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Coronary Angiography and Contrast-Induced Nephropathy

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1. Introduction

Radiologic procedures such as coronary angiography utilizing intravascular contrast media (CM) injections are being widely applied for diagnostic and therapeutic purposes. These led to a parallel increase in the incidence of contrast-induced nephropathy (CIN). Renal failure requiring dialysis after contrast media administration is associated with a 40% in-hospital mortality rate and has a 2-year mortality rate of 80%. Approximately \$180 million are spent annually to manage CIN in the US. The large number of patients who are severely affected by CIN underscores the importance of addressing known risk factors and preventions for CIN. Patients at risk for CIN can often be identified with a routine medical history, physical examination and laboratory analysis before the procedure. Two of the major risk factors of CIN are pre-existing renal failure and diabetes mellitus. After the high-risk patient population has been identified and risk factors addressed, the next step in preventing CIN is the use of different prophylactic therapies. The following chapter provides an overview of current risk factors and preventive methods of CIN.

2. Definition, differential diagnosis and incidence of CIN

The most commonly used definition for CIN in clinical trial is the elevation of serum creatinine by $\geq 0.5\text{mg/dl}$ or $\geq 25\%$ occurring within 48 hours after administration of CM, and the absence of an alternative etiology. Serum creatinine is the standard marker to detect CIN. However, serum creatinine demonstrates major limitations. Using the Cockcroft-Gault and the Modification of Diet in Renal Disease equations are useful in estimation of the GFR. Serum cystatin C has been proposed as an alternative endogenous marker of GFR showing higher correlation to standard clearance methods such as inulin or iohexol clearance. Serum cystatin C may detect CIN one to two days earlier than creatinine. Also, recent studies documented that serum and urine neutrophil gelatinase-associated lipocalin is an early predictive biomarker of CIN in patients underwent coronary angiography (Shaker et al., 2010). Cholesterol atheroemboli, volume depletion, and interstitial nephritis should consider in differential diagnosis of CIN. Before coronary angiography, the volume status of high-risk patients can be assessed through the inferior vena cava index or bioimpedance spectroscopy. The incidence of CIN is reported to be 0.6-2.3% in general population who do not have any risk factor for CIN, but the incidence can be increased to 90% in patients at high risk for CIN (Toprak, 2007).

2.1 Pathophysiology of CIN

The pathogenesis of CIN is unclear. The proposed mechanisms are medullary hypoxia due to decreased renal blood flow secondary to renal artery vasoconstriction, tubular obstruction and direct tubular toxicity of the CM due to apoptosis and oxidative damage. Endothelial dysfunction and renal microcirculatory alterations also may play a role. The development of CIN is affected by changes in renal hemodynamics, such as increased activity of renal vasoconstrictors and decreased activity of renal vasodilators. Other factors that may decrease renal blood flow include increased viscosity of CM and increased erythrocyte aggregation induced by CM, which results in diminished oxygen delivery. Contrast agents have been found to reduce antioxidant enzyme activity, and direct cytotoxic effects mediated by oxygen free radicals. Apoptosis is also involved as a result of cellular injury. Hyperosmolar contrast agents induce renal hemodynamic changes caused by osmolar-driven solute diuresis with activation of tubuloglomerular feedback or an increase in tubular hydrostatic pressures, which may cause compression of the intrarenal microcirculation and a decreased GFR. Also hyperosmolar contrast agents have direct toxic effects on renal epithelial cells. In addition, DNA fragmentation was increased in cells exposed to hyperosmolar CM.

2.2 Clinical course and outcomes

CIN may range in severity from asymptomatic, nonoliguric transient renal dysfunction to oliguric severe renal failure that necessitates permanent dialysis. CIN is reported to be the third leading cause of in-hospital acute renal failure after hypotension and surgery. Approximately \$180 million is spent annually to manage CIN in the US. Dangas et al. showed that in-hospital outcomes such as death (6.3% vs 0.8%), cardiac death (4.0% vs 0.5%), coronary artery bypass grafting (5.8% vs 0.5%), major adverse cardiac event (9.3% vs 1.1%), packed red cell transfusion (28% vs 6%), vascular surgery of access site (5.6% vs 2.6%), post-procedure length of stay (6.8 ± 7.1 vs 2.3 ± 2.5) were significantly higher in CIN developed patients compare with control ($p < 0.0001$). In cumulative one-year outcome death, out-of-hospital death and major adverse cardiac events were significantly higher in CIN developed patients ($p < 0.0001$) (Dangas et al., 2005). In a study of acute myocardial infarction patients undergoing primary angioplasty, it was found that CIN developed patients have significantly higher incidence of high-rate atrial fibrillation ($p = 0.01$), high-degree conduction disturbances requiring permanent pacemaker ($p = 0.04$), acute pulmonary edema ($p = 0.008$), respiratory failure requiring mechanical ventilation ($p < 0.0001$), cardiogenic shock requiring intra-aortic balloon ($p < 0.0001$), and acute renal failure requiring renal replacement therapy ($p < 0.0001$) (Marenzi et al., 2004).

2.3 Risk factors for CIN

Specific factors that increase the risks for development of CIN are related to the patient, the contrast media, and the procedure (Table 1).

2.3.1 Patient-related risk factors

Older age

The possible reasons of the high incidence of CIN in elderly were age-related changes in renal function, more difficult vascular access following tortuosity, calcification of the vessels

