Radiocontrast Nephropathy: The Dye Is Not Cast

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A significant source of morbidity and inhospital mortality following percutaneous coronary intervention is radiocontrast-induced nephropathy. Newer strategies, such as using low-osmolar nonionic contrast agents and selective dopamine agonists, are making it possible to greatly reduce the incidence of postcatheterization nephropathy.
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Key words: Contrast media, adverse effects • Diabetes mellitus • Kidney failure, acute

Safety and effectiveness of coronary interventions improved in the 1990s with the introduction and popularization of coronary stent implantation and platelet inhibition with glycoprotein IIb/IIIa receptor antagonists. Yet dye-induced nephrotoxicity persisted for 2 reasons: a lack of good prevention options, and the fact that interventional cardiologists and radiologists assumed the risk to patients was inherent in procedures using contrast. Fenoldopam, a selective dopamine receptor agonist (DA_1) with special renal protective properties approved for the management of severe hypertension, has refocused our interest and renewed our efforts to prevent radiocontrast-induced nephropathy (RCIN).

Epidemiology

The public health importance of RCIN has increased commensurate with the use of contrast agents for an increasingly wider variety of diagnostic and therapeutic procedures. There are a variety of definitions of RCIN, based on increases in serum creatinine level. One of the more commonly accepted definitions is a greater-than-0.5-mg/dL increase in the serum creatinine level within 48 hours of contrast exposure.[1] Once RCIN occurs, renal function remains depressed for 1 to 3 weeks but returns to normal or near-normal in most cases.[2]

To identify the incidence of, and the iatrogenic factors associated with, the development of inhospital renal insufficiency, 2262 consecutive medical and surgical inpatients were evaluated prospectively.[3] Some degree of new renal insufficiency occurred in 4.9% of the 2216 patients at risk. After decreased renal perfusion and postoperative renal insufficiency, the radiographic contrast medium was most

Table 1
Risk Factors for Contrast-Associated Nephropathy

Confirmed	Suspected
Serum creatinine > 1.5 mg/dL	Hypertension
Diabetic nephropathy	Abnormal liver function tests
Class III/IV NYHA congestive heart failure	Age
	Gender
Multiple myeloma	Concomitant use of loop diuretics
Volume of contrast media	
Repeat dye in < 48 h	

NYHA, New York Heart Association.
Adapted from Porter. GA *Am J Cardiol*.[1]

often responsible for inhospital renal insufficiency.

In another study, following an adjustment for differences in comorbidity, the development of inhospital renal failure was associated with an odds ratio of dying of 5.5.[4] The inhospital mortality rate for patients in whom renal insufficiency develops is directly related to the magnitude increase of serum creatinine concentration. The mortality rate ranges from 3.8% with an increase in the serum creatinine level of 0.5 to 0.9 mg/dL to 64% with an increase of more than 3 mg/dL.[2]

In a case control study, the risk of death increased 6-fold, and the length of hospital stays doubled, in patients with hospital-acquired acute renal failure.[5] Renal failure in patients appears to increase the subsequent likelihood of death from nonrenal conditions, such as sepsis, hemorrhage, and respiratory failure.[4]

Trials have shown an incidence of RCIN ranging between 3.7% and 70%.[6-9] This variance depends on whether the study was performed in a prospective or retrospective fashion as well as on the number of predisposing risk factors in the studied population. With the progressive aging of the American population, the prevalence of predisposing risk factors for RCIN is increasing (Table 1). Since multiple risk factors can coexist in the same patient, it is difficult to determine precisely how much each contributes to the development of acute renal insufficiency. The most important risk factor seems to be the presence of any underlying renal insufficiency. The second most important risk factor appears to be the presence of diabetes.[10] Azotemic patients with diabetes seem to have the highest risk from exposure to contrast media.[11]

