EVIDENCE SUMMARY

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Contrast-induced nephropathy

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Contrast-induced nephropathy (CIN) has been extensively studied since the 1950s due, in part, to its devastating adverse events. The intellectual push for additional investigation into pathogenesis and prevention has heightened in recent years due to increased utilization of contrast enhanced imaging studies. Lack of a universal CIN definition and varied glomerular filtration rate markers have resulted in a varied reported incidence. Risk assessment and risk reduction strategies have evolved over the past several years. Current evidence supports volume supplementation before the administration of intravascular contrast to reduce the hazard of CIN. Other strategies to reduce the risk of CIN, including low osmolar contrast media, N-acetylcysteine, and intrarenal fenoldopam therapy, have variable levels of evidence, and further randomized trials are necessary. (J Vasc Surg 2011;54:575-9.)

Contrast-induced nephropathy (CIN) is the sudden deterioration of renal function resulting from intravenous (IV) or intra-arterial (IA) administration of iodinated contrast media (CM).[1] Bartels and colleagues first described CIN in 1954.[2] Since that report, there has been an increased incidence in CIN from the mid-1970s, corresponding with an increase in procedures utilizing contrast administration.[1] Various definitions of CIN exist in the literature, including a serum creatinine (SCr) increase of ≥0.5 mg/dL, an estimated glomerular filtration rate (eGFR) decrease of ≥25%, a SCr increase ≥25%, or the composite, occurring 48 to 72 hours after contrast exposure.[3,4] Limitations in evaluation occur because SCr is not only determined by GFR but also by hydrational and nutritional status, proximal tubular function and other factors.[3] CIN is the third most common cause of hospital-acquired renal failure.

Currently, the reported incidence of CIN ranges from 0% to >50%. Wide reporting variability results from differences in the presence or absence of risk factors (such as underlying chronic kidney disease), the definition utilized, the amount and type of CM, the utilization of prospective vs retrospective reporting, the timing of SCr measurement, the type of eGFR marker used, and the type of radiologic procedure.[1,4]

This report aims to review the evidence published to date relating to CIN: pathogenesis, evaluation, reporting standards, and prevention. In addition, further areas of investigation are identified.

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Pathogenesis. There are several proposed mechanisms of the pathogenesis of CIN (Fig). Two major theories are renal vasoconstriction resulting in medullary hypoxemia (mediated by alterations in nitric oxide [NO], endothelin, or adenosine), and the direct cytotoxic effects of CM.

Risk assessment. Mehran and colleagues developed a risk-profiling score for IA contrast administration (Table I)[5] based upon amount of contrast administered, baseline GFR, hemodynamic instability, congestive heart failure, age, anemia, and diabetes. Four categories of risk are based on the sum of the points. The incidence of CIN increases from 8% to 57% as risk category increases; risk also increases as GFR falls below 60 mL/min/1.73 m^2. Other specific risk factors for CIN are IV CM administration, and inpatient vs outpatient setting.[6] The Dartmouth Dynamic Registry (DDR), a large prospective, clinical, consecutive registry of patients having diagnostic or interventional cardiovascular catheterization, found that renal dysfunction (0.5 mg/dL absolute increase in SCr) was associated with older age, female gender, increased comorbidities, severe coronary disease, baseline renal insufficiency, and urgent interventions.[7] The Mehran risk score was calculated for each of three groups: no renal dysfunction (average core 5.9 ± 2.8); transient renal dysfunction (average score 6.8 ± 2.7); and persistent renal dysfunction (average score 6.3 ± 2.8). Renal dysfunction was associated with increased risk for major cardiac events, in-hospital mortality, and new onset of dialysis dependent renal failure during hospitalization.[7] Notably, both transient and persistent renal dysfunction were associated with a twofold-threefold increased risk of reduced overall survival.

CIN PREVENTION STRATEGIES

Data collection and synthesis

Several strategies have been proposed to prevent CIN in high-risk patients. Data on the different methodologies was obtained through searches of the MEDLINE database.

