Radiocontrast Nephropathy: Identifying the High-Risk Patient and the Implications of Exacerbating Renal Function

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Radiographic procedures using contrast media are widely performed throughout the world. This necessitates physicians' awareness of radiocontrast nephropathy—the disorder that develops as a result of exposure to contrast agents. Although in the general population the risk of radiocontrast nephropathy is rather low, it may be very high in selected subsets of patients. This article focuses on the incidence, pathogenesis, risk factors, and prognosis of radiocontrast nephropathy and provides important insights on its prevention.
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Key words: Radiocontrast nephropathy • Percutaneous coronary intervention • Contrast media • Renal failure • Serum creatinine • Dialysis

Within the last decades, radiological procedures utilizing contrast media are being widely applied for both diagnostic and treatment purposes. This has resulted in an increasing incidence of renal function impairment caused by the exposure to contrast material—an iatrogenic disorder known as radiocontrast nephropathy (RCN).

Radiocontrast Nephropathy: Definition and Incidence

The definition of RCN is based on an absolute or relative increase in creatinine level, compared to baseline value, after a patient has been exposed to a contrast agent, when alternative explanations for renal impairment have been excluded. RCN occurs within 24 to 48 hours after the exposure, with a typical peak creatinine level after 3 to 5 days and a return to baseline or near baseline in 1 to 3 weeks.[1] The degree of increase in creatinine in definitions used in various studies has a rather wide range (20%–50%),[2-6] making difficult the comparison of the results and the assessment of the true incidence of RCN. Today, perhaps, the most commonly used definition is a ≥ 25% increase, or an absolute increase of ≥ 0.5 mg/dL in serum creatinine from baseline value, at 48 to 72 hours after the exposure to contrast media.[6–9] Based on this definition, the overall incidence of contrast nephropathy in the general population is reported to be 1.2% to 1.6%.[3,8] According to the reports on the use of contrast media given to the U.S. Food and Drug Administration, the incidence of renal failure from 1990 through 1994 was 0.6% and 2.3% in the cases with high- and low-osmolar contrast media, respectively.[10]

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In selected subsets, however, especially in patients with cardiovascular pathology, the incidence of RCN is much higher. Based on the data registry of the Mayo Clinic of 7586 patients who underwent percutaneous coronary interventions (PCIs), the incidence of RCN was 3.3%.[11] In a smaller study, of 1826 patients, McCullough and colleagues[12] found that RCN among the same category of patients occurred in 14.5% of the patients. Dialysis as a result of RCN in these two series was required in 0.7% and 0.3%, respectively.

Pathogenesis of Radiocontrast Nephropathy

Experimental Model of Radiocontrast Nephropathy

Researchers continue to gain a greater understanding of the pathogenesis of RCN. In order to investigate the precise mechanisms of RCN and to assess methods to protect the kidneys, the researcher needs a reliable animal model of this disorder. Until now, most studies have been performed on the two following models: The first model uses Madin Darby canine kidney (MDCK) for studies of RCN in vitro[13-17]; the second model, for in vivo experiments, is a spontaneously hypertensive adult male rat. As was shown in studies by Duarte and associates,[18] this animal spontaneously develops renal lesions that progress with age, similar to those of radiocontrast-induced renal damage. Until now, several pathophysiological mechanisms of RCN have been proposed, including disturbed renal perfusion/hypoxia, direct toxicity to renal tubular epithelium, apoptosis, altered glomerular function, and immunologic mechanisms.[19]

