Understanding the Consequences of Contrast-Induced Nephropathy

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Several investigations have discovered important physiologic links in the development of contrast-induced nephropathy (CIN). Studies using a canine kidney model showed that contrast media produce a direct cytotoxic effect on the renal structures. Also, there is increasing evidence that apoptosis is involved in CIN as a result of cell injury. It has been suggested that hemodynamic changes resulting from administration of contrast media may contribute to the development of CIN, although the data are not conclusive. Several vasoactive substances, such as endothelin, prostaglandins, nitric oxide, and adenosine, have been implicated in the pathogenesis of CIN, as have immune mechanisms. Several factors contribute to the development of CIN, including preexisting renal insufficiency, older age, diabetes mellitus, reduced left ventricular systolic function, advanced heart failure, acute myocardial infarction, and shock. The authors also present the risk score they developed to help clinicians identify patients with different responses to contrast exposure.

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Despite numerous experimental and clinical studies, pathogenesis of contrast-induced nephropathy (CIN) still is not entirely understood. The most important pathophysiologic links of CIN identified so far include direct toxicity to the renal tubular epithelium, apoptosis, disturbed renal hemodynamics, altered glomerular function, and immune mechanisms.

Direct Toxic Effect of Contrast Media

Using Madin-Darby canine kidney (MDCK) as a model of CIN, contrast media were shown to produce a direct cytotoxic effect on the renal structures. This was manifested in the form of reduction of transepithelial resistance, inulin permeability, polarized cellular enzyme release, and other parameters of renal tubular cell viability.[1] Contrast agents were shown also to induce cytotoxic effects in the form of redistribution of the tight junction–associated membrane proteins into a cytoplasm. In addition, contrast media were recognized to induce cytoplasmic vacuolization and lysosomal alteration in the proximal convoluted tubular cells and in the inner cortex.[2–5] Renal tubule cell injury after the exposure to contrast agents is accompanied by significant decreases in tubule potassium, adenosine triphosphate, total adenine nucleotide, and basal and uncoupled respiratory rates, as well as a significant increase in tubule Ca^{2+} content.[6] Importantly, repeated administration of contrast media compared with first exposure was shown to induce more severe damage of proximal tubular epithelia with prominent vacuolization, appearance of intracytoplasmic granular structure, and occasional cell necrosis, along with retarded recovery of the normal structure.[2]

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Enhanced production of oxygen free radicals has been documented in experimental rat models.[7] Subsequently, oxidant-mediated injury has been suggested as a mechanism of cytotoxic effect in pathogenesis of CIN. Contrast agents were found to reduce the activity of the antioxidant enzymes catalase and superoxide dismutase in the renal cortex of volume-depleted rats.[7]

Lipid peroxidation of biologic membranes is also implicated in tissue injury. Significant morphologic alterations in proximal tubules, along with elevated renal levels of malondialdehyde, a marker of lipid peroxidation, were found in rats after exposure to contrast media.[8]

There is much debate over whether contrast agents with lower osmolarity are of any benefit in diminishing the risk of CIN. Several studies in animals showed that high-osmolar contrast agents cause more prominent cytotoxic effects,[9,10] enzymuria,[11] and reductions in creatinine clearance[12] compared with low-osmolar contrast media. However, the study by Niu[2] using contrast media with various osmolarities failed to find significant histologic differences in degree of renal damage.

Several studies in animals showed that high-osmolar contrast agents cause more prominent cytotoxic effect, enzymuria, and creatinine clearance compared with low-osmolar contrast media.

The Role of Apoptosis

There is increasing evidence that apoptosis is involved in CIN as a result of cell injury. Fragmentation of DNA, a hallmark of apoptosis, and other morphologic characteristics of programmed cell death have been documented in cardiac myocytes and renal tubular, glomerular, vascular endothelial, and smooth muscle cells of the heart and kidneys in the rat model of CIN.[13] Using the MDCK model of CIN, it was demonstrated that hypertonicity-induced cell death was accompanied by pronounced increase in activity of 3rd, 8th, and 9th caspases. These cysteine proteases are considered today to be among the main executioners of programmed cell death.

One study provided evidence that apoptosis is related to the hypertonicity of radiocontrast material.[14] In this study, a highly hyperosmolar ionic radiocontrast agent, diatrizoate, caused DNA fragmentation in renal epithelial cells in a similar way to other hyperosmolar solutions (mannitol and sodium chloride), albeit more pronounced. The less hyperosmolar, nonionic agent, iopamidol, however, caused no detectable DNA breakdown. Based on the assumption that a hyperosmolar extracellular environment induces oxidative stress via reactive oxygen species, the same group investigated whether antioxidants (N-acetylcysteine and taurine) are able to decrease hypertonicity-induced apoptosis of renal epithelial cells.[14] The results showed that N-acetylcysteine failed to reduce DNA fragmentation *in vitro*, whereas taurine attenuated it. Based on this, the authors concluded that antioxidant properties are not sufficient for cytoprotective renal effect

and that taurine, a semiessential amino acid, may have cytoprotective effect through properties other than antioxidation, presumably as osmoregulator and/or intracellular Ca^{2+} flux regulator.[14]

Renal Hemodynamics

Hemodynamic changes resulting from administration of contrast media have been suggested as a contributory mechanism for the development of CIN. However, the data on this issue are scant and inconclusive.