Davidson and colleagues[12] prospectively studied 1144 patients undergoing diagnostic cardiac catheterization to help determine the predictors and incidence of RCIN. These patients were exposed to an average dose of 203 mL of a nonionic contrast agent. Though a small increase in the serum creatinine level occurred in about 75% of patients, a rise of at least 0.5 mg/dL occurred in 6% of patients. Baseline renal insufficiency was the only predictor of RCIN. In a prospective evaluation of 378 patients undergoing angiography, renal failure (defined as a greater-than-1-mg/dL increase in the serum creatinine level) developed in 2% of patients with baseline serum creatinine levels lower than 1.5 mg/dL but in 30% of patients with baseline creatinine levels higher than 1.5 mg/dL.[9]

A relationship has been established between radiocontrast quantity and degree of renal dysfunction. In 1 study, every 5-mL increment in quantity of radiocontrast agent increased the risk of RCIN by 65% in patients with chronic renal insufficiency.[6] Other studies have not confirmed the relationship of contrast volume and RCIN.[12]

Since the risk of mortality and morbidity increases with relatively small increments in serum creatinine, changes in renal function, no matter how small, should not be regarded as inconsequential.

Pathophysiology

The pathophysiology of RCIN is a subject of active investigation. Radiocontrast agents stimulate the renin-angiotensin system[13] and block renal synthesis of the vasodilating antiplatelet prostaglandin prostacyclin.[14] Radiocontrast infusion results in a reduction of renal blood flow (Figure 1) and renal function. Several mechanisms have been suggested to explain the etiology of RCIN, including tubular ischemia,[15] direct toxic effect of contrast,[16] uric acid precipitation,[17] and red blood cell sludging.[18] The relatively rapid onset of oliguria, low fractional excretion of sodium, and rapid resolution of renal insufficiency are consistent with a renal tubular ischemia model. The effect of contrast on renal tubular perfusion is biphasic,

with an initial, brief renal vasodilator response lasting up to 20 minutes, followed by a more intense and longer-lasting vasoconstrictor effect that can last up to 2 hours.[19] The vasoconstriction phase is associated with a decrease in creatinine clearance and the development of hypoxia in the outer region of the kidney—the medullary thick ascending limb (MTAL) (Figure 2).

In an animal model of RCIN,[15] predisposed salt-depleted rats receiving an infusion of indomethacin and radiocontrast (sodium iothalamate) experienced renal failure and significant reductions in creatinine clearance. The onset of dye-induced acute renal failure correlated with injury to the MTAL cells of the kidney. These very metabolically active cells have high oxygen demands but are located remotely from oxygen supplies; as a result, they live in a hypoxic environment, making them particularly sensitive to perturbations in blood flow. Though the renal medulla comprises one third of the renal mass, it receives less than 10% of renal blood flow, resulting in low medullary partial pressures of oxygen of 10 to 20 mm Hg.[20] This leaves the medullary cells on the verge of hypoxia, even in an unperturbed state. In a rat model of RCIN, Nygren[21] found that ionic and nonionic contrast agents increased renal cortical blood flow by 20% but reduced medullary blood flow by 40%. This shunting of blood flow leaves medullary cells in a more hypoxic state, explaining the preponderance of injury in these deeper medullary structures.

Preservation of renal medullary blood flow is an adaptive response in patients with congestive heart failure, in whom renal vascular resistance is often increased and renal blood flow is decreased.[22] Maintaining medullary