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Cytotoxicity

Several studies have provided evidence that contrast media have direct cytotoxic effects on the renal structures.[20-23] Using the MDCK model of RCN, investigators showed that contrast media reduced several parameters of renal tubular-cell viability (transepithelial resistance, inulin permeability, and polarized cellular-enzyme release).[16] Contrast agents are also known to induce a cytotoxic effect in the form of redistribution of the tight-junction–associated membrane proteins into a cytoplasm,[17] as well as to cause cytoplasmic vacuolization along with lysosomal alteration in the proximal convoluted tubular cells and in the inner cortex.[24–27] Radiocontrast-induced, renal tubular-cell injury has been accompanied by significant decreases in tubule K^+, adenosine triphosphate, total adenine nucleotide, and basal and uncoupled respiratory rates, as well as significant increases in tubule Ca^{2+} content.[28]

An increased production of oxygen free radicals was documented in an experimental model of RCN.[29] Based on this finding, oxidant-mediated injury has been suggested as a mechanism of cytotoxic effect in the pathogenesis of RCN. Contrast agents were found to reduce the activity of the antioxidant enzymes catalase and superoxide dismutase in the renal cortex of volume-depleted rats.[30]

Lipid peroxidation of biological membranes is known to be implicated in tissue injury. Significant morphological alterations in proximal tubules along with an increase

in renal levels of malondialdehyde, a marker of lipid peroxidation, was found in rats after they were exposed to contrast media.[31]

The Role of Apoptosis

There is increasing evidence that apoptosis is involved in RCN as a result of cell injury. DNA fragmentation, a hallmark of apoptosis, and other morphologic characteristics of programmed cell death were documented in cardiac myocytes, in renal tubular and glomerular cells, and in vascular endothelial and smooth muscle cells of the heart and the kidneys in the rat model of RCN.[22]

Hizoh and colleagues,[13,14] using an MDCK-model, indicated that apoptosis of the renal tubular cell is a feature of RCN. The authors provided evidence that apoptosis is related to the hypertonicity of radiocontrast material. The finding is based on data showing that the highly hyperosmolar, ionic radiocontrast agent diatrizoate caused DNA fragmentation in renal epithelial cells in a way similar to other hyperosmolar solutions (mannitol and sodium chloride), albeit more prominently. In contrast, less hyperosmolar, nonionic iopamidol caused no detectable DNA breakdown.

Based on the assumption that a hyperosmolal, extracellular environment induces oxidative stress via reactive oxygen species, the same group tested the hypothesis that the antioxidants N-acetylcysteine and taurine decrease in vitro hypertonicity-induced apoptosis of renal epithelial cells. According to the results, N-acetylcysteine failed to reduce DNA fragmentation, whereas taurine attenuated it. Based on these results, the authors assumed that 1) antioxidant properties are not sufficient to produce a cytoprotective renal effect; and 2) taurine, a semiessential amino acid, may have a cytoprotective effect through properties other than antioxidation, presumably as an osmoregulator and/or intracellular Ca^{2+} flux regulator.

In another study, Horio and associates,[15] using an MDCK-model of RCN, documented that hypertonicity-induced cell death was accompanied by a pronounced increase in the activity of the 3rd, 8th, and 9th caspases, respectively. These cysteine proteases are considered today to be among the major executioners of programmed cell death.

Renal Hemodynamics

Hemodynamic changes resulting from the administration of contrast media were suggested as a contributory mechanism for the development of RCN. Most of the animal studies[32–37] documented decreases in renal blood flow (RBF) and glomerular filtration rate (GFR) after exposure to contrast media, compared to baseline. Perhaps more important than the effect on global RBF is the contrast-induced shunting of RBF from the relatively hypoxic medullary regions to the renal cortex.[38] This level of renal medullary hypoxia can result in ischemic injury or cellular necrosis. Two studies showed that the decrease in RBF and GFR may be prevented by the use of an adenosine α1-receptor antagonist.[33,34] This raises the question of possible adenosine involvement in the renal hemodynamic response to contrast media.