Risk Factors	Odds Ratio (95%CI)	p Value
Kidney Related Risk Factors		
Pre-existing renal failure		
Preprocedural creatinine 2.0-2.9 mg/ dl	7.37 (4.78-11.39)	<0.0001
Preprocedural creatinine ≥ 3mg/ d	12.82 (8.01-20.54)	<0.0001
Diabetes mellitus-Diabetic nephropathy		
Preprocedural creatinine≤ 1.1mg/ dl	1.86 (1.20-2.89)	0.005
Preprocedural creatinine 1.2-1.9 mg/ dl	2.42 (1.54-3.79)	<0.001
Use of nephrotoxic drugs		
Low effective circulatory volume	1.19 (0.72-1.95)	0.05
Cardiovascular System Related Risk Factors		
Class III-IV congestive heart failure	2.20 (1.60-2.90)	<0.0001
Left ventricle ejection fraction<40%	1.57 (1.14-2.16)	0.005
Acute myocardial infarction ≤ 24 h	1.85 (1.31-2.63)	0.0006
Hypertension	2.00 (1.40-2.80)	0.0001
Periprocedural hypotension	2.50 (1.70-3.69)	<0.00001
Multi-vessel coronary involvement	3.24 (1.07-9.82)	0.038
Peripheral vascular disease	1.90 (1.40-2.70)	<0.0001
Preprocedure shock	1.19 (0.72-1.96)	0.05
Using intra-aortic balloon pump	15.51 (4.65-51.64)	<0.0001
Bypass graft intervention	4.94 (1.16-20.9)	0.03
Time-to-reperfusion ≥6 h	2.51 (1.01-6.16)	0.04
Pulmonary edema	2.56 (1.42-4.52)	0.001
Demographic Risk Factors		
Age >75 years	5.28 (1.98-14.05)	0.0009
Female gender	1.4 (1.25-1.60)	0.0001
Contrast Media Related Risk Factors		
High total dose of contrast agent (>300 ml)	2.8 (1.17-6.68)	0.02
Osmolality (Low- vs. high-osmolality)	0.50 (0.36-0.68)	
Short duration of two contrast administration	4.4 (2.9-6.5)	<0.0001
Other Possible Risk Factors		
Procedural success	0.27 (0.19-0.38)	<0.0001
Baseline hematocrit	0.95 (0.92-0.97)	<0.00001
Hyperuricemia	4.71 (1.29-17.21)	0.019
ACE inhibitors	3.37 (1.14-9.94)	0.028
Angiotensin Receptor Blockers	2.70 (1.25-5.81)	0.011
Metabolic Syndrome	426 (1.19-15.25)	0.026
Hypoalbuminemia	5.79 (1.71-19.64)	0.005
Hypercholesterolemia		
Renal transplant		
Multiple myeloma		
Diuretics		
Intra-arterial contrast administration		
Sepsis, cirrhosis		

Table 1. Risk factors for the development of contrast-induced nephropathy

requiring greater amount of CM, defective prostaglandin synthesis, and the presence of renovascular disease. Furthermore, hypovolemia is very common in elderly patients. In a prospective study in which elderly patients (≥ 70 years) were subjected to cardiac catheterization, 11% developed CIN (Rich & Crecelius, 1990). In another study, CIN incidence was 17% in elderly patients (>60 years) as compared with 4% in younger patients (Kohli et al., 2000). In 208 patients with acute myocardial infarction who underwent coronary intervention, it was found that an age of ≥ 75 years was an independent risk for CIN (OR=5.28, $p=0.0009$) (Marenzi et al., 2004).

Gender

In a retrospective study of 8628 patients who underwent PCI, female sex was an independent predictor of CIN (OR=1.4, $p<0.0001$). One-year outcome analyses by gender showed a higher mortality among females than among males in a cohort of CIN patients (14% vs 10%, $p=0.05$) (Iakovou et al., 2003). The findings of this study contradict those of a previous randomized controlled trial of ionic vs nonionic CM, in which a multivariate analysis identified male gender as an independent risk factor for CIN (Rudnick et al., 1995). Whether female gender is truly an independent predictor of CIN will require further confirmatory studies.

Pre-existing renal disease

The major risk factor for CIN is a $GFR < 60$ ml/min/1.73 m². Chronic kidney disease is associated with decreased vasodilatory response, which is important in developing CIN, and in patients with renal insufficiency, the clearance of CM is slower than in normal subjects. In a study of 7586 patients who underwent coronary intervention, CIN developed in 22.4% of the patients who had serum creatinine levels of 2.0 to 2.9 mg/dl and in 30.6% of those with serum creatinine levels of 3.0 mg/dl or higher, compared with 2.4% of patients with serum creatinine levels <1.1 mg/dl (Rihal et al., 2002). Two other studies (Moore et al., 1992; Barrett et al., 1992) reported that the incidence of CIN increased from 4% to 20% as the baseline serum creatinine increased from 1.2 to 2.9 mg/dl. In another study, the incidence of CIN increased from 8% to 92% as the serum creatinine increased from 1.5 to 6.8 mg/dl. Furthermore, the probability of CIN requiring dialysis increases from 0.04% to 48% as the baseline GFR decreases from 50 to 10 ml/min (McCullough et al., 1997).

Diabetes mellitus

Patients with diabetes constitute an important group at high risk of developing CIN. Patients with diabetic nephropathy and a mean serum creatinine of 6.8 mg/dl had a 92% incidence of CIN after coronary angiography (Weinrauch et al., 1977). Patients with diabetes who have advanced chronic renal failure because of causes other than diabetic nephropathy are at significantly higher risk of developing CIN like diabetic nephropathy. On the other hand, studies have shown that when pre-existing renal disease is present, patients with and without diabetes are similarly at risk of CIN, which correlates with the degree of renal disease. Some authors have suggested that DM in the absence of nephropathy, particularly in insulin-dependent patients with diabetes, is associated with an increased risk of CIN (McCullough et al., 1997; Toprak 2007). In a study, it was found 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 patients who had both diabetes and azotemia (Lautin et al., 1991). In another study, the incidence of CIN was found to be 2% in patients without diabetes and 3.7% in patients with

diabetes with a baseline creatinine of 1.1 mg/dl or less (OR=1.86, $p=0.005$). When renal function is mildly impaired (serum creatinine level 1.2 to 1.9 mg/dl), the risk of CIN in patients with diabetes mellitus increases to 4.5% (OR=2.42, $p<0.001$) (Rihal et al., 2002). Other studies have failed to corroborate this connection (Parfrey et al., 1989). However, given that, those with diabetes alone were found to be at slightly higher risk of CIN than the general population.