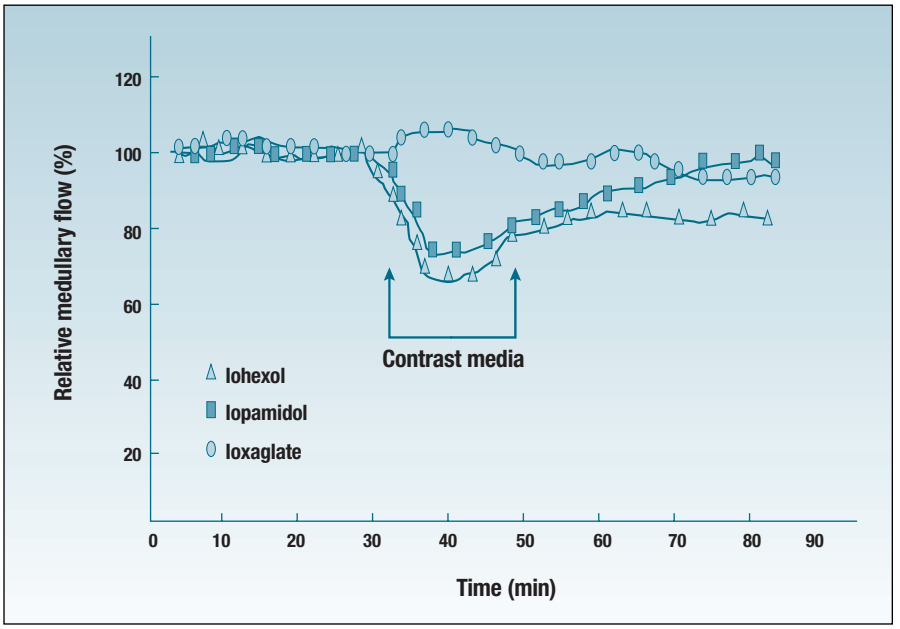

Figure 1. Medullary blood flow in a rat model following infusion of contrast medium. Those receiving ioxaglate had a moderate increase; those receiving iohexol or iopamidol had a moderate decrease. Adapted with permission from Nygren A.1989.[20]

blood flow, even with concomitant hypotension, is an adaptive response that may be mediated by local expression and activity of endothelin and nitric oxide. This response seems to guarantee against a diminution in medullary blood flow, which would result in medullary anoxia and deterioration of renal function.[23]

The effects of radiocontrast agents are 2-fold: they induce an osmotic diuresis (increasing the metabolic demand of the renal medullary tubules and, thereby, their oxygen consumption) and decrease the perfusion of the medullary region. This creates a significant oxygen supply-demand imbalance or an ischemic state. Based on the

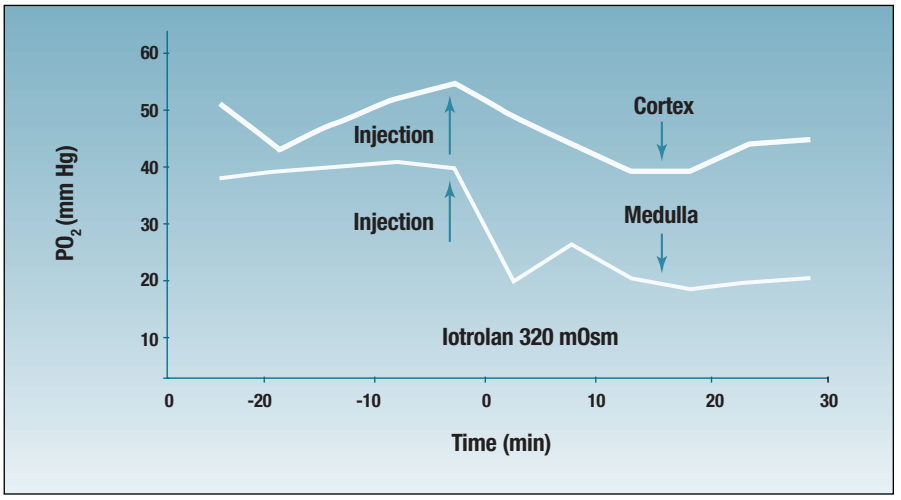

Figure 2. Preferential reduction by radiocontrast dye of oxygen saturation in the outer medulla. Adapted from Liss P. *Kidney Int.* 1998.[45]

sum of evidence available (most of which is based on animal models), RCIN seems to be mediated by the deep tubular injury that results from the shunting of renal blood flow away from the medulla to the renal cortex.