According to the study by Bakris and colleagues,[39] radiocontrast media induced a transient increase in RBF in dogs, followed by prolonged vasoconstriction. This vasoconstrictor phase was accompanied by a decrease in GFR. In this study, it was possible to reduce GFR further by using the dopamine-1 (DA_1) receptor antagonist Schering 23390. In these same dogs, pretreatment with the DA_1 receptor agonist fenoldopam fully attenuated the contrast-induced reduction of RBF and GFR. Hogstrom and coworkers[40] also found an initial increase in RBF after the administration of contrast media. In addition, the nonhomogeneity of flow in different capillaries of the renal cortex (increased in some capillaries, while decreased in the others) was observed by these authors.

As for human studies, the existing data are few and also conflicting. Using a thermodilution method, Weisberg and associates[41] assessed the effect of contrast media on RBF in a group of 12 patients. According to the results, mean RBF in the whole group tended to increase. However, a case-by-case analysis showed that in 4 out of 12 patients RBF primarily decreased below baseline, with further restoration in three of the cases. Another study by the same group showed that patients with diabetes mellitus have a significantly lower baseline RBF compared with patients without diabetes.[42] In a study by Russo and colleagues,[43] contrast media caused an immediate and progressive decline in renal plasma flow and GFR that was proportional to osmolality of the contrast material. In a study by Tumlin and coworkers,[6] confirming the ability of fenoldopam to prevent contrast-induced reductions in RBF in humans, reductions in RBF identified patients at higher risk for developing RCN.

Other Factors

Endothelin, a strong endogenous vasoconstrictor, may contribute to the pathogenesis of RCN. An increased level of serum endothelin is found both in animal models and in humans after exposure to contrast material.[44–46] The level of endothelin is especially high in patients with diabetes mellitus or impaired renal function.[47,48]

Table 1
Risk Factors for the Development of Radiocontrast Nephropathy (RCN)

Fixed (nonmodifiable) risk factors	Modifiable risk factors
Age	Volume of contrast media
Diabetes mellitus	Hemodynamic instability
Preexisting renal failure	Dehydration
Advanced congestive heart failure	Low serum albumin level (< 35 g/L)
Low left ventricle ejection fraction	Use of angiotensin-converting enzyme inhibitors
Acute myocardial infarction	Use of furosemide
Cardiogenic shock	Use of nonsteroidal anti-inflammatory drugs
Renal transplant	

Several studies raised the question of possible immunologic mechanisms in the genesis of RCN.[49,50] Based on the data that C5a of the complement system is unchanged whereas C3a is increased after contrast exposure, Gyoten[51] supposed that contrast agents activate the complement system through the alternative pathway by directly stimulating vascular endothelial cells. Of note, various radiocontrast agents have different complement activity.[52]

Risk Factors for Radiocontrast Nephropathy

Risk factors for the development of RCN have been thoroughly examined in several studies and are summarized in Table 1. By analogy with cardiovascular risk factors, those for RCN may be divided into two categories: fixed (nonmodifiable) and modifiable. Well-recognized nonmodifiable risk factors include older age,[4,53] diabetes mellitus,[11,54–56] preexistent renal insufficiency,[4,11,56,57] reduced left ventricle systolic function,[57,58] advanced heart failure,[2] acute myocardial infarction,[11] and shock.[11]

Age

The elderly are at increased risk of RCN,[4,8,53,59] with a reported incidence of 11%.[8] In multivariate analysis, age older than 70 years appeared to be an independent predictor of RCN.[53,59] The reasons why the elderly have a higher risk of developing RCN were not studied specifically and are likely multifactorial: eg, age-related changes in renal function (diminished GFR, tubular secretion, and concentration ability), more difficult vascular access following tortuosity and calcification of the vessels requiring greater amount of contrast, and the presence of renovascular disease.