Pre-diabetes

In a study of 421 patients who underwent coronary angiography with renal insufficiency, we presented that pre-DM increase the incidence of CIN 2.1-fold in comparison to patients with normal fasting glucose (NFG) but pre-DM is not as strong as DM as a risk of developing CIN. CIN occurred in 20% of the DM (RR=3.6, $p=0.001$), 11.4% of the pre-DM (RR 2.1, $p=0.314$) and 5.5% of the NFG group. The decrease of GFR was higher in DM and pre-DM ($p=0.001$ and $p=0.002$, respectively). Length of hospital stay was 2.45 ± 1.45 day in DM, 2.27 ± 0.68 day in pre-DM, and 1.97 ± 0.45 day in NFG ($p<0.001$, DM vs. NFG and $p=0.032$, pre-DM vs. NFG). The rate of major adverse cardiac events was 8.7% in DM, 5% in pre-DM, and 2.1% in NFG ($P=0.042$, DM vs. NFG). Hemodialysis was required in 3.6% of DM, and 0.7% in pre-DM ($P=0.036$, DM vs. NFG), and the total number of hemodialysis sessions during 3 months was higher in DM and pre-DM ($P<0.001$). Serum glucose ≥ 124 mg/dl was the best cut-off point for prediction of CIN (Toprak et al., 2007).

Congestive heart failure and reduced left ventricular ejection fraction

Studies have shown that reduced left ventricular ejection fraction (LVEF) ($\leq 49\%$) and advanced congestive heart failure are independent risk factors for CIN. In a study, Dargas et al. showed that LVEF below 40% is an independent predictor of CIN (Dargas et al., 2005). We have previously reported that if the LVEF is greater than 30%, this condition does not show any significant effect on the development of CIN (Toprak et al., 2003). In a study it was shown that congestive heart failure was an independent risk for CIN (OR=1.53, $p=0.007$) (Rihal et al., 2002). In a cohort study it was found that congestive heart failure is a risk for CIN in patients who underwent PCI (OR=2.2, $p<0.0001$) (Bartholomew et al., 2004).

Hypertension

Hypertension has been categorized as a risk factor for CIN in some research. In a study of 8628 patients who underwent percutaneous interventions, hypertension was found to be an independent predictor of CIN (OR=1.2, $p=0.0035$) (Iakovou et al., 2003). In another cohort study, hypertension was a risk for CIN in patients who underwent PCI (OR=2.0, $p=0.0001$) (Bartholomew et al., 2004).

ACE Inhibitors and angiotensin receptor blockers

ACE inhibitors have been identified as a risk factor for CIN because of their potential to reduce renal function. On the other hand, some small studies have shown that the nephrotoxicity of CM may be reduced because of decreased renal vasoconstriction by inhibition of angiotensin II. In a randomized controlled study with 71 patients with diabetes who underwent coronary angiography randomized to captopril or control, 25-mg captopril was given three times daily. There was a significant decrease in CIN in the patients who received captopril compared with the control group (6% vs 29%, respectively, $p<0.02$) (Gupta et al., 1999). We have performed a randomized controlled study in 80 patients with serum creatinine below 2 mg/dl who underwent coronary angiography. Captopril was

administered in 48 patients before coronary angiography. Five patients (10.4%) in the captopril group developed CIN, compared with only one patient (3.1%) in the control group ($p=0.02$) (Toprak et al., 2003). In a study of 230 patients with renal insufficiency and age ≥ 65 years we found that chronic ACE inhibitor administration was a risk for developing CIN. CIN occurred in 17 patients (15.6%) in the ACE inhibitor group and 7 patients (5.8%) in the control group ($p=0.015$). Chronic ACE inhibitor administration was a risk indicator of CIN ($OR=3.37$, $p=0.028$) (Cirit et al., 2006). In another study, 421 patients with renal insufficiency who underwent coronary angiography, use of ACE inhibitors or ARB was a risk for CIN in multivariate analysis ($OR=2.7$, $p=0.011$) (Toprak et al., 2007). In a recent study, the impact of renin-angiotensin and aldosterone system blockade on the frequency of CIN was assessed retrospectively. Patients treated with ACE inhibitors or ARB ($n=269$) and were not treated with them ($n=143$) underwent coronary angiography included to the study. CIN developed 11.9% in ACE-inhibitor using group and 4.2% in control group ($p=0.006$). Use of ARB or ACE inhibitors was found as a risk for CIN ($OR=3.08$, $p=0.016$) (Kiski et al., 2010). Checking the use of ACE inhibitors or ARB before coronary angiography seems to be a useful guide in tracking risk assessment for CIN.

Nephrotoxic drugs

Sulfonamides, aminoglycosides, and their combination with furosemide are particularly potent. Cyclosporin A may intensify medullary hypoxia, and cisplatin can attach to sulfhydryl groups. Mannitol can increase the metabolic workload in the kidney, and amphotericin B can cause the effect of a combination of mannitol and cyclosporine A. However, the individual roles of these medications as independent risk factors of CIN have not been determined in large trials. Nonetheless, it seems quite likely that nonselective NSAIDs and selective COX-2 inhibitors decrease the vasodilatory prostaglandins in the kidney and potentiate the vasoconstrictive effect of CM.

Multiple myeloma

The pathomechanism of this process has been explained by the precipitation of CM molecules together with Tamm-Horsfall proteins and other abnormal proteins, tubular epithelial cells damaged and desquamated as a result of ischemia, direct contrast toxicity, or disturbed function of integrins. In studies conducted on animals, intratubular light chains, particularly in the setting of intravascular volume depletion, have been found to augment the nephrotoxic potential of CM (Holland et al., 1985). Studies showed an incidence of CIN of only 0.6–1.25% in patients with myeloma if dehydration is avoided (McCarthy & Becker, 1992).

Metformin

The oral antidiabetic agent metformin is not itself nephrotoxic, but it is known that patients who are receiving metformin may develop lactic acidosis as a result of CIN. A decline in renal function after contrast exposure could adversely affect the clearance of metformin. The complication was almost always observed in diabetic patients with decreased renal function before injection of CM. It seems safer to instruct patients especially at high risk for CIN not to take this drug for 48 h or so after CM administration and resume taking the drug only if there are no signs of nephrotoxicity.

Hypercholesterolemia

In the literature, there are limited studies on the relationship between hypercholesterolemia and CIN. According to these studies, hypercholesterolemia aggravates CIN through the

reduced production of nitric oxide (Yang et al., 2004). Altered nitric oxide-dependent renal vasodilatation, which is important in the pathogenesis of CIN, is prevalent in hypercholesterolemia.