Prevention

A variety of interventions have been assessed to determine their roles in preventing RCIN. The use of low osmolar, nonionic contrast agents in patients with baseline renal insufficiency has been shown to modestly reduce the risk of RCIN. In a randomized trial of ionic and nonionic contrast in 1196 patients, acute nephrotoxicity was observed in 7% of patients receiving the ionic agent diatrizoate and in 3% using the nonionic agent iohexol ($P < .002$).[24] Differences in nephrotoxicity between the ionic and nonionic agents were only in patients with baseline renal insufficiency or in those with renal insufficiency and diabetes mellitus. In a prospective trial by Davidson and colleagues[12] of 1144 patients with a mean baseline creatinine of 1 mg/dL who were undergoing cardiac catheterization using a nonionic contrast agent, 8.3% of patients developed RCIN, with another 75% developing some degree of creatinine elevation from baseline levels.

Weisberg and coworkers[25] compared the effects of low-dose dopamine, atrial natriuretic peptide, mannitol, or saline in preventing RCIN in patients with chronic renal insufficiency (with and without diabetes mellitus) who were undergoing cardiac catheterization. Patients with diabetes who were randomized to receive either low-dose dopamine, atrial natriuretic peptide, or mannitol had worse outcomes than those randomized to receive saline alone. The outcome of this trial has eliminated the then-common practice of mannitol infusions during dye studies. The Prevention of Radiocontrast Induced Nephropathy Clinical Evaluation (PRINCE)[26] tested the hypothesis (in 98 patients with preexisting renal insufficiency) that forced diuresis while maintaining intravascular volume (by matching urine output with intravenous fluids) would reduce the rate of contrast-induced renal injury. There was no difference between study patients and controls in serum creatinine levels at 48 hours following dye infusion.

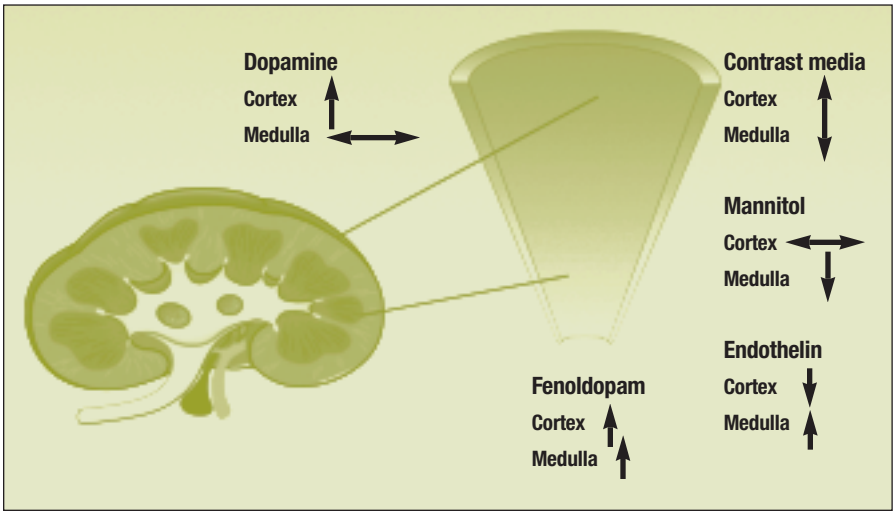

Figure 3. Varying effects of parenteral vasodilators on regional blood flow in the kidney. From Tumlin JT.1999.[46]