Most animal studies have documented decrease in renal blood flow (RBF) and glomerular filtration rate (GFR) after the exposure to contrast media compared with baseline.[15–17] Rats exposed to contrast material were shown to have reduction in renal medullary blood flow along with decrease in red blood cell velocity and oxygen tension.[16,17] Importantly, the decrease in GFR and renal plasma flow after contrast media injection has been found to be more pronounced in dehydrated rats compared with animals with euvolemic fluid condition, indicating that dehydration enhances the adverse effect of contrast media on renal hemodynamics.[18] In dogs, radiocontrast media induced a transient increase in RBF, followed by prolonged vasoconstriction.[19] The vasoconstrictor phase was accompanied by a decrease in GFR. Notably, it was possible to reduce GFR further through the use of a dopamine-1 receptor antagonist, and to improve it by the use of the selective dopamine-1 receptor agonist fenoldopam.

The decrease in GFR and renal plasma flow after contrast media injection has been found to be more pronounced in dehydrated rats compared with animals with normal fluid condition, indicating that dehydration enhances the adverse effect of contrast media on renal hemodynamics.

Sunnegardh and colleagues[20] investigated the systemic, pulmonary, and renal hemodynamic effects of two contrast media with various osmolarity intravenously infused in pigs. Both contrast agents induced a significant increase in mean arterial, right atrial, pulmonary arterial, and pulmonary wedge pressure, along with an increase in cardiac output and a decrease in systemic vascular and pulmonary vascular resistance. However, no significant changes in renal blood flow and renal vascular resistance have been observed.

In isolated human renal arterial segments obtained from tumor nephrectomy specimens, contrast media caused relaxation and not constriction of the renal arterial rings. Based on these data, it has been assumed that contrast agents probably have no direct vasoconstrictive effect on vascular smooth muscle and that vasoconstriction is hormone mediated.[21]

As for human studies, the data are few and also conflicting. Using the thermodilution method, Weisberg and associates[22] assessed the effect of contrast media on RBF in a group of 12 patients. Overall, the mean RBF in the whole group tended to increase. However, case-by-case analysis showed that in 4 of 12 patients, RBF primarily decreased below baseline, with further restoration in three cases. In a study by Russo and coworkers,[23] contrast media caused an immediate and progressive decline in renal plasma flow and GFR that was proportional to osmolarity of contrast material.

Vasoactive Substances Believed to Be Involved in the Pathogenesis of CIN

Endothelin

An increased serum level of endothelin, a strong endogenous vasoconstrictor, has been found after exposure to contrast material both in animal models and in humans, and the level is especially high in patients with diabetes mellitus or impaired renal function.[24–26] Pollock and colleagues[27] studied the effect of endothelin receptor blockade in a rat model of CIN. When indomethacin, N(varpi)-nitro-L-arginine methyl ester (L-NAME), or the contrast agent diatrizoate was administered without A-127722, an endothelin receptor antagonist, rats displayed typical signs of nephrotoxicity. On the contrary, A-127722 has been shown to prevent, in a dose-dependent manner, the rise in protein excretion and plasma serum creatinine.

Prostaglandins and Nitric Oxide

There is some evidence of a protective role of prostaglandins and nitric oxide (NO) in the genesis of CIN. Inhibition of NO production resulting from the direct effect of nonionic contrast media on the endothelium has been demonstrated in the isolated arterial preparations in rabbits and dogs.[28] Administration of indomethacin or L-NAME before contrast exposure has been shown to cause vasoconstriction with a prolonged significant reduction in medullary blood flow in rats.[29] A decreased level of medullary oxygenation in rats as a result of inhibition of prostaglandins and NO, as well as after intravenous administration of contrast media, also has been reported.[30,31]

Adenosine

Increased release of renal adenosine and stimulation of renal adenosine receptors have been proposed to be important mechanisms in the development of CIN.[32,33] Some authors attribute the higher incidence of CIN in diabetic patients following contrast exposure to the higher sensitivity of the renal vasculature to adenosine because experimental studies showed increased adenosine-induced vasoconstriction in the kidneys of diabetic animals.[33] The decrease in RBF and GFR following contrast administration has been shown to be prevented by an adenosine A1 receptor antagonist.[15]

It is of note that various radiocontrast agents have been shown to cause different complement activity.