Hyperuricemia

It has been suggested that tubular obstruction by uric acid plays a role in the pathogenesis of CIN. In a prospective cohort study we evaluated 266 patients who undergoing elective coronary angiography and we found that patients with hyperuricemia are at risk of developing CIN (OR=4.71, $p=0.019$). CIN occurred in 15.1% of the hyperuricemic group and 2.9% of the normouricemic group ($p<0.001$). Length of hospital stay ($p<0.001$) and CIN requiring renal replacement therapy ($p=0.017$) were significantly higher in hyperuricemic group. Serum uric acid ≥ 7 mg/dl in males and ≥ 5.9 mg/dl in females were found the best cut-off value for prediction of CIN (Toprak et al., 2006).

Multivessel coronary involvement, peripheral vascular disease, and renal artery stenosis

Factors related to accelerated or diffuse atherosclerosis are linked to the development of CIN. The treatment of multivessel disease, challenging chronic total occlusions and extensively diseased coronary segments, may require high doses of CM for providing an optimal image quality, thus enhancing the potential toxic effects on the renal function. If a patient has multivessel coronary involvement, the other vessels in the body, such as the renal artery, can be involved. In a study of 177 patients who underwent cardiac catheterization, subjects were also evaluated for renal artery stenosis. Coronary artery disease was detected in 110 patients (62%), and significant renal artery stenosis was detected in 19 patients (11%). Using multivariate analysis, it was found that the extent of coronary artery disease was an independent predictor of renal artery stenosis (Weber-Mzell et al., 2002). In a study a total of 5571 patients who underwent PCI were evaluated for CIN risk factors, and it was found that multivessel coronary involvement was only a univariate predictor of CIN ($p=0.003$) (Mehran et al., 2004). In two other cohort studies it was found that peripheral vascular disease is a risk for CIN in patients who underwent PCI (OR=1.9, $p<0.0001$ and OR=1.71, $p=0.001$, respectively) (Bartholomew et al., 2004; Rihal et al., 2002). In a study a total of 219 non-diabetic patients who underwent coronary angiography we have found that multivessel coronary involvement is a risk for CIN (OR=3.24, $p=0.038$) (Toprak et al., 2006).

Hypovolemia

Decreased effective circulating volume and reduced renal perfusion potentiate renal vasoconstriction after administration of intravascular CM. The toxic effects of CM on the renal tubular lumen may be exacerbated in hypovolemia. At present the most convincing preventive procedure of CIN is adequate hydration with isotonic saline or sodium bicarbonate, and intravenous hydration seems to have better results than does oral hydration. Before angiography, the volume status of patients can be assessed through the inferior vena cava index, mean atrial pressure, noninvasive pulmonary-capillary wedge pressure or bioimpedance spectroscopy (Toprak & Cirit, 2005).

Renal transplantation

Patients with renal transplantation may be at a higher risk of CIN due to concomitant use of cyclosporine and higher prevalence of diabetes and renal insufficiency. In a study, 33 patients with a functioning renal allograft who underwent different contrast studies, the incidence of CIN was 21.2% (Ahuja et al., 2000).

Acute myocardial infarction

A study by Rihal et al. showed that acute myocardial infarction within 24 h before administration of the CM is a risk factor for CIN (OR=1.85, $p=0.0006$). This study demonstrates that CIN is a frequent complication in acute myocardial infarction, even in patients with a normal baseline renal function. (Rihal et al., 2002). In a study of 208 acute myocardial infarction patients who underwent primary PCI, anterior acute myocardial infarction was significantly higher in patients who developed CIN ($p=0.0015$). However, in multivariate analysis, anterior acute myocardial infarction (OR=2.17, $p=0.09$) was not a risk for CIN (Marenzi et al., 2004). In 2082 percutaneous interventions for acute myocardial infarction, it was reported a more than seven-fold (3.2% vs 23.3%) increase in 1-year mortality in patients who developed CIN (Sadeghi et al., 2003).

Low hematocrit level

A baseline hematocrit value of less than 39% for men and less than 36% for women is a risk for CIN. The relationship between low hematocrit levels and CIN has been investigated in a prospective study of 6773 patients who underwent PCI (Nikolsky et al., 2005). A lower baseline hematocrit was an independent predictor of CIN; and each 3% decrease in baseline hematocrit resulted in a significant increase in the odds of CIN in patients with and without chronic kidney disease (11% and 23%, respectively). Dangas et al. showed that the baseline hematocrit level is an independent predictor of CIN in patients with chronic kidney disease (OR=0.95, $p<0.00001$) (Dangas et al., 2005).

Low serum albumin

Hypoalbuminemia impairs endothelial function, enhances renal vasoconstriction, impairs the synthesis and release of nitric oxide, and decreases antioxidant enzyme activity. In a study, low serum albumin (<3.5 g/dl) was identified as a risk factor for CIN in patients 70 years of age or older who underwent cardiac catheterization (Rich, et al., 1990). Also we have found that in 230 patients who underwent coronary angiography with renal insufficiency, serum albumin level ≤ 3.5 g/dl was a risk factor for CIN (OR=5.79, $p=0.005$) (Cirit et al., 2006).

Hypotension, sepsis, cirrhosis, and pulmonary edema

A systolic blood pressure of less than 80 mm Hg for at least 1 h that requires inotropic support with medications is a risk factor for CIN. A study by Dangas et al showed that periprocedural hypotension and pulmonary edema are independent predictors of CIN in patients with chronic kidney disease (OR=2.50, $p<0.00001$ and OR=2.56, $p=0.001$, respectively) (Dangas et al., 2005). Sepsis, through direct damage by bacterial toxins to renal tubules and impairment of circulation, has also been reported as a risk factor. Reduction of effective intravascular volume caused by liver cirrhosis has been reported as contributing to pre-renal reduction in renal perfusion, thus enhancing the ischemic insult of CM (Toprak, 2007).

