Past and Present Attempts to Prevent Radiocontrast Nephropathy

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Radiocontrast nephropathy is an under-recognized event after coronary and radiographic angiography, with major morbidity and mortality. Patients at greatest risk for RCN can be defined prior to the procedure based on age, presence of diabetes, and presence of preexisting renal dysfunction. Despite attempts to alter preprocedural hydration, amount of dye administered, and postprocedural therapies, this clinical event continues to affect over 25% of patients at high risk. This discussion will review the literature in order to understand the attempts that have been made to prevent radiocontrast nephropathy. [Rev Cardiovasc Med. *2001;2(suppl 1):S14–S18*]

Key words: Radiocontrast nephropathy • Creatinine • Forced diuresis • Dopamine receptors • Hydration

Radiocontrast nephropathy (RCN) is the third most common cause of acute renal failure, occurring in 5% to 12% of all patients exposed to radiocontrast agents and in 13% of all patients with acute renal failure.[1,2] When RCN develops, the mortality rate is approximately 30%.[3] This potentially preventable condition can be predicted based on several clinical features. The confirmed predisposing clinical conditions are a serum creatinine of greater than 1.5 mg/dL, diabetic nephropathy, congestive heart failure of class III or IV, multiple myeloma, repeat exposure to contrast in less than 48 hours, and the volume of contrast used. The strongest association is with the baseline creatinine prior to the procedure. In a study by Berns,[4] patients with a creatinine of less than 2.0 mg/dL had an RCN incidence of 3.6%. This rose to 47% in patients with a baseline creatinine between 2.0 and 4.0 mg/dL and peaked at over 80% in those with a serum creatinine greater than 4.0.

To understand previous attempts at decreasing RCN we must understand the three mechanisms involved.[5] Macro- and microcirculatory vasoconstriction occur in response to radiocontrast dye, as described in this supplement. In addition, direct tubular toxicity and precipitation of dye crystals within the tubules occur. To treat RCN effectively, one or all of these problems must be addressed.

Initial therapies for RCN were directed at treating the crystallization of dye in the tubules by improving urine output. The use of hydration alone was examined in the 1980s, and the earliest trials[6] demonstrated some improvement over baseline results in small randomized studies. Following upon this line of reasoning, some investigators evaluated forced diuresis using furosemide as prophylactic therapy to prevent dye-associated acute renal failure.[6] This study suggested that forced diuresis may be harmful instead of helpful. A randomized trial by Solomon and colleagues[7] demonstrated that saline alone was better therapy than saline coupled with forced diuresis. In fact, the addition of furosemide increased the risk of acute renal failure three-fold compared to diuresis alone. Finally, volume expansion has been suggested as an appropriate therapy to decrease the risk of radiocontrast nephropathy. Mannitol was also studied in the series by Solomon and colleagues and was also found to increase the incidence of acute renal failure over that observed in patients who received only saline infusion (Figure 1).

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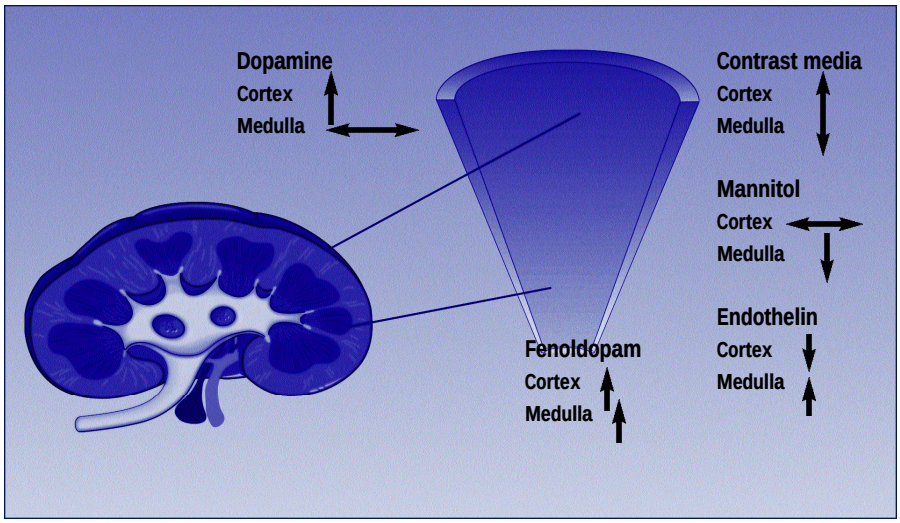
The availability of new low-osmolar contrast agents was evaluated in vitro and in animal models. These studies suggested that there is a benefit to the use of newer agents to decrease the incidence of dye-associated acute renal insufficiency, and promoted the use of these agents as possible treatments to decrease RCN. The largest series to date[8] included 1196 patients who received either iohexol, a low-osmolar contrast agent, or sodium diatrizoate, a high-osmolar contrast agent. Whereas those patients with normal renal function did not appear to benefit, patients with elevated baseline creatinine had lower rates of acute renal failure. Review of the currently available studies has not demonstrated a conclusive benefit of nonionic media in this situation.[9]

