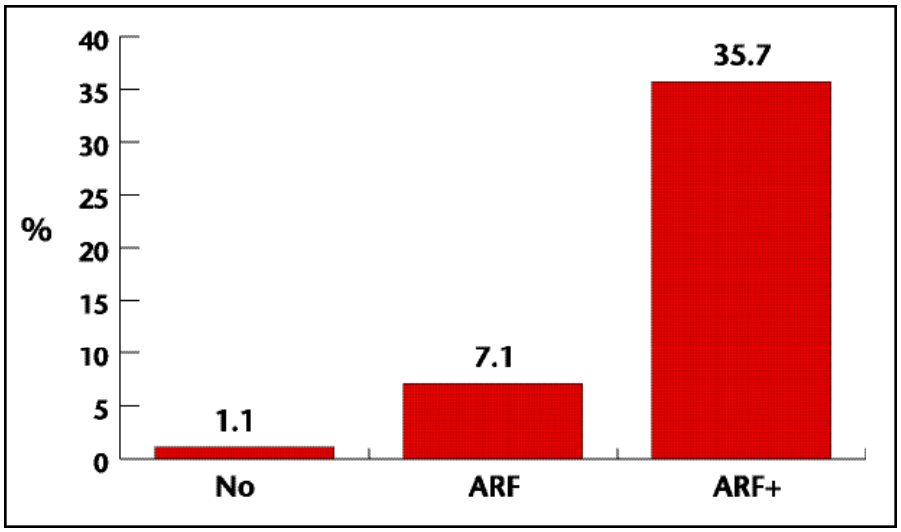
In a study of 1826 consecutive patients undergoing PCI, the incidence of acute renal failure (ARF) without the need for dialysis occurred in 14.5% of patients, and ARF requiring dialysis occurred in 0.7% of patients

We studied 439 consecutive patients with a baseline creatinine concentration ≥ 1.8mg/dL who underwent a PCI.[3] All patients were well hydrated before the procedure and most received the ionic low-osmolality contrast agent ioxaglate meglumine. Contrast nephropathy, defined as a ≥25% increase in serum creatinine, occurred in 37% of patients. In-hospital mortality was 14.9% for patients with contrast nephropathy, compared to 4.9% with no creatinine increase (P = .001). Thirty-one patients required hemodialysis, and their in-hospital mortality was 22.6%. The cumulative 1-year mortality was 45.2% for those who required dialysis, 35.4% for those who had contrast nephropathy and did not require dialysis, and 19.4% for those with no creatinine increase.

Table 1
Risk Factors for Contrast-Induced Nephropathy

- Pre-existing renal insufficiency
- Diabetes
- Contrast volume
- Dehydration
- Advanced age
- Nephrotoxic drugs (ACE I, NSAIDs)
- Multiple myeloma
- Congestive heart failure
- Liver disease

Figure 1. *Contrast nephropathy in-hospital mortality among 1826 consecutive patients undergoing PCI. No, no diabetes and normal renal function; ARF, acute renal failure; ARF+, ARF plus diabetes. Data from McCullough et al.[4]*



Pathophysiology of Contrast Nephropathy

It is now accepted that radiocontrast agents cause their toxic effects on the kidneys by inducing ischemia and subsequent tubular cell injury in the outer medullary thick ascending limb of the renal tubule. Under normal conditions, the medulla's environment is hypoxic, with the medullary partial pressure of oxygen in the range of 10 to 20 mm Hg (cf partial pressure of oxygen in the renal cortex of about 50 mm Hg).[6] Any stressor, such as dehydration,

salt and volume depletion, and renal hypoperfusion, will cause an increase in urinary concentration and hence worsen the hypoxia of the medullary tubular cells. Cell injury and death may follow. Radiographic contrast agents worsen the situation by increasing the hypoxic environment of the medulla by increasing urine concentration, having a direct toxic effect on the tubular cells and shunting blood flow from the renal medulla to the cortex. Because physiologically the medullary system already exists in a relative state of hypoxia and the insults that exist to create further hypoxia in the medulla (dehydration, non-steroidal anti-inflammatory drugs [NSAIDs], contrast agents) are synergistic in their effect, it is vital to avoid as many of these risk factors as possible.