"Renal dose" dopamine has been proposed as a measure to prevent RCIN through its effect on tubular function,[27] renal vasodilatory effects,[28] and increased cardiac output.[29] In low doses (0.5 to 2.5 µg/kg/min), dopaminergic receptors are stimulated in the renal vasculature, resulting in vasodilation. At renal dose, dopamine increases glomerular filtration rates, renal blood flow, and sodium excretion.[28] At higher doses, dopamine will stimulate ß- and α-adrenergic receptors. A small, prospective, nonrandomized trial by Hall and colleagues[30] did show some renal protection with low-dose dopamine; however, this comparison consisted of only a subgroup of 24 patients with baseline creatinine levels higher than 2.0 mg/dL. A study by Hans and associates[31] revealed that dopamine administration for 12 hours following dye exposure resulted in a small improvement in renal function that was not sustained for more than 1 day. In a prospective, double-blind protocol,[32] 66 patients were randomized either to 120 mL/d of normal saline plus dopamine (2 µg/kg/min) or to saline alone. All patients received intravenous hydration 8 to 12 hours before, and 36 to 48 hours following, angiography with at least 100 mL/h of 0.45% saline. There was no beneficial effect of dopamine and, in the subset of patients with peripheral vascular disease, there was actually a deleterious effect. Previous disappointing results with low-dose dopamine and other vasodilators may be related to their inability to reverse the redistribution of renal blood flow from the cortex back to the renal medulla (Figure 3). In patients who developed RCIN, low-dose dopamine

used as a treatment resulted in significantly worse outcomes than did saline alone (Figure 4).[33] The only conclusion that can be drawn from the results of dopamine trials is the lack of a consistent clinical benefit in preventing RCIN.

A prospective trial by Solomon and colleagues[33] comparing the effects of saline, mannitol, and furosemide on renal function in patients with renal insufficiency who were undergoing cardiac catheterization showed that saline infusion alone was superior to either mannitol or forced diuresis with furosemide in preventing RCIN. The evaluation of the effectiveness of calcium channel blockers has been hampered by studies involving small numbers of patients and by differences in outcomes measures.[34] Abizaid and coworkers[35] showed no benefit to the use of aminophylline or dopamine in preventing RCIN (Figure 5). Diabetic persons appear to have a deficient endothelium-derived relaxing factor. This could explain the exaggerated renal vasodilation with dopamine, atrial natriuretic protein, and mannitol, all of which have endothelium-independent vasodilatory action.[36] Since the vasodilatation is predominantly in the cortical regions of the kidney, a medullary "steal" could develop that would reduce medullary oxygen tension, producing tubular ischemia and tubular dysfunction.

The above trials concerning prevention of RCIN have shown no consistent benefit from and, in some cases, have shown a deleterious effect with the use of dopamine, mannitol, forced diuresis with furosemide, atrial natriuretic protein, or aminophylline. Their use for this purpose, therefore, is not recommended, based on currently available data. There did seem to be some benefit from low-osmolality nonionic contrast agents in patients who had preexisting renal insufficiency as well as from volume repletion.