Immune Mechanisms

Several studies have raised the question of possible immune mechanisms in the genesis of CIN.[34–37] Based on data showing that C5a of the complement system is unchanged, whereas C3a is increased after contrast exposure, Gyoten[37] suggested that contrast agents activate complement through the alternative pathway by directly stimulating vascular endothelial cells. It is of note that various radiocontrast agents have been shown to cause different complement activity.[35]

Epidemiology of CIN

Based on the definition of CIN as an increase of ≥ 25% or an absolute increase of ≥ 0.5 mg/dL in serum creatinine from baseline value at 48–72 hours after exposure to contrast media, the overall incidence of CIN in the general population is estimated to be 1.2%–1.6%.[38,39] According to the information on contrast media use made available to the U.S. Food and Drug Administration, the incidence of renal failure from 1990 through 1994 ranged from 0.6%–2.3%.[40] Still, it is important to recognize that in selected subsets, (especially in patients with cardiovascular pathology) the incidence of CIN is much higher. Based on the data of the Mayo Clinic registry, including 7586 patients treated with percutaneous coronary interventions (PCI), the incidence of CIN was 3.3%.[41] In a smaller study of 1826 patients undergoing PCI, CIN occurred in 14.5% of the cases.[42] Dialysis as a result of CIN in these two series was required in 0.7% and 0.3%, respectively.

Risk Factors for CIN

A listing of risk factors for CIN can be found on page S6 in the previous article by Dr. McCullough. The most important of these factors include preexistent renal insufficiency, older age, diabetes mellitus, reduced left ventricular systolic function, advanced heart failure, acute myocardial infarction, and shock.

Preexisting renal disease with elevated creatinine is the most important risk factor in the development of CIN. In patients with underlying renal disorders, CIN rates are extremely high, ranging from 14.8%–55%.[41,42] Importantly, the risk of CIN is directly proportional to the baseline creatinine value. If baseline serum creatinine level is 1.2 mg/dL or less, the risk of CIN is only 2%.[43] In patients with serum creatinine in the range of 1.4–1.9 mg/dL, the risk of CIN compared with the previous group increases fivefold (10.4%). As for patients with a baseline creatinine level of 2.0 mg/dL or greater, over half (62%) subsequently develop CIN. Our data showed that despite preprocedure hydration and the use of nonionic contrast media, CIN occurred in one third of 439 consecutive patients who underwent PCI and had baseline serum creatinine of 1.8 mg/dL or more.[44] Using multivariate analysis, baseline serum creatinine was identified as an independent predictor of CIN.[41]

Diabetes mellitus is another well-recognized risk factor for CIN. The incidence of CIN in diabetic patients varies from 5.7%–29.4%.[38,45,46] Importantly, in diabetics with preserved renal function and absence of other risk factors, the rates of CIN are similar to those in healthy individuals,[38] whereas clinically significant CIN usually occurs in the subset of diabetics with underlying renal insufficiency.[40,41,43] This is well demonstrated in the study by Lautin and associates,[43] reporting that the incidence of CIN was rather low (2%) in patients with neither diabetes nor azotemia, significantly higher (16%) in individuals with diabetes but preserved renal function, and much higher (38%) in

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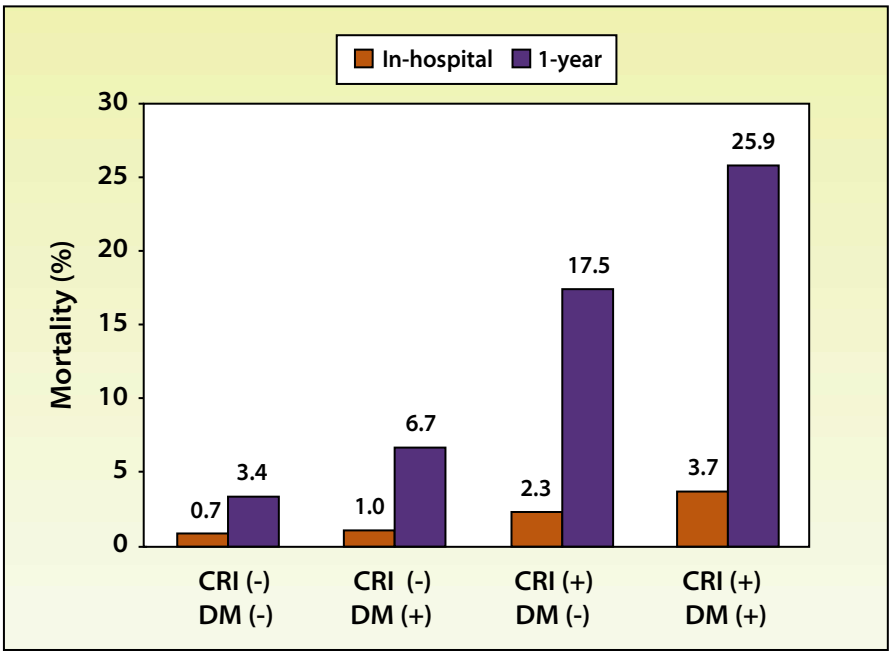

Figure 1. *In-hospital and 1-year mortality after percutaneous coronary intervention in patients with (+) or without (–) chronic renal insufficiency (CRI) and diabetes mellitus (DM).*

patients who had both diabetes and azotemia. The study by Berns[47] confirmed the correlation between the degree of renal impairment and the incidence of CIN in the diabetic population: 27% in patients with baseline serum creatinine of 2.0–4.0 mg/dL and 81% in those with serum creatinine > 4.0 mg/dL.