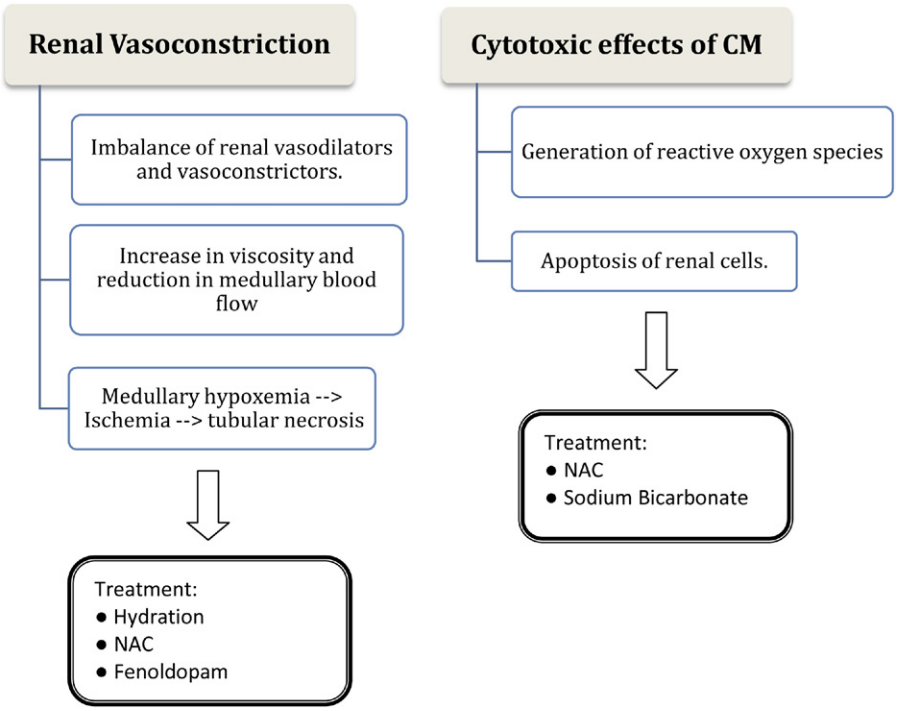

Fig. Putative pathogenetic mechanisms of contrast-induced nephropathy (CIN). The pathogenesis of CIN is linked to renal vasoconstriction and the cytotoxicity of contrast media (*CM*). Renal vasoconstriction is mediated by contrast-induced release of endothelin and adenosine and by the high osmolality of CM. Vasodilators such as nitric oxide (NO) are decreased by way of depletion of NO synthesis cofactors such as tetrahydrobiopterin, the modification of NO substrates such as L-arginine, and the interference with NO synthesis through nuclear factor KB (NFKB).[29] This imbalance between vasoconstrictors and vasodilators leads to medullary ischemia, hypoxia, and eventual endothelial dysfunction.[30] N-acetylcysteine (*NAC*) and fenoldopam target this vasoconstriction. NAC increases NO production, thus reversing renal vasoconstriction, and fenoldopam vasodilates and increases renal plasma flow. CM alters the mitochondrial function of renal cells, resulting in the generation of reactive oxygen species and apoptosis. NAC acts as an antioxidant and sodium bicarbonate alkalinizes urine and protects against free radical damage.[13]

Emphasis was given to meta-analyses and randomized control trials comparing CIN prevention strategies.

CIN prevention: Data overview and results

Hydration. Volume supplementation has been a cornerstone in the prevention of CIN.[8] Several studies have compared hydration protocols and their effectiveness in preventing CIN (Table II). Despite an early belief that hydration combined with diuretics would be useful in CIN prevention, studies have shown that furosemide and mannitol increase rather than reduce CIN risk.[9]

Taylor et al compared CIN rate for inpatient vs outpatient hydration protocols. The outpatient protocol was comparable to the inpatient protocol in preventing CIN. They concluded that hospital admission for IV hydration is unnecessary in patients with mild-moderate renal disease undergoing contrast exposure.[10] Trivedi et al compared IV and oral hydration strategies and found that patients receiving IV fluids for 12 hours preprocedure and 12 hours postprocedure had a much lower incidence of CIN than patients who received oral hydration.[11]

Bader et al found that in patients with *normal* renal function, IV prehydration (2000 mL of saline within 12 hours before and after CM application) significantly prevented a decline in GFR after contrast exposure compared with hydration given only during CM exposure (300 mL of).[12]

Another issue in CIN prophylaxis has been the use of hydration with or without sodium bicarbonate. Bicarbonate is thought to prevent CIN by alkalinizing the urine, thereby protecting against CIN induced free radical damage to the renal tubules. Merten et al found that the incidence of CIN was significantly lower in patients who received bicarbonate compared with those who did not (1.7% vs 13.6%, $P = .02$).[13] Silva et al conducted a literature review as well as a small randomized study assessing the effectiveness of bicarbonate in preventing CIN. While the literature review "strongly suggested" a protective effect of sodium bicarbonate, the randomized study failed to show a significant difference in efficacy between 0.9% saline solution alone and a solution of 1.3% sodium bicarbonate. However, it should be noted that the randomized study

Table I. Mehran scoring based on risk factors for CIN

Risk factor	*Point value*
Systolic blood pressure <80 mm Hg	5
Intra-arterial balloon pump	5
Congestive heart failure (class III/IV or history of pulmonary edema)	5
Age >75-years-old	4
Hematocrit level (<39% for men and <35% for women)	3
Diabetes	3
Contrast media volume	1 point for each 100 mL given
Renal insufficiency	4 points for serum creatinine >1.5 g/dL 2 points for GFR of 40-60 mL/min/1.73 m^2 4 points for GFR of 20-40 mL/min/1.73 m^2 6 points for GFR of <20 mL/min/1.73 m^2

Risk score	*Risk of CIN*	*Risk of dialysis*
5 or less	7.5%	0.04%
6-10	14.0%	0.12%
11-16	26.1%	1.09%
>16	57.3%	12.8%

CIN, Contrast-induced nephropathy; *GFR*, glomerular filtration rate.