Metabolic syndrome, impaired fasting glucose and hypertriglyceridemia

In a prospective cohort study of 219 non-diabetic elderly patients with reduced kidney function who underwent elective coronary angiography, we reported that metabolic syndrome was a risk indicator of CIN (OR=4.26, $p=0.026$). CIN occurred in 14% of the metabolic syndrome group and 3.6% of the non-metabolic syndrome group (relative risk 3.93, $p=0.007$). Impaired fasting glucose (OR=4.72, $p=0.007$), high triglyceride (OR=4.06,

$p=0.022$); and multi-vessel involvement ($OR=3.14$, $p=0.038$) in the metabolic syndrome group were predictors of CIN (Toprak et al., 2006).

2.3.2 Procedure-related risk factors

Short duration of the two contrast administration and urgent/emergency procedure

In those who have no risk factors for CIN, angiography should be delayed more than 48 hours after a previous exposure to intravascular contrast media. In patients with diabetes or preexisting renal disease, this time interval should be increased to more than 72 hours. In a cohort study, urgent/emergency procedure was found as a predictor of CIN ($OR=4$, $p<0.0001$) (Bartholomew et al., 2004). The higher risk of developing CIN in patients with urgent status was irrespective of baseline renal function.

Use of intra-aortic balloon pump

In 208 consecutive acute myocardial infarction patients undergoing percutaneous coronary intervention, use of intra-aortic balloon pump was a risk predictor of CIN ($OR=15.51$, $p<0.0001$) (Marenzi et al., 2004). In a study, it has demonstrated that, intra-aortic balloon pump use is an independent predictor of CIN in patients with chronic kidney disease ($OR=2.27$, $p=0.004$) (Dangas et al., 2005). In another study, it was found that the use of intra-aortic balloon pump was a risk factor for CIN requiring dialysis after PCI ($OR=1.94$) (Gruberg et al., 2001). In another derivation and validation cohort study, intra-aortic balloon pump use was a risk for CIN in patients undergoing coronary intervention ($OR=5.1$, $p<0.0001$) (Bartholomew et al., 2004).

Bypass graft intervention and delayed reperfusion

Procedures with bypass angiography and intervention may be associated with higher complexity, longer duration, and limited success, thus indicating an unstable post-procedural period with impaired cardiac output. Gruberg et al. showed that the risk of CIN requiring dialysis after PCI was increased with bypass graft intervention ($OR=4.94$) (Gruberg et al., 2001). In a study of 208 acute myocardial infarction patients undergoing primary PCI, the risk of CIN was increased if the time-to-reperfusion is ≥ 6 h ($OR=2.51$, $p=0.04$) (Marenzi et al., 2004).

2.3.3 Contrast medium-related risk factors

Increased dose of contrast medium

According to different sources, the relatively safe cutoff point of contrast amount varies from 70 ml up to 220ml. However, doses as low as 20 to 30 ml are capable of inducing CIN. In a study that patients undergoing coronary angiography, each 100 ml of contrast medium administered was associated with a significant increase of 12% in the risk of CIN ($OR=1.12$, $p=0.02$) (Rihal et al., 2002). Marenzi et al. showed that contrast volume >300 ml is an independent risk for CIN ($OR=2.80$, $p=0.02$) (Marenzi et al., 2004). In another study patients with preexisting renal failure revealed a 10-fold risk of CIN when more than 125 ml of contrast media was administered (Taliencio et al., 1986).

High-osmolar and ionic CM

In a large study which comparing the non-ionic low-osmolality agent iohexol to the ionic high-osmolality agent meglumine/sodium diatrizoate in patients with pre-existing renal

dysfunction undergoing angiography, patients with renal insufficiency receiving diatrizoate were 3.3 times as likely to develop CIN compared to those receiving iohexol (Rudnick et al., 1995). NEPHRIC trial is a randomized, prospective study comparing the nonionic iso-osmolar CM iodixanol with the nonionic low-osmolar CM iohexol in 129 renal impairment patients with diabetes undergoing coronary or aorto-femoral angiography. The incidence of CIN was 3% in the iodixanol group and 26% in the iohexol group ($p=0.002$) (Aspelin et al., 2003). In another randomized study, the renal tolerance of iodixanol and iohexol was compared in 124 patients with creatinine >1.7 mg/dl. The incidence of CIN was 3.7% in iodixanol group and 10% in iohexol group ($p>0.05$) (Chalmers et al., 1999). The available data do not provide clear evidence that the whole iso-osmolar CM class offers an improvement over the low-osmolar CM class. Other studies with iodixanol in renal failure patients have shown a higher incidence of CIN than that observed in the NEPHRIC study (21% in the RAPPID trial, 30% in the CONTRAST trial) (Baker et al., 2003; Stone et al., 2003). In addition to their osmolality, contrast medias are characterized as ionic versus non-ionic. Small clinical trials of low-risk patients undergoing coronary angiography have shown little difference in the risk of CIN between the 2 types of CM. However, a randomized trial of 1196 patients undergoing coronary angiography showed that non-ionic CM reduced the incidence of CIN in patients with preexisting renal disease with or without diabetes (Rudnick et al., 1995). In addition, symptomatic or hemodynamic adverse drug events have been shown to occur less often with non-ionic, low-osmolality CM compared with ionic, high-osmolality CM. In high-risk patients, it is reasonable to don't use the high-osmolar and ionic CM to minimize the risk of CIN.

Intra-arterial administration of the contrast media

Intra-arterial contrast administration is a risk for CIN. This effect is thought to be due to the fact that the acute intra renal concentration of CM is much higher after intra arterial rather than intravenous injection.

2.3.4 Scoring method to predict high risk patients for CIN

Mehran et al. developed a simple scoring method that integrates eight baseline clinical variables to assess the risk of CIN after percutaneous coronary intervention (PCI). These are hypotension (score 5), use of intra-aortic balloon pump (score 5), congestive heart failure (score 5), serum creatinine >1.5 mg/dl (score 4), age >75 years (score 4), anemia (score 3), diabetes mellitus (score 3), and volume of CM (score 1 per 100 ml). If the total score is 5 or less, the risk category is low; if the total score is 16 or higher, the risk category is very high (Mehran et al., 2004)

2.4 Prevention strategies for CIN

Extracellular volume expansion with intravenous saline or sodium bicarbonate, minimizing the dose of CM, using low-osmolar non-ionic CM instead of high osmolar ionic CM, stopping the intake of nephrotoxic drugs and avoiding short intervals between procedures requiring CM have all been shown to be effective in reducing CIN. Alternatives to ordinary CM, such as carbon dioxide or gadolinium chelates, can be used in patients at high risk of CIN (Table 2).