We further analyzed the impact of diabetes, chronic renal insufficiency (CRI), or both in 7445 consecutive patients treated with PCI by stratifying the patients into four groups (Figure 1): low-risk patients who had neither CRI nor diabetes had very low rates of hospitalization and 1-year mortality after PCI (0.7% and 3.4%, respectively); patients with diabetes but without CRI had in-hospital and 1-year death rates similar to the previous group (1.0% and 6.7%, respectively); patients with CRI but without diabetes had significantly increased rates of mortality compared with the previous groups (2.3% and 17.5%, respectively); and patients with both diabetes and CRI had further increases of in-hospital and 1-year mortality (3.7% and 25.9%, respectively) [unpublished data].

The elderly are at increased risk of CIN, with reported incidence of 11%.[39,48–50] The reasons for this higher risk have not been studied specifically but are probably multifactorial, including age-related changes in renal function, the presence of multivessel disease, and more difficult vascular access due to tortuosity and calcification of the vessels requiring relatively larger amounts of contrast.

The volume of contrast media administered during the procedure is of primary importance in the development of CIN, and it is the main modifiable risk factor. The correlation between amount of contrast and risk of CIN has been documented in several studies. According to McCullough and colleagues,[42] the risk of CIN is minimal in patients receiving less than 100 mL of contrast. However, according to different sources, the relatively safe cutoff amount for contrast may be as high as 220 mL.[49,51,52]

As mentioned previously, there is much uncertainty over whether the use of contrast agents with a different osmolarity, ie, different concentration of osmotically active particles, is of any benefit in diminishing the risk of CIN. In a meta-analysis of 45 trials, the greater increase in serum creatinine after administration of high- compared with low-osmolar contrast media was seen only in patients with pre-existing renal failure.[53]

The controversy also exists over whether the use of nonionic versus ionic contrast agents is of any benefit in diminishing the risk of CIN. The incidence of nephrotoxicity occurring with the nonionic contrast agent iohexol and the ionic contrast agent diatrizoate was compared in 1196 patients undergoing angiography in a prospective, randomized, double-blind multicenter trial by Rudnick and associates.[54] CIN was observed in 7% of patients receiving diatrizoate compared with 3% of patients receiving iohexol ($P < .002$). However, the differences in nephrotoxicity between the two groups were confined to patients with pre-existing impaired renal function. These results were corroborated in a randomized study by Taliercio and coworkers[55] showing that the degree of renal function deterioration in high-risk patients (serum creatinine ≥ 1.5 mg/dL) was less pronounced in the group exposed to nonionic (iopamidol) versus ionic (diatrizoate) contrast. On the other hand, a randomized study by Schwab and colleagues[56] failed to show a significant difference in rates of CIN in the group exposed to iopamidol versus nonionic diatrizoate, either in low- or high-risk patients.

The recent randomized, double-blind, prospective, multicenter Nephrotoxicity in High-Risk Patients Study of Iso-osmolar and Low-Osmolar Non-Ionic Contrast Media (NEPHRIC) trial[57] provided evidence that CIN may be less likely to develop in high-risk patients when the iso-osmolar contrast medium (IOCM) iodixanol is used rather than the low-osmolar contrast medium (LOCM) iohexol. In this study, the mean rise in creatinine from day 0 to 3 was significantly lower in the IOCM versus the LOCM group (0.13 mg/dL versus 0.47 mg/dL, respectively; $P = .001$). The same was true regarding the proportion of patients with increased serum creatinine > 0.5 mg/dL (3% and 25%, respectively; $P = .003$).

Several pharmacologic agents (eg, nonsteroidal anti-inflammatory drugs, cyclosporines, and cisplatin) have been shown to exacerbate the nephrotoxic effects of contrast media.[58–60]

Implications of CIN

Today, CIN is one of the most common causes of acute renal failure among hospitalized patients. Several studies demonstrated the close relationship between contrast-induced renal failure and prognosis after PCI.[61–62] It is associated with increased morbidity, mortality, hospitalization, and cost. In a retrospective analysis of 16,248 patients exposed to contrast media, in-hospital mortality rates were almost fivefold higher in patients who developed CIN (34%) compared with those without renal failure (7%).[63] Similarly, in our study, patients with CIN versus those without CIN had significantly elevated rates of hospitalization (4.7% vs 0.9%, respectively) and 1-year mortality (32.3% vs 13.9%) (Table 1).[64]