Preexisting Renal Disease

Preexisting renal disease with an elevated level of serum creatinine is a crucial risk factor in the development of RCN. In patients with underlying renal disorder, the incidence is extremely high; reports range from 14.8% to 55.0%.[11,12,60–64] The data in our study confirm these dreadful statistics: despite preprocedural hydration and the use of nonionic contrast media, RCN occurred in one third of 439 consecutive patients with a baseline creatinine ≥ 1.8 mg/dL who underwent PCI.[58]

Of importance, the higher the baseline creatinine value, the greater the risk of RCN.[65] With a baseline plasma creatinine level ≤ 1.2 mg/dL, the risk of RCN is only 2.0%. In patients with creatinine values ranging from 1.4 to 1.9 mg/dL, however, the risk of RCN, compared with the previous group, increases five-fold (to 10.4%). As for patients with a baseline creatinine level ≥ 2.0 mg/dL, more than half of them (62.0%) subsequently develop RCN. On multivariate analysis, baseline creatinine represented an independent predictor of RCN in most of the studies.[11,56,66]

Concomitant use of nephrotoxic drugs (eg, cyclosporine) along with a higher prevalence of diabetes and renal insufficiency results in a high risk of RCN in patients with a renal transplant. Ahuja and colleagues[67] retrospectively assessed data on 144 patients with a functioning renal allograft who were exposed to contrast media. The incidence of RCN, which was 21.2% in the whole group, was especially high (42.8%) among those who had not received hydration before the procedure.

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Diabetes Mellitus

Diabetes mellitus is another well-recognized risk factor for contrast-induced nephropathy. With the high prevalence of diabetes in the general population and the increased incidence of vascular disease in this population—necessitating utilization of contrast—diabetic patients represent a significant proportion of those undergoing contrast exposure.[59] The incidence of RCN in diabetics varies from 5.7% to 29.4%.[3,53,54,64] Of note, in diabetics with preserved renal function and absence of other risk factors, including proteinuria, the rate of RCN is comparable to that in a healthy population.[3] Clinically important RCN usually occurs in subsets of diabetics who have underlying renal insufficiency[3,11] and/or in patients with albuminuria.[54] In a study by Berns,[1] for example, RCN occurred in 27% of diabetics with a baseline serum creatinine from 2.0 to 4.0 mg/dL and in 81% of those with a serum creatinine > 4.0 mg/dL. Among diabetic patients with severe underlying renal insufficiency, those who were especially prone to RCN had received larger amounts of contrast media, had lower intraprocedural mean arterial blood pressure, and had a reduced left ventricle ejection fraction (< 50%).[68]

The combination of diabetes and renal insufficiency presents a greater risk for RCN than either alone. The greater the number of risk factors for RCN, the greater the risk of developing RCN. In a study by Rich and Crecelius,[8] RCN occurred in 1.2% of the patients without risk factors, 11.2% of those with one risk factor (contrast volume > 200 mL, serum albumin level < 35 g/L, diabetes mellitus, serum sodium level < 135 mmol/L, and baseline creatinine level > 133 μmol/L), and in > 20% of the patients with two or more risk factors.

Volume of Contrast Media

The volume of contrast media administered during the procedure plays an important role in the development of RCN. The correlation between the amount of contrast media used and the risk of RCN was documented in a number of studies.[69,70] According to McCullough and colleagues,[12] the risk of RCN is minimal in patients receiving < 100 mL of contrast. However, according to different sources, the relatively safe cutoff point of contrast amount varies up to 220 mL.[7,59,71] Defining a "safe" level of contrast exposure is not possible at the present time as it will depend on the level of risk and patient-specific characteristics, such as body mass.

Advances in interventional cardiology have resulted in the treatment of more complex disease. This inevitably causes an increased use of contrast media per procedure and, consequently, enhances the risk of RCN. The rate of RCN among 228 patients with normal baseline creatinine levels who received high-load contrast media (250–800 mL) was 4.3%.[72] The incidence of RCN was even higher (11.0%) among 54 patients who received > 400 mL of contrast agent.[73] This either points to the lack of sensitivity of the serum creatinine relative to more precise assessments of kidney function, such as GFR, in identifying patients at risk, or to the potential toxicity of contrast agents, even in the "normal" kidney.