Volume expansion

Volume expansion is the single most important measure that has been documented to be beneficial in preventing CIN. A standardized saline hydration protocol has been proven

Clinical evidence advocating their use	Don't use	With conflicting or limited evidence
Extracellular volume expansion	Nonsteroidal anti-inflammatory drugs, COX-2 inhibitors, aminoglycoside, cisplatin	Acetylcystein
Saline or sodium bicarbonate	Loop diuretics	Theophylline
Low or iso-osmolar contrast	Mannitol	Calcium channel blockers
Minimizing the dose of contrast	Multiple use of contrast within 72 h	Fenoldopam
Alternative imaging techniques	Large doses of contrast	Captopril
Monitoring serum creatinine	High-osmolar contrast	Ascorbic acid
Delaying contrast procedures until hemodynamic status is corrected	Metformin usage especially in patients with renal failure	Atrial natriuretic peptide
≥48 h between contrast procedures		Endothelin antagonist
		PGE1
		Hemofiltration
		Nebivolol
		Statins
		B-type natriuretic peptide
		Pentoxifylline

Table 2. Prevention strategies for contrast-induced nephropathy in high-risk patients

effective in reducing the risk of CIN and should be used routinely. The most widely accepted protocol is administering isotonic saline at 1 to 1.5 ml/kg/h beginning 6 to 12 hours prior to the procedure and continuing for up to 12 hours following contrast administration. In a randomized trial, two different hydration regimens were compared in 1620 patients undergoing coronary interventions. They showed that the incidence of CIN was significantly lower among patients given an isotonic saline solution than among those given a hypotonic saline solution (0.7% vs. 2.0% respectively, p=0.04) (Mueller et al., 2002). In another trial, a total of 119 patients with serum creatinine exceeding 1.1 mg/dl were randomized to receive isotonic solution of sodium bicarbonate (n=59) or isotonic saline (n=60) at a rate of 3 ml/kg/h for 1 hour before and 1 ml/kg/h for 6 hours after contrast administration. CIN developed in only 1 patient (1.7%) compared with 8 patients (13.6%) in the saline group (p=0.02) (Merten et al., 2004). The authors postulated that a reduction in oxidative injury may have conferred protection against CIN. However, further studies are required to clarify the role of hydration with sodium bicarbonate in preventing CIN. In a prospective study, the effect of combination intravenous and oral volume supplementation on the development of CIN was studied in 425 patients undergoing percutaneous coronary intervention. Patients were randomly assigned to receive hydration with either isotonic or half-isotonic. In addition patients were encouraged to drink plenty of fluids (at least 1500 ml). They found that applying the combination of intravenous and oral volume supplementation results in a very low incidence of CIN (1.4%)

(Mueller et al., 2005). Most studies have found that hydration alone is better than hydration combined with a diuretic. In a study, 78 patients with serum creatinine >1.6 mg/dl were randomized to three groups: hydration alone, hydration with mannitol and hydration with furosemide. Half-isotonic saline was used for hydration. CIN occurred in 11%, 28% and 40% of patients in the three groups, respectively ($p=0.02$), thus showing that forced diuresis is of no benefit in preventing CIN. In a meta-analysis it was found that the administration of sodium bicarbonate is superior to the administration of saline alone in the prevention of CIN (Solomon et al., 1994). However, further controlled clinical trials are needed due to significant study heterogeneity and publication bias. The effectiveness of sodium bicarbonate treatment to prevent CIN in high-risk patients remains uncertain.

N-acetylcysteine

It had been postulated that antioxidant N-acetylcysteine (NAC) might scavenge oxygen free radicals, thus attenuate the cytotoxic effects of CM. NAC may also have direct vasodilating effects on the kidneys through an increase in the biologic effects of nitric oxide. Tepel et al. were evaluated the effects of NAC (600 mg orally twice daily), at first time, in 83 patients undergoing computed tomography. Two percent of the patients in the NAC group had CIN versus 21% in the placebo group ($p=0.01$) (Tepel et al., 2000). Since then, a number of trials have been published. Results from these trials have been inconsistent. In a randomized, placebo-controlled study it was found that NAC is protective against CIN. Fifty-four patients were randomized to receive either 600 mg of NAC twice daily for 4 doses or placebo. The incidence of CIN was 8% in the NAC group versus 45% in the placebo group ($p=0.005$) (Diaz-Sandoval et al., 2002). In addition to oral administration, intravenous administration of NAC to protect against CIN has also been evaluated. In a study, Baker et al. randomly assigned 80 patients to receive either NAC infusion ($n=41$) versus saline infusion ($n=39$). CIN developed in only 2 (5%) of patients in the NAC group compared with 8 (21%) in the saline group ($p=0.04$) (Baker et al., 2003). The authors concluded that NAC infusion protects against CIN. In a meta-analysis, evaluating more than 800 patients at high risk of developing CIN also documented a positive impact of NAC prophylaxis on CIN (Birck et al., 2003). In another meta-analysis, nine randomized controlled trials were included and the difference in mean change in creatinine between the NAC treated group and controls was -0.27 mg/dl. The relative risk of developing CIN was 0.43 in subjects randomized to NAC. They suggest that NAC helps prevent declining renal function and CIN (Liu et al., 2005). In contrast to these reports, some studies failed to find a significant effect of NAC on the occurrence of CIN. A total of 183 patients with preexisting renal insufficiency undergoing contrast study were randomly assigned to receive NAC at a dose of 600 mg twice daily on the day before and the day of the contrast study plus saline infusion or saline alone. The incidence of CIN was 6.5% in the NAC group versus 11% in the control group ($p=0.22$) (Briguori et al., 2002). In a multi centric double blind clinical trial 156 patients undergoing coronary angiography or percutaneous coronary intervention with creatinine clearance <50 ml/min were randomly assigned to receive N-acetylcysteine 600 mg orally twice daily for two days or placebo. Sixteen patients developed CIN. Eight of 77 patients (10.4%) in the NAC group and eight of 79 patients (10.1%) in the placebo group ($p=1.00$). No difference was observed in the change in endogenous creatinine clearance, $p=0.28$). They concluded that oral NAC did not prevent CIN in patients at low to moderate risk undergoing cardiac catheterisation with ionic low osmolality CM (Gomes et al., 2005). In another study, 50 patients undergoing elective diagnostic coronary angiography with serum creatinine values