Table 1
Contrast-Induced Nephropathy (CIN): Outcomes and Resource Utilization

Outcomes	Patients		*P* value
	With CIN	Without CIN	
In-hospital death, %	4.7	0.9	.0003
In-hospital cardiac death, %	2.4	0.7	.07
In-hospital other death, %	2.4	0.2	.004
In-hospital length of stay, days	9.6 ± 7.2	4.9 ± 6.4	<.0001
ICU length of stay, days	2.3 ± 4.4	0.6 ± 1.8	<.0001
Need for hemodialysis, %	12	0	<.0001
1-year death, %	32.3	13.9	<.0001

Adapted from Iakovou et al.[64]

The prognosis is especially unfavorable in patients with preexisting renal disease, in whom contrast material causes further deterioration of renal function, and those on dialysis.[45,63] In-hospital mortality in these subsets was 14.9% and 27.5%, respectively, versus 4.9% in patients with preserved renal function.[45,61] In a study from the Mayo Clinic, in-hospital mortality in patients undergoing PCI and developing CIN was 22% versus only 1.4% in patients without CIN.[41] According to the data of McCullough and coworkers,[42] in-hospital mortality in patients requiring dialysis after the radiocontrast procedure was as high as 36%.

During the first year after exposure to contrast, mortality rates in patients with underlying renal disease remain very high at 45.2% in patients dependent on dialysis and 35.4% in patients with deterioration of renal function not requiring dialysis, compared with 19.4% in patients with no further exacerbation of renal function.[45] The study by Rihal and colleagues[41] analyzing data from 7586 consecutive patients further showed that even 5 years after PCI, the adjusted combined risk of death or myocardial infarction was significantly higher in patients who developed acute renal failure after PCI compared with those who did not ($P < .0001$).

According to the Mayo Clinic PCI registry, 1-year mortality correlates directly with creatinine clearance and is 1.5% in individuals with creatinine clearance ≥ 70 mL/min and 18.3% in patients with creatinine clearance ≤ 30 mL/min.[62] The study of Gruberg and associates[45] analyzed independent predictors of poor outcomes after PCI and showed that newly instituted dialysis was the strongest predictor of 1-year mortality, with an odds ratio of 4.15.

Regardless of revascularization method, the management of patients developing acute renal failure is associated with high resource utilization. In a Multicenter Study of Perioperative Ischemia Research Group on 2222 patients who underwent coronary artery bypass grafting, the length of hospitalization was dramatically longer in patients who developed acute renal failure compared with those with intact renal function.[65] The presence of acute renal failure more than doubled the

length of stay in the intensive care unit in patients undergoing coronary artery bypass surgery (6.8 and 3.1 days in patients with and without acute renal failure, respectively). As expected, patients requiring dialysis had especially prolonged periods of hospitalization in the intensive care unit (mean 15.4 days). Similar relationships were observed when the length of hospitalization in the general medical ward was analyzed. Similarly, in patients treated with PCI, the development of CIN was associated with markedly increased length of hospitalization (9.6 vs 4.9 days in patients with vs without CIN) (Table 1).[64]

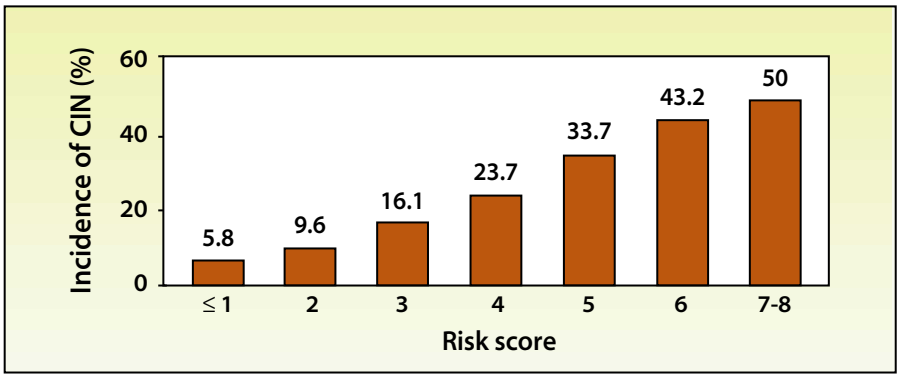

Figure 2. *Risk score in the assessment of contrast-induced nephropathy (CIN). Adapted with permission from Mehran et al.*[66]

Integral Prediction of CIN: Risk Score

It is important to recognize that apart from the known unfavorable combination of diabetes and renal insufficiency, the presence of two or more other risk factors for CIN further influences rates of CIN. In the study by Rich and Crecelius,[39] CIN occurred in 1.2% of 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, baseline creatinine level > 133 μmol/L), and in more than 20% of those with two or more risk factors.