All the risk factors [for contrast nephropathy] can be elicited from medical history and simple baseline blood tests.

Prevention of Contrast Nephropathy

Contrast nephropathy is a form of acute renal failure amenable to prophylaxis, because administration of the radiocontrast agent is planned, and a high-risk population has been identified. By identifying the risk factors (Table 1), methods of prevention can be put into place to minimize the risk of contrast nephropathy. All of the risk factors can be elicited from medical history and simple baseline blood tests. In the at-risk patient, nephrotoxic drugs, such as NSAIDs and ACE I should be withheld before the procedure. Trials of numerous treatments to reduce the risk of contrast nephropathy have been conducted. Unsuccessful prophylactic treatments to prevent contrast nephropathy have included mannitol, diuretics, calcium channel antagonists, renal dose dopamine, and atrial natriuretic peptide.[7–11] Successful treatments are hydration stategies and acetylcystine.

Saline Hydration

The PRINCE Study tested the hypothesis that forced diuresis with maintainance of intravascular volume after contrast exposure would protect against contrast nephropathy in a high-risk group of patients undergoing PCI.[12] The 98 patients, all with baseline renal impairment, were randomized to one of two regimens: an aggressive IV fluid regimen with 0.45 saline with furosemide, mannitol (if pulmonary capillary wedge pressure is <20 mm Hg), and low-dose dopamine; or the same aggressive IV fluid regimen with 0.45 saline and no furosemide and placebo infusions. Overall there was no statistical difference in the primary endpoint of change in serum creatinine at 48 hours. Two patients in the experimental arm and five patients in the control arm required dialysis (P = ns), with all seven patients having measured urine flow rates of <145 mL/hr in the 24 hours after the procedure. Combining the two groups, the rates of renal failure in those with urine flow rates of >150 mL/hr in the post-procedure period were significantly lower at 21.6% versus 45.9% for the patients whose urine output dropped below 150 mL/hr post-procedure (P = .03). Thus, an important way to prevent contrast nephropathy is to keep the patient well hydrated to maintain a urine output of at least 150 mL/hr.

An important way to prevent contrast nephropathy is to keep the patient well hydrated to maintain a urine output of at least 150 mL/hr.

Contrast Agents

The volume and, to a lesser extent, type of contrast agent are important in preventing contrast nephropathy from occurring. The less volume of contrast used the better, and strategies to lower the contrast load, such as avoiding ventriculography in high-risk patients, can help. In subgroup analysis of ionic high-osmolality versus nonionic low-osmolality radiocontrast agent trials, nonionic low-osmolality contrast agents caused less contrast nephropathy in high-risk patients, such as those with diabetes and chronic renal impairment.[13,14] Thus, to try to prevent ARF in patients with risk factors for contrast nephropathy, low-osmolality contrast agents are preferred, and the volume used should be minimized. Although nonionic low-osmolality contrast agents are associated with decreased contrast nephropathy in high-risk patients, they may cause more thrombotic events in patients undergoing PCI than ionic low-osmolality contrast agents.[15–17] Given this potential adverse

Although nonionic low osmolality contrast agents are associated with decreased contrast nephropathy in high-risk patients, they may cause more thrombotic events in patients undergoing PCI than ionic low-osmolality contrast agents.

Table 2
Methods to Prevent Contrast Nephropathy in High-Risk Patients

- Identify the at-risk patient prior to the procedure
- Avoid volume depletion prior to procedure
- Hold nephrotoxic drugs (eg, ACE I, NSAIDs)
- Aggressive hydration with IV 0.45 saline to keep urine output >150 mL/hr pre-procedure, during, and 12 hours post-procedure
- If LVF develops or PCWP >15 mm Hg, use diuretics, but maintain hydration if possible
- Use nonionic low-osmolality contrast if pre-existing renal dysfunction and diabetes coexist
- Minimize contrast volume
- N-acetylcysteine 600 mg twice a day (start the day before and cease 48 hours post-procedure)
- Space procedures using radiographic contrast at least 5 days apart

property of the nonionic low-osmolality radiocontrast agents in the setting of PCI, they should be reserved for patients with risk factors for contrast nephropathy.