The clinical observation that dopamine receptors are important in regulating renal flow was duplicated in animal models. These basic studies have been responsible for several clinical studies to evaluate the effects of dopamine in preventing acute renal insufficiency. The prospective randomized trial of prevention measures in patients at high risk for contrast nephropathy (PRINCE) study[10] randomized patients to receive forced diuresis combined with furosemide, mannitol, and low-dose dopamine in 43 patients versus a control group of 55 patients, who received only intravenous crystalloid with matching placebo infusions. There was no statistically significant difference in the two patient populations with regard to the rates of renal failure. The only correlation was with the urine flow rate. Flow rates greater than 150 cc/min correlated with the lowest risk of developing acute renal failure. A second study, by Abizaid and colleagues,[11] also evaluate dopamine infusion in a high-risk population with mean baseline serum creatinine levels greater than 2.0 mg/dL (see Figures 2 and 3). This trial evaluated patients divided into three arms. The control arm of forced diuresis was compared to low-dose dopamine or intravenous aminophylline. The results of this trial demonstrated convincingly that low-dose dopamine increased the incidence of acute renal failure after radiocontrast exposure. In retrospect, this finding fits with basic science data demonstrating that renal blood flow is

Figure 1. *Varying effects of parenteral vasodilators on regional blood flow in the kidney. From Tumlin JT. Parenteral vasodilators: role of prophylaxis of radiocontrast dye nephropathy. Transcatheter Therapeutics Symposium; October 1999; Washington,DC, with permission.*



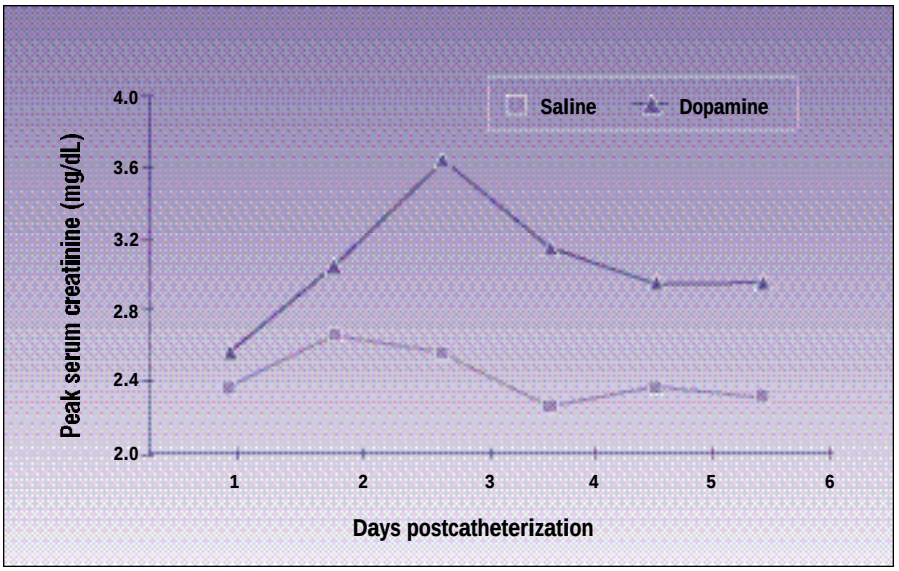


Figure 2. *Effect of low-dose dopamine on patients who developed contrast-induced acute renal failure. Hospital stay was higher in the dopamine-treated group; 4 of the dopamine-treated patients required dialysis. Adapted, with permission, from Abizaid AS, Clark CE, Mintz GS, et al. Effects of dopamine and aminophylline on contrast-induced acute renal failure after coronary angioplasty in patients with preexisting renal insufficiency.* Am J Cardiol. *1999;83:260–263(A5).*