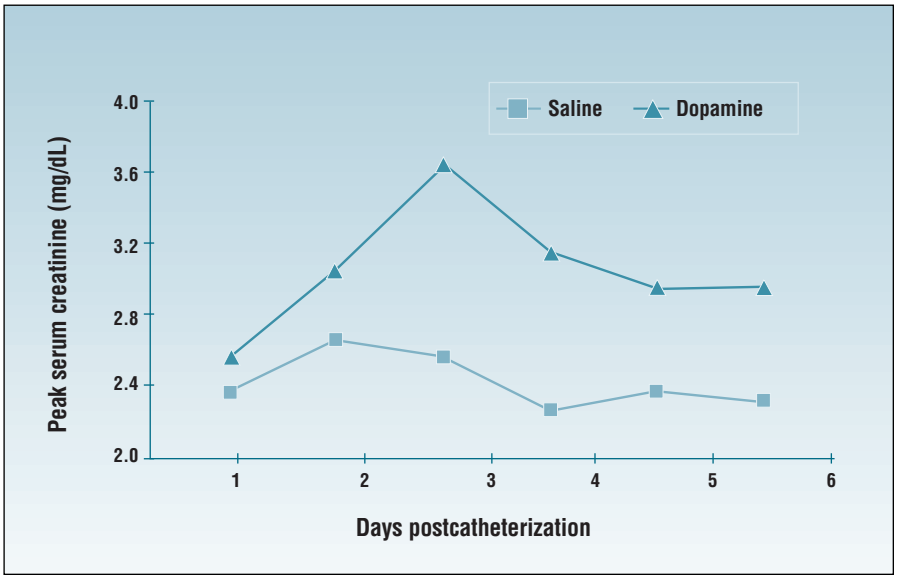

Figure 4. Effect of low-dose dopamine on patients who developed contrast-induced acute renal failure. Hospital stay was higher in the dopamine-treated group; 4 of the dopamine-treated patients required dialysis. Adapted from Abizaid AS et al. *Am J Cardiol*.[35]

Selective Dopamine Receptor Agonism

In 1979, Kebabian and Calne[37] classified the renal dopamine receptor into DA_1 and DA_2 subtypes. DA_1 receptor activation induces an increase in renal blood flow (most marked in the inner cortex and medulla) and increases the glomerular filtration rate (Table 2). Activation of the DA_2 receptor reduces renal blood flow and glomerular filtration rate. In contrast to dopamine, fenoldopam mesylate, a selective DA_1 receptor agonist, increased renal medullary blood flow, compared with cortical flow, in a hypotensive dog model.[38] Unlike dopamine, fenoldopam has no DA_2 and exerts no α- or ß-

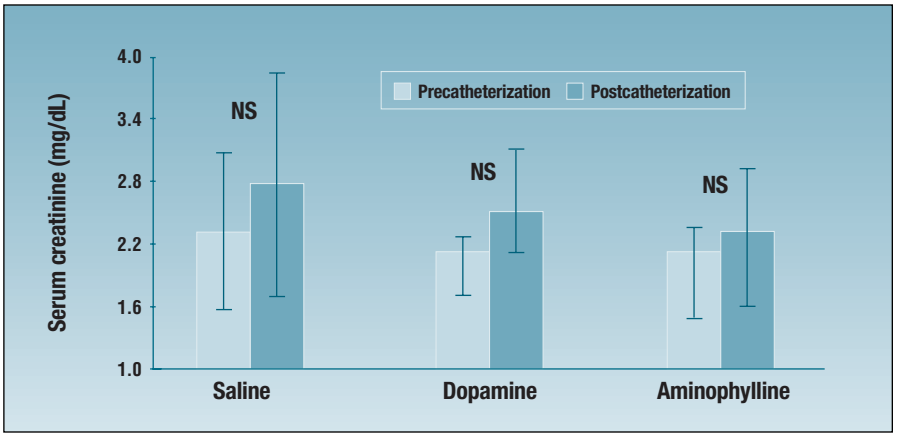

Figure 5. Failure of dopamine and aminophylline to prevent radiocontrast nephropathy in a study of 60 patients. Adapted from Abizaid AS et al. *Am J Cardiol*.[35]

adrenergic agonism.

In patients with hypertension and renal insufficiency, Cordingly and associates[39] and Woods and coworkers[40] found that blood pressure reduction with sodium nitroprusside was complicated by deterioration of renal function; however, fenoldopam demonstrates improved renal function during blood pressure reduction. Swan and colleagues[41] determined that a dose of fenoldopam of 0.03 µg/kg/min was associated with a significant increase in both renal blood flow and urine volume, without alterations in blood pressure or heart rate, in normotensive patients. The greatest increase in renal blood flow occurred at doses of fenoldopam between 0.03 and 0.1 µg/kg/min.[42] Higher doses (0.1 to 0.3 µg/kg/min) of fenoldopam (which, in hypertensive patients, reduces blood pressure) produced minimal cardiovascular changes in the normotensive group of patients. In a volume-depleted, anesthetized dog model, fenoldopam prevented reductions in glomerular filtration rate and blunted the maximal reduction in renal blood flow following infusion of diatrizoate sodium.[43] This confirmed the significant changes in renal function and blood flow that are due to contrast agent infusion as well as the ability to prevent these adverse changes with fenoldopam pretreatment.