above 1.3 mg/dl were included and CIN was detected in 3 of 25 patients (12%) in the NAC group and 2 of 25 patients (8%) in the control group ($p>0.05$). It was detected that in patients planned to undergo elective diagnostic coronary angiography with renal dysfunction, oral NAC and hydration before the procedure was not more effective than hydration alone in the prevention of CIN (Gulel et al., 2005). A direct renoprotective effect of NAC remains questionable. To date, only a few trials described the effects of NAC not only on serum creatinine but also on clinical end points. The serum creatinine can be decrease in administration of NAC without renoprotective effect. In a prospective study, NAC was given at a dose of 600 mg every 12 h for a total of four doses to the volunteers with a normal renal function who did not receive contrast agent. There was a significant decrease of the mean serum creatinine ($p<0.05$) and a significant increase of the GFR ($p<0.02$), whereas the cystatin C concentration did not change significantly (Hoffmann et al., 2004). In patients undergoing emergency diagnostic procedures, in whom a full hydration protocol is not possible, an abbreviated hydration regimen plus oral or intravenous administration of NAC can be recommended. NAC may be of benefit mostly in high-risk patients. If NAC is to be used as a preventative measure, it should be given at a dose of 600 mg orally twice daily on the day before and day of the procedure.

Ascorbic acid

Prophylactic oral administration of ascorbic acid may protect against CIN. In a randomized, placebo-controlled trial in 231 patients with serum creatinine concentration ≥ 1.2 mg/dl who undergoing coronary angiography showed that the use of ascorbic acid was associated with a significant reduction in the rate of CIN. CIN occurred in 11 of the 118 patients (9%) in the ascorbic acid group and in 23 of the 113 patients (20%) in the placebo group (OR=0.38; $p=0.02$) (Spargias et al., 2004). Further prospective studies are needed to validate these preliminary results.

Fenoldopam

Fenoldopam mesylate is a selective dopamine-1 receptor agonist that produces systemic, peripheral and renal arterial vasodilatation. Several investigators have reported a positive impact of fenoldopam against CIN in small studies. In a placebo-controlled, double-blind, multicenter trial, 315 patients with creatinine clearance of less than 60 ml/min were randomized to receive fenoldopam infusion [0.05 $\mu\text{g/kg/min}$ titrated to 0.1 $\mu\text{g/kg/min}$ ($n=157$)] or matching placebo ($n=158$). CIN occurred in 33.6% of patients in the fenoldopam group compared with 30.1% of patients in the placebo group ($p=0.61$) (Stone et al., 2003). The authors concluded that fenoldopam did not protect against CIN. In 2 other large studies comparing fenoldopam with NAC treatment with fenoldopam either had a similar, non significant effect as that of NAC or was inferior to it (Allaqaband et al., 2002; Briguori et al., 2004). Therefore, the routine use of fenoldopam cannot be recommended at the present time.

Adenosine antagonists

CM stimulate the intrarenal secretion of adenosine, which binds to the renal adenosine receptor and acts as a potent vasoconstrictor, reducing renal blood flow and increasing the generation of oxygen free radicals as it is metabolized to xanthine and hypoxanthine. Theophylline and aminophylline, adenosine antagonists, have also been studied in the prevention of CIN in a number of trials. Studies with these agents have used varying doses and dosage forms and yielded conflicting results (Erley et al., 1999; Kapoor et al., 2001).

Based on the conflicting information found in clinical studies, adenosine antagonists should not be routinely used in patients as a preventative measure at this time.

Calcium channel blockers

The calcium channel antagonists verapamil and diltiazem have been found to attenuate the renal vasoconstrictor response after exposure to CM. However, when the efficacy of the felodipine, nitrendipine and nifedipine was evaluated, results were inconsistent. Two small studies performed the use of sublingual nifedipine given prior to contrast administration. Patients (n=20) who received sublingual nifedipine did not have a significant increase in serum creatinine, while those in the placebo group did (Rodicio et al., 1990). In another study, patients (n=30) who received nifedipine had an increase in renal plasma flow following administration of contrast, while patients in the placebo group had a decrease in renal flow (Russo et al., 1990). One other study showed that nitrendipine use cause a significant reduction in the GFR in the placebo group compared to little or no change in GFR in the nitrendipine group (Neumayer et al., 1989). In another study, 27 patients with normal to moderately reduced renal function underwent femoral angiography randomized to receive either oral felodipine or placebo. Patients in the felodipine group had a significant increase in serum creatinine from baseline, while patients in the placebo group did not demonstrate a similar increase (Spangberg-Viklund et al., 1996). More large-scale trials are needed before calcium channel blockers can be routinely recommended in patients prior to contrast administration.

Prostaglandin E₁

PGE₁ has vasodilatory effects that may be beneficial in preventing CIN. In one study, 130 patients were randomly assigned to receive either placebo or one of three doses of PGE₁. The increase in serum creatinine level was smaller in all of the three PGE₁ groups than in the placebo group, but the difference was significant only in the medium-dose (20 ng/kg/min) of PGE₁ group (Koch et al., 2000). More studies need to be done to better understand the role of prostaglandin E₁, but results from this pilot study appear promising.

Atrial natriuretic peptide (ANP)

ANP may prevent CIN by increasing renal blood flow. In a study, ANP was included in one of the four arms. In which dopamine, mannitol, and ANP caused an increase in CIN in diabetic patients as compared to saline alone (Weisberg et al., 1994). In another trial patients were randomized to one of four treatment arms: fluid alone or one of three doses of ANP. Results showed no statistically significant differences in the incidence of CIN between any of the four treatment arms (Kurnik et al., 1998) Based on these results and the limited clinical data, ANP cannot be advocated in the prevention of CIN.