This dictates the integral assessment of the impact of these variables on the development of CIN. We therefore developed a simple risk score that can be readily applied by clinicians to identify patients with different responses to contrast exposure.[66] Using our database of patients treated with PCI, the following variables were chosen by a stepwise logistic regression as predictors of postprocedure CRI: age, gender, diabetes mellitus, acute coronary syndrome as an indication for PCI, intervention on more than one vessel and/or on saphenous vein graft, creatinine clearance < 50 mL/min, and use of an intra-aortic balloon pump. After assigning each of the multivariate predictors a risk score, we found that the incidence of CIN increased in a linear fashion ($P < .0001$) as the risk score increased (Figure 2). The proposed risk score model is currently being validated on other databases. ■

References

1. Haller C, Schick CS, Zorn M, Kubler W. Cytotoxicity of radiocontrast agents on polarized renal epithelial cell monolayers. *Cardiovasc Res*. 1997;33:655–665.
2. Niu G. Experimental histopathological studies of renal lesions induced by high- or low-osmolality contrast media [Japanese]. *Nippon Ika Daigaku Zasshi*. 1993;60:390–405.
3. Rees JA, Old SL, Rowlands PC. An ultrastructural histochemistry and light microscopy

Main Points

- In several studies, it was shown that contrast media have a direct cytotoxic effect on renal structures. Whether radiocontrast agents with high osmolarity are more damaging than those with lower osmolarity is still being debated.
- Several vasoactive substances are believed to be involved in the pathogenesis of contrast-induced nephropathy (CIN), including endothelin, prostaglandins, nitric oxide, and adenosine. Immune mechanisms have also been implicated.
- The overall incidence of CIN in the general population is 1.2%–1.6%. However, in selected subsets, such as patients with cardiovascular pathology, the rates are much higher.
- The most important risk factor in the development of CIN is preexisting renal disease. Other predisposing factors are diabetes mellitus, older age, and volume of radiocontrast agent used.
- The NEPHRIC trial provided evidence that CIN may be less likely to develop in high-risk patients when the iso-osmolar agent iodixanol is used instead of the low-osmolar agent iohexol.
- Several studies demonstrated a close relationship between contrast-induced renal failure and prognosis after percutaneous coronary interventions (PCI). It is associated with increased morbidity, mortality, length of hospital stay, and cost.