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Other Risk Factors

Several experimental and clinical studies recognized advanced congestive heart failure and compromised left ventricle systolic performance to be prognostic factors of RCN.[2,57,58,68,74,75] In addition, several drugs have been proposed to increase the risk of RCN.

Main Points

- Radiocontrast nephropathy (RCN) in the healthy population is rare.
- Preexisting renal insufficiency, diabetes mellitus, and older age are the main risk factors for RCN.
- The volume of administered contrast media is of great importance in the development of RCN.
- Multiple risk factors have an additive influence in the development of RCN.
- Patients with preexisting renal insufficiency who develop RCN after percutaneous coronary intervention have an unfavorable prognosis.
- To prevent the development of RCN, high-risk patients must be identified, and the use of contrast media must be maximally restricted.

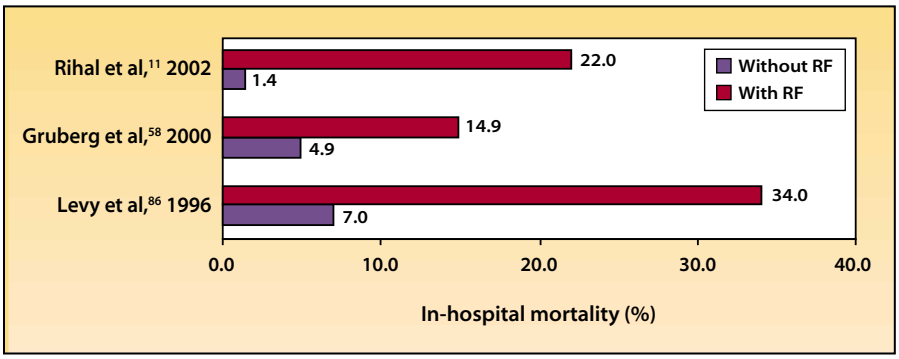


Figure 1. *Rates of in-hospital mortality in patients with radiocontrast nephropathy with and without preexisting renal failure (RF) in three retrospective studies.*

The role of angiotensin-converting enzyme inhibitors (ACEIs) has been controversial. In a study by Kini and colleagues,[59] patients receiving ACEIs had a significant increase in serum creatinine after the procedure, compared with patients without such therapy. However, prior use of ACEIs in this study predicted the occurrence of RCN only on univariate, but not on multivariate, analysis. According to the data in a study by Louis and associates,[76] the administration of ACEIs predicted RCN in diabetic patients. The use of furosemide was also defined as a predictive factor for RCN in the study by Moore and coworkers.[55]

The Type of Contrast Agent: Does It Matter?