Acetylcysteine

In a recent study, Tepel and colleagues have shown that the thiol-containing antioxidant acetylcysteine markedly reduces the rate of contrast nephropathy in high-risk patients.[18] They studied 83 patients with chronic renal insufficiency who were undergoing computed tomography with a nonionic low-osmolality contrast agent. Patients were randomized to acetylcysteine (600 mg twice daily for the day prior to, the day of, and two days after the procedure) and 0.45% saline intravenously pre- and post-procedure, or to receive placebo and saline hydration. One of the 41 patients in the acetylcysteine group (2%) and 9 of the 42 patients in the control group (21%) had an increase of at least 0.5 mg/dL in serum creatinine, which was significant (P = .01, relative risk = 0.1). In the acetylcysteine group, the mean serum creatinine concentration decreased significantly (P < .001) at 48 hours over baseline level, whereas in the control group there was a nonsignificant increase in the 48-hour serum creatinine concentration.

Acetylcysteine probably protects against contrast nephropathy via its antioxidant properties. Acetylcysteine improves the survival of cells under oxidant stress, which appears to be the major cause of the death and injury to the renal medullary cells. Larger studies to confirm the benefit of acetylcysteine in the prevention of contrast nephropathy are expected.

Dopamine and Selective Dopamine Receptor Agonism

In a randomized, prospective trial testing renal dose dopamine and saline hydration versus placebo and saline hydration, there was no difference in the rate of development of contrast nephropathy.[19] The disappointing effects of low-dose dopamine may be related to its inability to reverse the redistribution of renal blood flow from the renal cortex back to the renal medulla. Dopamine stimulates both renal dopamine

Main Points

- Radiocontrast-induced nephropathy causes significant morbidity and mortality and increase in hospital length of stay and costs.
- RCN can be largely preventable by identifying the patients at risk before the procedure.
- Pre-existing renal impairment, diabetes, and contrast volume are the main risk factors for the development of contrast nephropathy.
- Successful methods of prevention are keeping the patient well hydrated, use of low osmolar contrast agents, and limiting contrast volume.
- The role of oral acetylcysteine still needs to be determined in larger scale studies.
- The dopamine DA_1 agonist fenoldopam has been shown to increase renal medullary blood flow, with a randomized prospective trial of its ability to prevent contrast nephropathy currently underway.

receptor subtypes. Activation of the renal DA_1 receptor results in an increase in renal blood flow, which is most marked in the inner cortex and renal medulla, and an increase in the glomerular filtration rate (GFR). Activation of the renal DA_2 receptor reduces the renal blood flow and the GFR.

The drug fenoldopam mesylate is a selective agonist of the DA_1 receptor that may have potential to prevent contrast nephropathy. Fenoldopam has been shown to increase renal medullary flow compared with cortical flow in a study of hypotensive dogs.[20] Randomized prospective trials to assess the efficacy of fenoldopam in the prevention of contrast nephropathy are underway.

Clinical Prevention of Contrast Nephropathy

The most important way to prevent contrast nephropathy is to identify the patient at risk before the procedure. Once the at-risk patient is identified the measures listed in Table 2 should be implemented.

Conclusion

Radiocontrast-induced nephropathy causes significant morbidity and mortality and increase in hospital length of stay and costs. The pathophysiology of contrast nephropathy involves the shunting of blood away from the renal medulla, causing ischemic injury to the tubules. It can be minimized by the identification of patients with risk factors before their procedure. The risk factors are synergistic, and the most important two are the presence of pre-existing renal impairment and diabetes. Once the at-risk patient is identified, ways to prevent the development of ARF are: avoiding volume depletion, aggressive saline hydration with the aim of keeping the urine output over 150 mL/hour, and the use of low-osmolality contrast agents, with as little volume used as possible. If the at-risk patient requires a second procedure involving radiocontrast, then at least 5 days should elapse between procedures. There is theoretical potential for the dopamine DA_1 agonist fenoldopam as an agent to prevent radiocontrast-induced nephropathy, and this is currently being tested in randomized trials. ■