study of the early development of renal proximal tubular vacuolation after a single administration of the contrast enhancement medium 'Iotrolan.' *Toxicol Pathol*. 1997;25:158–164.
4. Tervahartiala P, Kivisaari L, Kivisaari R, Virtanen I. Contrast media-induced renal morphologic lesions in diabetic rats. *Acta Radiol*. 1993;34:220–225.
5. Tervahartiala P, Kivisaari L, Kivisaari R, et al. Structural changes in the renal proximal tubular cells induced by iodinated contrast media. *Nephron*. 1997;76:96–102.
6. Humes HD, Hunt DA, White MD. Direct toxic effect of the radiocontrast agent diatrizoate on renal proximal tubule cells. *Am J Physiol*. 1987;252:F246–F255.
7. Yoshioka T, Fogo A, Beckman JK. Reduced activity of antioxidant enzymes underlies contrast media-induced renal injury in volume depletion. *Kidney Int*. 1992;41:1008–1015.
8. Parvez Z, Rahman MA, Moncada R. Contrast media-induced lipid peroxidation in the rat kidney. *Invest Radiol*. 1989;24:697–702.
9. Potier M, Lagroye I, Lakhdar B, et al. Comparative cytotoxicity of low- and high-osmolar contrast media to human fibroblasts and rat mesangial cells in culture. *Invest Radiol*. 1997;32:621–626.
10. Schick CS, Haller C. Comparative cytotoxicity of ionic and non-ionic radiocontrast agents on MDCK cell monolayers in vitro. *Nephrol Dial Transplant*. 1999;14:342–347.
11. Haragsim L, Zima T. The preventive effect of calcium-channel blockers (nifedipine, verapamil) on the tubular toxicity of radiographic contrast media (Verografin, Hexabrix) [Czech]. *Cas Lek Cesk*. 1993;132:737–742.
12. Idee JM, Santus R, Beaufils H, et al. Comparative effects of low- and high-osmolar contrast media on the renal function during early degenerative gentamicin-induced nephropathy in rats. *Am J Nephrol*. 1995;15:66–74.
13. Zhang J, Duarte CG, Ellis S. Contrast medium- and mannitol-induced apoptosis in heart and kidney of SHR rats. *Toxicol Pathol*. 1999; 27:427–435.
14. Hizoh I, Strater J, Schick CS, et al. Radiocontrast-induced DNA fragmentation of renal tubular cells in vitro: role of hypertonicity. *Nephrol Dial Transplant*. 1998;13:911–918.
15. Erley CM, Heyne N, Rossmeier S, et al. Adenosine and extracellular volume in radiocontrast media-induced nephropathy. *Kidney Int*. 1998;67(Suppl):S192–S194.
16. Liss P, Nygren A, Olsson U, et al. Effects of contrast media and mannitol on renal medullary blood flow and red cell aggregation in the rat kidney. *Kidney Int*. 1996;49:1268–1275.
17. Liss P. Effects of contrast media on renal microcirculation and oxygen tension. An experimental study in the rat. *Acta Radiol Suppl*. 1997;409:1–29.
18. Nygren A, Ulfendahl HR. Effects of high- and low-osmolar contrast media on renal plasma flow and glomerular filtration rate in euvolaemic and dehydrated rats. A comparison between ioxithalamate, iopamidol, iohexol and ioxaglate. *Acta Radiol*. 1989;30:383–389.
19. Bakris GL, Lass NA, Glock D. Renal hemodynamics in radiocontrast medium induced renal dysfunction: a role for dopamine-1 receptors. *Kidney Int*. 1999;56:206–210.
20. Sunnegardh O, Hietala SO, Wirell S, Ekelund L. Systemic, pulmonary and renal haemodynamic effects of intravenously infused iopentol. A comparison in the pig of a new low osmolar non-ionic medium with saline and iohexol. *Acta Radiol*. 1990;31:395–399.
21. Uder M, Humke U, Pahl M, et al. Nonionic contrast media iohexol and iomeprol decrease renal arterial tone: comparative studies on human and porcine isolated vascular segments. *Invest Radiol*. 2002;37:440–447.
22. Weisberg LS, Kurnik PB, Kurnik BR. Radiocontrast-induced nephropathy in humans: role of renal vasoconstriction. *Kidney Int*. 1992;41:1408–1415.
23. Russo D, Minutolo R, Cianciaruso B, et al. Early effects of contrast media on renal hemodynamics and tubular function in chronic renal failure. *J Am Soc Nephrol*. 1995; 6:1451–1458.
24. Duarte CG, Zhang J, Ellis S. Effects of radiocontrast and endothelin administration on systolic blood pressure and renal damage in male spontaneously hypertensive and Wistar Kyoto rats with phentolamine-induced adrenergic blockade. *Invest Radiol*. 1998;33:104–112.
25. Clark BA, Ducksoo K, Epstein FH. Endothelin and atrial natriuretic peptide levels following radiocontrast exposure in humans. *Am J Kidney Dis*. 1997;30:82–86.
26. Heyman SN, Clark BA, Kaiser N, et al. Radiocontrast agents induce endothelin release in vivo and in vitro. *J Am Soc Nephrol*. 1992;3:58–65.
27. Pollock DM, Polakowski JS, Wegner CD, Opgenorth TJ. Beneficial effect of ETA receptor blockade in a rat model of radiocontrast-induced nephropathy. *Ren Fail*. 1997;19:753–761.
28. Hutcheson IR, Griffith TM, Pitman MR, et al. Iodinated radiographic contrast media inhibit shear stress- and agonist-evoked release of NO by the endothelium. *Br J Pharmacol*. 1999; 128:451–457.
29. Agmon Y, Peleg H, Greenfeld Z, et al. Nitric oxide and prostanoids protect the renal outer medulla from radiocontrast toxicity in the rat. *J Clin Invest*. 1994;94:1069–1075.
30. Prasad PV, Priatna A, Spokes K, Epstein FH. Changes in intrarenal oxygenation as evaluated by BOLD MRI in a rat kidney model for radiocontrast nephropathy. *J Magn Reson Imaging*. 2001;13:744–747.
31. Heyman SN, Brezis M, Epstein FH, et al. Early renal medullary hypoxic injury from radiocontrast and indomethacin. *Kidney Int*. 1991; 40:632–642.
32. Oldroyd SD, Fang L, Haylor JL, et al. Effects of adenosine receptor antagonists on the responses to contrast media in the isolated rat kidney. *Clin Sci (Lond)*. 2000;98:303–311.
33. Pflueger A, Larson TS, Nath KA, et al. Role of adenosine in contrast media-induced acute renal failure in diabetes mellitus. *Mayo Clin Proc*. 2000;75:1275–1283.
34. Hoffmeister HM, Fuhrer G, Pirschel J, Heller W. Changes in the kallikrein-kinin and complement system in angiography using nonionic contrast media [German]. *Klin Wochenschr*. 1988;66:760–763.
35. Eaton S, Tsay HM, Yost F, Tweedle MF. Assays for plasma complement activation by x-ray contrast media. *Invest Radiol*. 1990;25:789–792.
36. Mikkonen R, Lehto T, Koistinen V, et al. Suppression of alternative complement pathway activity by radiographic contrast media. *Scand J Immunol*. 1997;45:371–377.
37. Gyoten M. Activation of the complement system and cytokine production by radiographic contrast media in vascular endothelial cells in vitro. *Nippon Igaku Hoshasen Gakkai Zasshi*. 1998;58:811–815.
38. Parfrey PS, Griffiths SM, Barrett BJ, et al. Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both. A prospective controlled study. *N Engl J Med*. 1989;320:143–149.
39. Rich MW, Crecelius CA. Incidence, risk factors, and clinical course of acute renal insufficiency after cardiac catheterization in patients 70 years of age or older. A prospective study. *Arch Intern Med*. 1990;150:1237–1242.
40. Lasser EC, Lyon SG, Berry CC. Reports on contrast media reactions: analysis of data from reports to the US Food and Drug Administration. *Radiology*. 1997;203:605–610.
41. Rihal CS, Textor SC, Grill DE, et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation*. 2002;105:2259–2264.
42. 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.
43. Lautin EM, Freeman NJ, Schoenfeld AH, et al. Radiocontrast-associated renal dysfunction: incidence and risk factors. *AJR Am J Roentgenol*. 1991;157:49–58.
44. Hall KA, Wong RW, Hunter GC, et al. Contrast-induced nephrotoxicity: the effects of vasodilator therapy. *J Surg Res*. 1992;53:317–320.
45. Gruberg L, Mehran R, Dangas G, et al. Acute renal failure requiring dialysis after percutaneous coronary interventions. *Catheter Cardiovasc Interv*. 2001;52:409–416.
46. Kurnik BR, 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.
47. Berns AS. Nephrotoxicity of contrast media. *Kidney Int*. 1989;36:730–740.
48. Gussenhoven MJ, Ravensbergen J, van Bockel JH, et al. Renal dysfunction after angiography: a risk factor analysis in patients with peripheral vascular disease. *J Cardiovasc Surg (Torino)*. 1991; 32:81–86.
49. Kini AS, Mitre CA, Kim M, et al. A protocol for prevention of radiographic contrast nephropathy during percutaneous coronary intervention: effect of selective dopamine receptor agonist fenoldopam. *Catheter Cardiovasc Interv*. 2002;55:169–173.
50. Heller CA, Knapp J, Halliday J, et al. Failure to demonstrate contrast nephrotoxicity. *Med J Aust*. 1991;155:329–332.
51. Albert SG, Shapiro MJ, Brown WW, et al. Analysis of radiocontrast-induced nephropathy by dual-labeled radionuclide clearance. *Invest Radiol*. 1994;29:618–623.
52. Diaz-Sandoval LJ, Kosowsky BD, Losordo DW. Acetylcysteine to prevent angiography-related renal tissue injury (the APART trial). *Am J Cardiol*. 2002;89:356–358.
53. Barrett BJ, Carlisle EJ. Metaanalysis of the relative nephrotoxicity of high- and low-osmolar-