Table II. Incidence and risk of CIN with different therapeutic strategies

Study	*Infusate(s)*	*Incidence of CIN in treated group*	*Incidence of CIN in control group*	*Relative risk*
Solomon et al[9] (1994)	0.45 saline + mannitol	28%	—	—
	0.45 saline + furosemide	40%		
	0.45 saline	11%		
Taylor et al[10] (1998)	0.45 saline at 75 mL/h	11.1%	—	—
	0.45 saline at 300 mL/h	5.6%		
Trivedi et al[11] (2003)	0.9 saline administered 12 h before and 12 h after CM administration	3.7%	—	—
	Hydration with unrestricted oral fluids	34.6%		
Bader et al[12] (2004)	0.9 saline administered 12 h before and 12 h after CM administration	5.3%	—	—
	300 mL saline bolus given during CM exposure	15%		
Merten et al[13] (2004)	154 mEq/L sodium bicarbonate	1.7%	—	—
	154 mEq/L sodium chloride	13.6%		
Tepel et al[17] (2000)	NAC	2%	21%	0.11 (95% CI, 0.02-0.86)
Allaqaband et al[18] (2002)	NAC	18%	15%	1.18 (95% CI,
Briguori et al[19] (2002)	NAC	7%	10%	0.59 (95% CI, 0.22-1.57)
Diaz-Sandoval et al[20] (2002)	NAC	8%	45%	0.18 (95% CI, 0.04-0.72)
Durham et al[21] (2002)	NAC	26%	22%	1.20 (95% CI, 0.55-2.63)
Shyu et al[22] (2002)	NAC	3%	25%	0.14 (95% CI, 0.03-0.57)
Kay et al[23] (2003)	NAC	4%	12%	0.32 (95% CI, 0.11-0.96)

CI, Confidence interval; *CIN*, contrast-induced nephropathy; *NAC*, N-acetylcysteine.

consisted of a relatively small sample size (n = 27) and that no patients in either group developed CIN. The authors concluded that the small number of patients did not allow definite conclusions.[28]

Contrast osmolarity. Studies are conflicted as to whether low-osmolar or iso-osmolar CM is more beneficial in preventing CIN. Aspelin et al, in the NEPHRIC trial, found that CIN was less likely to develop when iso-osmolar CM was used (iodixanol) rather than low-osmolar CM (iohexol).[14] However, a much larger study by Liss et al involving over 57,000 patients, showed that the risk for developing acute renal failure and dialysis was *higher* when patients received the iso-osmolar iodixanol vs the low-osmolar media ioxaglate or iohexol. A key difference from the NEPHRIC trial was that this study evaluated rehospitalization of patients for acute renal failure rather than SCr levels as a marker for CIN (Table III).[15]

Acetylcysteine (NAC). NAC is thought to protect against CIN via direct antioxidant effect (preventing free-radical damage) and also by increasing NO production. This increase in NO is thought to reverse the medullary renal vasoconstriction associated with CM.

Table III. Odds ratios for developing renal failure after administration of iso-osmolar iodixanol vs low-osmolar ioxaglate (modified from reference 15)

Subset	*Contrast medium*	*Odds ratio*	*95% CI*	P *value*
No previous renal history	Iodixanol	1	—	—
	Ioxaglate	0.48	(0.39-0.58)	<.001
Previous renal failure	Iodixanol	1	—	—
	Ioxaglate	0.54	(0.34-0.86)	.009
Diabetic patients	Iodixanol	1	—	—
	Ioxaglate	0.59	(0.40-0.86)	.007
Patients requiring dialysis after CM exposure	Iodixanol	1	—	—
	Ioxaglate	0.48	(0.24-0.96)	.039

CI, Confidence interval; *CM,* contrast media.