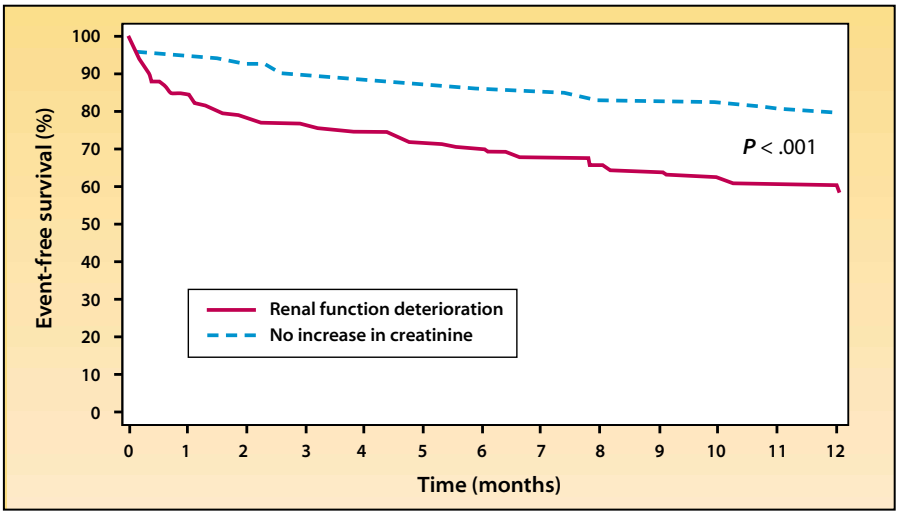
Controversy exists whether the use of different contrast agents is of any benefit in diminishing the risk of RCN. In the study by Katholie and colleagues,[77] the decrease in creatinine clearance was more pronounced and lasted longer in the group that received high-osmolar contrast media compared to the arm exposed to a low-molecular contrast agent. Harris and associates[78] also reported higher rates of RCN in patients who received high-osmolar (14%) compared with low-osmolar (2%) contrast media. In contrast, Schwab and colleagues,[79] Deray and associates,[80] and Barrett and coworkers[81] did not show any significant differences in nephrotoxic effect between the contrast agents they studied. In a meta-analysis of 45 trials, the study authors found that a greater increase in serum creatinine after administration of high-osmolar compared with low-osmolar contrast media was seen only in patients with preexisting renal failure.[82] Of note, even within the currently available low-osmolar contrast media, there are certain differences in nephrotoxic effect that seem to be more evident with ionic than nonionic agents.[83]

Despite still existing uncertainty regarding the degree of nephrotoxicity produced by various contrast agents, in current practice, nonionic low-osmolar contrast media are the preferred agents in patients with renal impairment. Further study is warranted to clarify the issue of minimizing renal damage while using the different contrast materials.

Prognosis of Radiocontrast Nephropathy

Today, RCN is one of the most common sources of acute renal failure among hospitalized patients.[84,85] RCN is associated with prolonged in-hospital stays, increased morbidity, mortality, and costs. In a retrospective analysis by Levy and colleagues[86] of 16,248 patients exposed to contrast media, the in-hospital mortality rates were almost five-fold higher (34.0%) in patients who developed RCN than in those without renal failure (7.0%) (Figure 1). The prognosis is especially unfavorable in patients with preexisting renal disease, those in whom contrast exposure causes further deterioration of renal function, and those on dialysis.[58,86,87] Reported in-hospital mortality rates in patients with further deteriora-

Figure 2. *Kaplan-Meier estimates of survival for groups with (solid line) and without (dashed line) renal function deterioration. Adapted, with permission, from Gruberg et al.[58]*



tion of renal function was 14.9% versus 4.9% in patients with preserved renal function,[58] and 27.5% in those who required dialysis.[87] In the recently published data from the Mayo Clinic registry,[11] in-hospital mortality in patients undergoing PCI and developing RCN was 22.0% compared with only 1.4% in patients without RCN (Figure 1). In-hospital mortality was especially high (36%) in patients who required dialysis following the radiocontrast procedure.[12]

The data in our study show that during the first year after exposure to contrast agents, the rates of mortality in patients with underlying renal disease remained very high (Figure 2), being 45.2% in patients requiring dialysis, 35.4% in patients with deterioration of renal function, and 19.4% in those with stable renal function.[58] According to a study reporting data from the Mayo Clinic PCI registry,[88] 1-year mortality correlated directly with creatinine clearance, being 1.5% in patients with a creatinine clearance ≥ 70 mL/min and 18.3% in individuals with a creatinine clearance < 30 mL/min.

Conclusions

Radiocontrast nephropathy is an iatrogenic disorder, resulting from exposure to contrast media. Contrast-induced hemodynamic and direct cytotoxic effects on renal structures are highly evident in its pathogenesis, whereas other mechanisms are still poorly understood. Although rare in the general population, RCN has a high incidence in patients with an underlying renal disorder, and in diabetics and the elderly. The risk factors are synergistic in their ability to produce RCN. Identifying the patient at risk will allow clinicians to implement risk-reducing protocols to prevent RCN. ■

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