ity iodinated contrast media. *Radiology*. 1993; 188:171–178.
54. 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.
55. Taliercio CP, Vlietstra RE, Ilstrup DM, et al. A randomized comparison of the nephrotoxicity of iopamidol and diatrizoate in high risk patients undergoing cardiac angiography. *J Am Coll Cardiol*. 1991;17:384–390.
56. Schwab SJ, Hlatky MA, Pieper KS, et al. Contrast nephrotoxicity: a randomized controlled trial of a nonionic and an ionic radiographic contrast agent. *N Engl J Med*. 1989;320:149–153.
57. Aspelin P, Aubry P, Fransson SG, et al. Nephrotoxicity in high-risk patients study of iso-osmolar and low-osmolar non-ionic contrast media study investigators. Nephrotoxic effects in high-risk patients undergoing angiography. *N Engl J Med*. 2003;348:491–499.
58. Oymak O. Contrast media induced irreversible acute renal failure in a patient treated with intraperitoneal cisplatin. *Clin Nephrol*. 1995; 44:135–136.
59. Raynal-Raschilas N, Deray G, Bagnis C, Jacobs C. Severe acute renal failure after administration of contrast media in a patient treated with cisplatin. *Nephrol Dial Transplant*. 1996;11:2522–2523.
60. Ahuja TS, Niaz N, Agraharkar M. Contrast-induced nephrotoxicity in renal allograft recipients. *Clin Nephrol*. 2000;54:11–14.
61. Gruberg L, Mintz GS, Mehran R, et al. The prognostic implications of further renal function deterioration within 48 h of interventional coronary procedures in patients with pre-existent chronic renal insufficiency. *J Am Coll Cardiol*. 2000;36:1542–1548.
62. Best PJ, Lennon R, Ting HH, et al. The impact of renal insufficiency on clinical outcomes in patients undergoing percutaneous coronary interventions. *J Am Coll Cardiol*. 2002; 39:1113–1119.
63. Levy EM, Viscoli CM, Horwitz RI. The effect of acute renal failure on mortality. A cohort analysis. *JAMA*. 1996;275:1489–1494.
64. Iakovou I, Dangas G, Lansky AJ, et al. Incidence, predictors, and economic impact of contrast induced nephropathy: results in 8628 patients treated with percutaneous coronary interventions [abstract]. *J Am Coll Cardiol*. 2002;39:2A.
65. Mangano CM, Diamondstone LS, Ramsay JG, et al. The Multicenter Study of Perioperative Ischemia Research Group. Renal dysfunction after myocardial revascularization: risk factors, adverse outcomes, and hospital resource utilization. *Ann Intern Med*. 1998;128:194–203.
66. Mehran R, Aymong ED, Dangas G, et al. A risk score for prediction of contrast induced nephropathy after percutaneous coronary intervention [abstract]. *J Am Coll Cardiol*. 2003;41:37A.