shunted to the cortex at the expense of the medulla. The lack of effectiveness of "renal-dose dopamine" may be related to the fact that dopamine agonizes both the renal DA_1 and DA_2 receptors as well as alpha and beta receptors. The DA_1 receptor increases renal blood flow and the glomerular filtration rate; however, this effect could be countered by the simultaneous activation of the DA_2 receptor by dopamine, which decreases both renal blood flow and glomerular filtration. In addition, there is no good relationship between dose of dopamine and resulting plasma levels.[12] Therefore, some patients who are receiving infusions of dopamine in the "renal-dose" range may be achieving levels causing alpha receptor stimulation, causing vasoconstriction and possibly worsening medullary hypoxemia, and beta receptor stimulation, predisposing to arrhythmias. This alteration in medullary blood flow also occurs with the administration of mannitol and likely explains the results of mannitol administration.

The use of agents directing and improving arteriolar flow is in its infancy. The use of endothelin antagonists and nitric oxide agents has been reported in limited detail. The initial experience with a nonselective endothelin[13] has been published. This agent demonstrated an increased incidence of renal failure. Other more selective endothelin agents are reported to be currently under investigation.

The recent report of the use of acetylcysteine for prophylaxis against radiocontrast-associated acute renal failure is intriguing but limited by the size of the study and lack of corroborative studies.[14] The fact that all patients had a small volume of dye (75 cc) used for elective CT scan makes this study's results difficult to extrapolate to coronary angiographic studies. It is also interesting that the control group developed acute renal failure in 21% of patients, a much higher number than predicted for this patient population. This therapy awaits corroboration by other randomized trials but does provide hope that such therapies are on the horizon.

Preprocedural hydration remains the only proven therapy to decrease acute renal failure.

Use of selective DA_1 receptor agonists have been reported to prevent radiocontrast-associated renal failure. The best trial to date is the one by Tumlin and colleagues,[15] which demonstrated a 50% reduction in the incidence of renal failure after RCN.

Figure 3. *Failure of dopamine and aminophylline to prevent radiocontrast nephropathy in a study of 60 patients. Adapted, with permission, from 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;83:260–263(A5).*

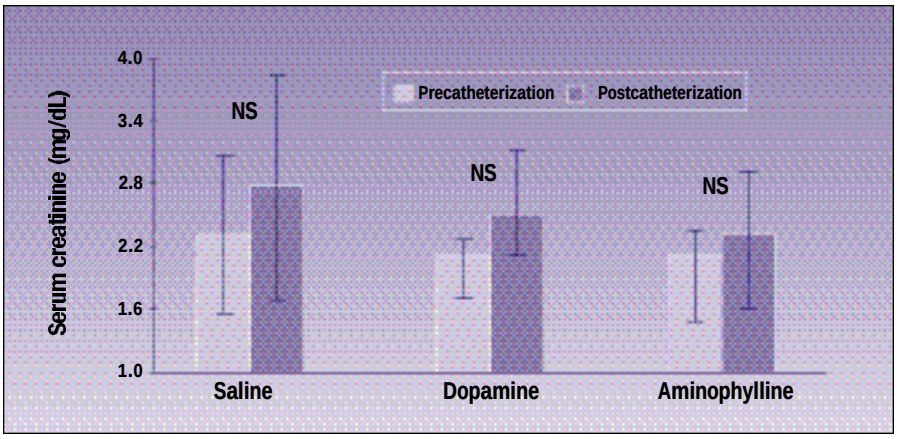


Table 1

Author	Year	No. Patients	Treatment	Baseline Creatinine	Control Population	Treated Population
Rudnick[8]	1995	1196	Iohexol vs meglumine/ sodium diatrizoate	2.7	N/A	Iohexol 3% Meglumine/ sodium diatrizoate 7%
Solomon[7]	1994	78	½ Normal saline Mannitol Dopamine	2.1		11%
Abizaid[11]	1999	60	Saline Dopamine Aminophylline	2.3 1.9 1.9	2.6 (30%)	 3.3 (50%) 3.0 (35%)
Stevens[10]	1999	98	½ Normal saline with furosemide and dopamine vs ½ normal saline	2.4 2.55		
Tepel[14]	2000	83	½ Normal saline Acetylcysteine	2.4	(21%)	(2%)
Tumlin[15]	2000	44	½ Normal saline vs fenoldopam	2.61 2.63	3.55 (41%)	2.77 (20 %)