References

1. Porter GA. Contrast-associated nephropathy. *Am J Cardiol*. 1989;649(9 Suppl):22E-26E.
2. Berns AS. Nephrotoxicity of contrast media. *Kidney Int*. 1989;36:730-740.
3. Gruberg L, Mintz GS, Mehran R, et al. The prognostic implications of further renal function deterioration within 48 hours of interventional coronary procedures in patients with pre-existent chronic renal insufficiency. *J Am Coll Cardiol*. 2000;36:1542-1548.
4. 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;103:368-375.
5. Parfrey PS, Griffiths SM, Barrett BJ, et al. Contrast material induced renal failure in patients with diabetes mellitus, renal insufficiency or both. *N Engl J Med.* 1989;320:143-149.
6. Brezis M, Rosen S. Hypoxia of the renal medulla_its implication for disease. *N Engl J Med.* 1995;332:647-655.
7. Anto HR, Chou SY, Porush JG, Shapiro WB. Infusion intravenous pyelography and renal function: effect of hypertonic mannitol in patients with chronic renal insufficiency. *Arch Intern Med*. 1981;141:1652-1656.
8. Weinstein JM, Heyman S, Brezis M. Potential deleterious effect of furosemide in radiocontrast nephropathy. *Nephron*. 1992;62:413-415.
9. Seyss C, Foote EF. Calcium channel blockers for prophylaxis of radiocontrast-associated nephrotoxicity. *Ann Pharmacother.* 1995;29:187-188.
10. Weisberg LS, Kurnik PB, Kurnik BRC. Risk of radiocontrast nephropathy in patients with and without diabetes mellitus. *Kidney Int*. 1994;45:259-265.
11. Kurnik BRC, Allgren RL, Genter FC, et al. Prospective study of atrial natriuretic peptide for the prevention of radiocontrast-induced nephropathy. *Am J Kidney Dis.* 1998;31:674-680.
12. Stevens MA, McCullough PA, Tobin KJ, et al. A prospective randomized trial of prevention measures for contrast nephropathy. Results of the PRINCE Study. *J Am Coll Cardiol*. 1999;33:403-411.
13. Rudnick MR, Goldfarb S, Wexler L, et al. Nephrotoxicity of ionic and nonionic contrast media in 1196 patients: a randomized trial. The Iohexol Cooperative Study. *Kidney Int*. 1995;47:254-261.
14. Barrett BJ, Parfrey PS, Vavasour HM, et al. Contrast nephropathy in patients with impaired renal function: high versus low osmolar media. *Kidney Int*. 1992;41:1274-1279.
15. Piessens JH, Stammen F, Vrolix MC, et al. Effects of an ionic versus a nonionic low osmolar contrast agent on the throbotic complications of coronary angioplasty. *Cathet Cardiovasc Diagn*. 1993;28:99-105.
16. Grines CL, Schreiber TL, Savas V, et al. A randomised trial of low osmolar ionic versus nonionic contrast media in patients with myocardial infarction or unstable angina undergoing percutaneous transluminal coronary angioplasty. *J Am Coll Cardiol*. 1996;27:1381-1386.
17. Qureshi NR, den Heijer P, Crijns HJ. Percutaneous coronary angioscopic comparison of thrombus formation during percutaneous coronary angioplasty with ionic and nonionic low osmolality contrast media in unstable angina. *Am J Cardiol*. 1997;80:700-704.
18. 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;343:180-184.
19. Gare M, Haviv YS, Ben-Yehuda A, et al. The renal effect of low dose dopamine in high risk patients undergoing coronary angiography. *J Am Coll Cardiol*. 1999;34:1682-1688.
20. Kien ND, Moore PG, Jaffe RS. Cardiovascular function during induced hypotension by fenoldopam or sodium nitroprusside in anesthetized dogs. *Anesth Analg*. 1992;74:62-78.