A meta-analysis by Birck et al compared seven studies that looked at the role of NAC in CIN prevention (Table II). Through a random-effects model, the researchers concluded that NAC provided a 56% relative risk reduction of CIN in patients with renal insufficiency undergoing contrast procedures.[16]

Hoffman et al, however, cited the fact that most studies use SCr as a measure of renal function and postulated that NAC does not alter GFR but rather causes a decrease in SCr levels through another mechanism. They found that NAC caused no significant change in levels of cystatin C. Because serum cystatin C concentrations are independent of age, gender, and muscle mass, they concluded that measuring SCr to assess renal function when assessing the role of NAC might be misleading.[24]

Fenoldopam. Fenoldopam is a selective dopamine D1 agonist, causing vasodilatation of both renal and systemic vessels. It is thought to protect against contrast-mediated renal vasoconstriction and increase renal plasma flow (RPF).

Kini et al looked at CIN incidence in patients who received IV fenoldopam during and after angiography (in addition to saline hydration) vs patients who received hydration only (n = 159). The incidence of CIN was 4.7% when fenoldopam was given, compared with 18.8% in the control group ($P < .001$). Notably, IV administration may cause clinically significant hypotension (due to its systemic vasodilatory effects) limiting its widespread use.[25]

Targeted renal therapy (TRT) with fenoldopam. TRT refers to the delivery of therapeutic medications directly to the kidneys via the renal arteries. This intrarenal (IR) drug administration improves the therapeutic window by increasing intrarenal drug concentration and reducing systemic effects. The Benephit Infusion Catheter (Angiodynamics, Queensbury, NY) is a bifurcated infusion catheter that allows TRT during coronary or peripheral catheterization to reduce CIN risk in patients with renal insufficiency.

Tierstein et al compared the effect of TRT vs IV fenoldopam administration on GFR, RPF, plasma fenoldopam levels, and systolic blood pressure. Patients who received TRT had significantly higher RPF, GFR, and nadir systolic blood pressure than those who received IV fenoldopam. TRT was also associated with lower systemic plasma drug concentration and a +25% change in GFR level 2 hours after CM administration (compared with a −14% change with IV administration).[26]

Table IV. TRT with fenoldopam: Effect of dosing and duration on incidence of CIN[10,27]

	Risk of CIN (based on Mehran score)	*Actual incidence of CIN*
TRT administration of 0.2 μg/kg/min fenoldopam	28.3%	33.3% ($P = .79$)
TRT administration of 0.4 μg/kg/min fenoldopam	26.9%	3.0% ($P < .0001$)
TRT duration <60 min	26.5%	29.1% ($P > .99$)
TRT duration >60 min	27.2%	2.8% ($P < .001$)

CIN, Contrast-induced nephropathy; *TRT,* targeted renal therapy.

The Benephit System Renal Infusion Therapy (Be–RITe!) Multicenter Registry was a postmarket registry that followed patients treated using the Benephit systems for TRT. A total of 501 patients were enrolled who were considered high risk for developing CIN during angiography. In patients who received TRT with fenoldopam (n = 285), the incidence of CIN was 71% lower than predicted (8.1% actual CIN vs 28.0% predicted; $P < .0001$). Also, it was shown that higher drug doses and longer duration of TRT were more effective (Table IV).[27]

DISCUSSION

CIN remains a substantial problem because of the magnitude of patients receiving contrast-enhanced imaging studies. Although the overall reported prevalence of CIN varies depending on definition and the timing of measurement, the adverse impact on CIN on short- and long-term mortality are well studied. Thus, strategies are warranted to mitigate CIN in high-risk populations, particularly patients with baseline renal insufficiency with or without diabetes mellitus. Although there remains some controversy about the best preventive approach, a preponderance of level 2 data supports the routine use of prehydration. As suggested by Mueller et al,[8] intravenous normal saline volume supplementation reduces the hazard of CIN, is relatively cost-effective and safe, and should be considered in all patients undergoing procedures with intravascular contrast.

Other strategies to reduce CIN have variable or conflicting levels of evidence. In terms of contrast osmolarity, the NEPHRIC trial found that iso-osmolar CM may be better than low-osmolar CM in preventing CIN.[14] However, a much larger study done by Liss et al[15] demonstrated disparate results. The use of NAC may prevent significant increases in SCr in patients with chronic renal insufficiency undergoing contrast procedures. However, because NAC may be simply lowering the SCr without actually preventing renal damage, future studies should address the issue of reduction of morbidity and mortality rates with this agent. Evidence supports the role of fenoldopam on improving renal function, although IV administration should be used with caution due to the potential for hypotension. TRT appears to improve safety and efficacy, although larger randomized trials are needed to ensure intermediate and long-term benefit.

AUTHOR CONTRIBUTIONS

Conception and design: JR
Analysis and interpretation: JR, VY, DN
Data collection: VY, DN
Writing the article: JR, VY, DN
Critical revision of the article: JR, VY, DN
Final approval of the article: JR
Statistical analysis: Not applicable
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Overall responsibility: JR

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