Table 1 presents a summary of trials to date. A review of this data demonstrates that the studies show great variability in patient populations and the definition of RCN.

Conclusions

Radiocontrast-associated renal failure is a significant problem in patients with cardiovascular disease. The risk factors for cardiovascular disease also predispose these patients to an increased risk of renal failure. Preprocedural hydration remains the only proven therapy to decrease acute renal failure; however, new therapies using agents that increase renal medullary perfusion, such as fenoldopam, or decrease oxidative stress appear promising. ■

References

1. Porter GA. Contrast-associated nephropathy. *Am J Cardiol*. 1989;64:22E–26E.
2. Eisenberg RL, Bank WO, Hedgcock MW. Renal failure after major angiography can be avoided with hydration. *AJR Am J Roentgenol*. 1981;136:859–861.
3. Levitz CS, Friedman EA. Failure of medical protective measures to prevent contrast media induced renal failure. *Arch Intern Med*. 1982;142:642–648.
4. Berns AS. Nephrotoxicity of contrast media. *Kidney Int*. 1989;36:730–740.
5. Brady HR, Brenner BM, Lieberthal W: Acute

Main Points

- Radiocontrast nephropathy is the third most common cause of acute renal failure and the mortality rate is approximately 30%.
- Predisposing clinical conditions are a serum creatinine of greater than 1.5 mg/dL, diabetic nephropathy, congestive heart failure of class III or IV, multiple myeloma, repeat exposure to contrast in less than 48 hours, and the volume of contrast used.
- Hydration is used to treat the crystallization of dye in the tubules by improving urine output.
- Forced diuresis by saline infusion with furosemide or mannitol was found to increase the incidence of acute renal failure over that of patients who received only saline infusion.
- Low-dose dopamine increased the incidence of acute renal failure after radiocontrast exposure.
- Studies suggest that new low-osmolar contrast agents may decrease the incidence of dye-associated acute renal insufficiency.

renal failure. In: Brenner BM, ed. *The Kidney*. 5th ed. Philadelphia: WB Saunders, 1996:1200–1252.
6. Brown RS, Ransil B, Clark BA. Prehydration protects against contrast nephropathy in high risk patients undergoing cardiac catheterization [abstract]. *J Am Soc Nephrol*. 1990;1:330A.
7. Solomon R, Werner C, Mann D, et al. Effects of saline, mannitol, and furosemide on acute decreases in renal function induced by radiocontrast agents. *N Engl J Med*. 1994;331:1416–1420.
8. 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.
9. 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.
10. Stevens MA, McCullough PA, Tobin KJ, et al. A prospective randomized trial of prevention measures in patients at high risk for contrast nephropathy: results of the P.R.I.N.C.E. Study: Prevention of Radiocontrast Induced Nephropathy Clinical Evaluation. *J Am Coll Cardiol*. 1999;33:403–411.
11. 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;83:260–263.
12. Rage D, Steegmuller U, Mikus G, et al. Dopamine infusion in healthy subjects and critically ill patients. *Clinical & Experimental Pharmacology & Physiology*. 1990;17:361-369.
13. Wang A, Holcslaw T, Bashore TM, et al. Exacerbation of radiocontrast nephrotoxicity by endothelin receptor antagonism. *Kidney Int*. 2000;57:1675–1680.
14. Tepel M, van Der Giet M, Schwarzfeld C, Laufer U, Liermann D, Zidek W. Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. *N Engl J Med*. 2000;343:180–184.
15. Tumlin J, Mathur VS. Fenoldopam prevents post–coronary angiography acute renal failure. Results from a randomized, double-blind, placebo-controlled trial. *J Vasc Interv Radiol*. 2000:11:175.