At Cedars-Sinai Medical Center, fenoldopam was used in a group of 20 patients with high-risk characteristics undergoing diagnostic and/or interventional coronary procedures. The fenoldopam infusion was initiated in the cardiac catheterization laboratory before dye injection and was continued, at 0.1 µg/kg/min, for up to 4 hours following the procedure. In this group of patients, half of whom had diabetes as well as a mean serum creatinine level of 2.1 mg/dL, 2 patients (10%) developed a greater-than-0.5-mg/dL increase in the serum creatinine level following the procedure. This is a patient population in whom, historically, the incidence of RCIN would be as high as 30%. In an unpublished experience from Madyoon and colleagues (Stockton, Calif; personal communication), 21 patients with a mean serum creatinine level of 2.3 mg/dL underwent angiography. There was no significant change in renal function following the index procedure when patients received concurrent fenoldopam.

Because the ability of fenoldopam to lower blood pressure is predictable and stable with constant dose infusion, only standard blood pressure monitoring is required. Arterial line placement may not be needed. Ten clinical trials involving patients with severe hypertension were conducted safely without the use of invasive hemodynamic monitoring, including arterial lines. However, since this agent is an intravenous vasodilator, due caution should be observed while developing experience with it. Since the half-life of fenoldopam is about 4 to 5 minutes, steady state is achieved within 20 to 30 minutes.[44] Fenoldopam mesylate is not metabolized by cytochrome P-450 and has no major drug interactions.

Table 2
Activation and Renal Physiology of Dopaminergic Receptors

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

DA, dopamine agonist.
Adapted from Garwood S, Hines R. *Semin Anesthesia*.[47]

Practical Implications

The ability to more effectively prevent RCIN in high-risk patients will provide significant public health benefits as we reduce inhospital mortality rates, hospital stays, and the need for dialysis, while preserving baseline renal function. Patient convenience and medical care costs will also benefit from an effective strategy of RCIN prevention. Measures currently accepted to prevent RCIN include the following:

- Providing generous intravenous hydration, except in the presence of congestive heart failure.
- Avoiding postprocedural volume depletion.
- Avoiding the use of mannitol and furosemide in patients with renal insufficiency.
- Minimizing contrast volume use.
- Allowing a 5-day interval between 2 procedures using contrast media, when possible.

- Minimizing the development of hypotension and hypoxia.
- Eliminating the administration of nephrotoxic drugs, such as NSAIDs, in advance of procedures using radiocontrast.

Successful prevention of RCIN would diminish the mortality and morbidity associated with acute renal failure. Patient convenience and medical care costs would also be positively impacted by negating the need to admit patients before procedures for intravenous hydration, extend hospital stays to monitor renal function, and perform diagnostic and interventional procedures at separate sittings to minimize dye loads. ■

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Main Points

- Radiocontrast-induced nephropathy (RCIN) is a significant source of morbidity and inhospital mortality related to interventions in the cardiac catheterization laboratory.
- Patients at risk for RCIN include those with baseline renal insufficiency, especially in association with diabetes.
- The pathophysiology of RCIN seems to be related to both the renal vasoconstrictive effects and the shunting of blood from the medullary segments to the cortical segments, resulting in medullary ischemia and tubular injury; if this injury is severe, permanent loss of tubular function can result.
- There is no evidence that the use of mannitol, furosemide, aminophylline, natriuretic peptide, or low-dose dopamine provides any significant prophylactic benefit.
- The use of aggressive hydration strategies before contrast infusion has been shown to be important in preventing RCIN.
- Using low-osmolar nonionic contrast agents seems to benefit patients with preexisting renal insufficiency.
- Evidence is accumulating showing a potential benefit of fenoldopam, a selective DA_1, in preventing RCIN; a multicenter, randomized, blinded clinical trial assessing this hypothesis is planned.

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