Endothelin antagonists

Endothelin-1 is a potent endogenous vasoconstrictor, is thought to play a role in the development of CIN. Endothelin-1 has two primary receptors. In animal studies, endothelin-A antagonists were shown to reduce the incidence of CIN (Liss et al., 2003). However, in a randomized study of 158 patients, the use of a mixed endothelin-A and B antagonist was associated with a significantly higher incidence of CIN than was placebo (56% vs. 29%, p=0.002) (Wang et al., 2000). Endothelin antagonists currently have no role in prevention of CIN.

Low-dose of dopamine

At low doses (1-3 mcg/kg/min), dopamine activates two types of dopamine (DA) receptors, DA-1 and DA-2. Activation of the DA-1 receptor results in an increase in natriuresis and renal blood flow. Since dopamine, at low doses, is believed to be more selective for the DA-1 receptors, it has been investigated in the prevention of CIN. Kapoor et al. randomized 40 patients with diabetes scheduled to undergo a coronary angiography to either dopamine or placebo control. None of the patients in the dopamine group developed CIN compared to 50% of patients receiving placebo (Kapoor et al., 2002). In another prospective, randomized trial, Hans et al. evaluated 55 patients (40% had diabetes) with chronic renal insufficiency. Patients were randomized to receive dopamine or an equal volume of saline. The group receiving dopamine had a significantly lower incidence of CIN as compared to the control group (Hans et al., 1998). In contrast to the trials showing a potential benefit of dopamine, other studies have failed to demonstrate this benefit. Abizaid et al. performed a randomized, prospective study involving patients with renal insufficiency who underwent coronary angioplasty. Patients were randomized to continue with the saline, receive aminophylline in addition to the saline, or receive dopamine plus saline. In the dopamine plus saline group, 50% of patients developed CIN, while only 30% of the patients in the saline-alone group developed CIN. This difference did not reach statistical significance, but it appeared that use of dopamine might worsen outcomes (Abizaid et al., 1999). Low-dose dopamine use cannot be supported at this time.

Statins

Whether additional benefits can be achieved with the use of statin in decreasing the risk of CIN remains undetermined. In a recent meta analysis of randomised controlled trials comparing statin pretreatment with non-statin pretreatment for the prevention of CIN, it was found that, the incidence of CIN was not significantly lower in statin pretreatment group as compared with control group (RR=0.76, p=0.30) (Zhang et al., 2011). The current cumulative evidence suggests that statin pretreatment may neither prevent CIN nor reduce the need for renal replacement therapy.

Hemofiltration and hemodialysis

Currently available data do not support use of prophylactic hemodialysis for prevention of CIN. In a trial of 113 patients, reported that CIN occurred in 24% of the hemodialysis group as compared with 16% of non-hemodialysis group (Vogt et al., 2001). Clinically relevant events also were not different in two groups. Only continuous venovenous hemofiltration has been shown to protect against CIN. In a study, 114 patients with chronic renal failure undergoing percutaneous coronary intervention were divided in two groups: 56 patients received normal saline and 58 patients underwent hemofiltration at a rate of 1000 ml/h (Marenzi et al., 2003). Hemofiltration seems to have a protective effect, including significant reduction in in-hospital and 1-year mortality compared with routine hydration. The mechanisms of this benefit are not clear. Further studies are needed to confirm the results of this trial.

New types of contrast medias

Gadolinium-enhanced magnetic resonance coronary angiography is a non-invasive method for evaluation of coronary arteries. It has been suggested that gadolinium-based CM could be used in stead of iodinated CM for radiological examinations in patients with significant

renal impairment. However, its use has been questioned on the basis of reports of nephrotoxicity and its association with nephrogenic systemic fibrosis, a rare and serious syndrome that involves fibrosis of skin, joints, eyes, and internal organs. In a study by Hoffmann et al. the effect of gadopentetate dimeglumine (iodine-based CM) was studied in 181 patients with normal renal function and the effect of gadolinium was studied in 198 patients with pre-existing renal failure. There was no statistically significant change in serum creatinine concentration after gadopentetate dimeglumine. In contrary, serum creatinine levels decreased significantly after the administration of gadolinium ($p < 0.01$) (Hoffmann et al., 2005). In a retrospective study, the safety of gadolinium was evaluated in 91 patients with stage 3 and 4 renal failure who underwent angiographic MRI procedures. Eleven of 91 patients developed CIN (12.1%) (Ergun et al., 2006). In another randomized study gadobutrol, a gadolinium-based CM, was compared with standard iohexol, an iodinated CM, in 21 patients with renal dysfunction. The incidence of CIN was 50% in gadobutrol group and 45% in iohexol group ($p = 0.70$). In this study, gadolinium showed no benefit over iohexol in patients with severely impaired renal function (Erley et al., 2004). More studies need to be done to better understand the role of gadolinium on CIN. Ultrasound contrast agents are micro-bubbles which produce acoustic enhancement. They are pharmacologically almost inert and safe.

3. Conclusion

The development of CIN is associated with adverse outcomes including prolonged hospitalization, the potential need for renal replacement therapy, and most important, increased mortality. The treatment of established CIN is limited to supportive measures and dialysis. For this reason, screening for high-risk patients before CM including cardiac procedures and taking the appropriate prophylactic regimens is important in reducing CIN. Pre-existing renal dysfunction, especially when secondary to diabetic nephropathy, is the most important risk factor. Extra cellular volume expansion and use of low osmolar CM are the two most effective measures to prevent CIN. Acetylcysteine may use in high-risk patients, but this finding has not been uniform or always demonstrated by currently available trials.

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Coronary artery disease (CAD) and its consequences are most important morbidity and mortality reasons in the developed and developing countries. To prevent hard end-points, early definitive diagnosis and optimum therapy play significant role. Novel advanced diagnostic tests which are biomarkers of inflammation, cell adhesion, cell activation and imaging techniques provide to get the best result in the detection and characterization of calcified or uncalcified atherosclerotic plaques. In spite of last developments in the imaging methods, coronary catheterization is still frequently performed. Following the first cardiac catheterization performed in 1844, date by date historical developments and the mechanics of cardiac catheterization techniques, risks associated with coronary angiography, and also, preventions and treatments of possible complications have been presented in this book. Other important issue is radiation exposure of patients and staff during coronary angiography and scintigraphy. Radiation dose reduction techniques, general radiation protection principles have been discussed in related chapters.

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