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Contrast-induced nephropathy: Definition, epidemiology, and patients at risk

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Radiological procedures utilizing intravascular iodinated contrast media injections are being widely applied for both diagnostic and therapeutic purposes. This has resulted in an increasing incidence of procedure-related contrast-induced nephropathy (CIN). The definition of CIN includes absolute (⩾0.5 mg/dl) or relative increase (⩾25%) in serum creatinine at 48–72 h after exposure to a contrast agent compared to baseline serum creatinine values, when alternative explanations for renal impairment have been excluded. Although the risk of renal function impairment associated with radiological procedures is low (0.6–2.3%) in the general population, it may be very high in selected patient subsets (up to 20%), especially in patients with underlying cardiovascular disease. This review provides information on the known risk factors for the development of CIN, and completes with describing user-friendly CIN risk score based on the readily available information.

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CIN: DEFINITION, INCIDENCE, AND TIMING

Contrast media (CM) are increasingly used in diagnostic and interventional procedures. This results in the rising incidence of iatrogenic renal function impairment caused by the exposure to CM, a condition known as CIN. Radiographic CM are responsible for 11% of cases of hospital-acquired renal insufficiency, the third most common cause of renal failure after impaired renal perfusion and the use of nephrotoxic medications.[1] Among all procedures utilizing CM for diagnostic or therapeutic purposes, coronary angiography and percutaneous coronary interventions (PCI) are associated with the highest rates of CIN.[1]

The definition of CIN includes three necessary components:[1] an absolute or relative increase in serum creatinine compared to the baseline values;[2] a temporal relationship between the rise in serum creatinine and exposure to a contrast agent, and[3] the exclusion of alternative explanations for renal impairment (e.g. cholesterol embolism).

The most common definition of CIN today is an increase of 25% or more, or an absolute increase of 0.5 mg/dl or more in serum creatinine from baseline value, at 48–72 h following the exposure to CM. The first 24 h post-exposure appear to be crucial in the development of CIN. A study of the trajectory of serum creatinine elevation in the randomized Prevention of Radiocontrast Induced Nelphropathy Clinical Evaluation trial indicated that in 80% of CIN cases serum creatinine started to rise within the first 24 h post-CM exposure, and nearly all patients who progressed to serious renal failure (one requiring either nephrology consultation or dialysis) had a rise in serum creatinine within this time frame.[2,3] The same study showed that patients with less than 0.5 mg/dl rise in serum creatinine within the first 24 h were unlikely to have any clinically meaningful form of CIN.[3] The serum creatinine typically peaks 3–5 days after contrast administration and returns to baseline or near baseline within 1–3 weeks.[4]

An overall incidence of CIN in the general population is reported to be 0.6–2.3%.[5] However, in several patient subsets the prevalence of CIN is significantly higher.[6–9] This is especially true in patients with cardiovascular pathology. In the interventional cardiology registry from Mayo Clinic including 7586 patients, the incidence of CIN was 3.3%.[8] In a smaller study from William Beaumont Hospital, among 1826 patients treated with PCI, CIN occurred in 14.5% of the

Table 1 | Risk factors for the development of CIN

Fixed (non-modifiable) risk factors	Modifiable risk factors
Older age	Volume of CM
Diabetes mellitus	Hypotension
Pre-existing renal failure	Anemia and blood loss
Advanced CHF	Dehydration
Low LVEF	Low serum albumin level (<35 g/l)
Acute myocardial infarction	ACE inhibitors
Cardiogenic shock	Diuretics
Renal transplant	Non-steroidal anti-inflammatory drugs
	Nephrotoxic antibiotics
	IABP

Abbreviations: ACE, angiotensin-converting enzyme; CHF, congestive heart failure; CIN, contrast-induced nephropathy; CM, contrast media; IABP, intra-aortic balloon pump; LVEF, left ventricular ejection fraction.

cases.[9] Dialysis as a result of CIN in these two series was required in 0.7 and 0.3%, respectively.[8,9] The risk of CIN is especially high (19%) in the setting of primary PCI for acute myocardial infarction.[10]

Identification of patients at high risk for the development of CIN is of major importance. Table 1 summarizes the risk factors for the development of CIN. Non-modifiable risk factors include pre-existent renal insufficiency, diabetes mellitus, older age, reduced left ventricle systolic function, advanced heart failure, acute myocardial infarction, and shock, while volume and type of CM, concomitant use of nephrotoxic medications, hypotension, dehydration, hypoalbuminemia, anemia, and the use of intra-aortic balloon pump (IABP) represent the modifiable risk factors for CIN.

RISK FACTORS

Pre-existing renal disease

Pre-existing renal disease with an elevated level of serum creatinine is the most crucial risk factor in the development of CIN. The incidence of CIN in patients with underlying chronic kidney disease is extremely high, ranging from 14.8 to 55%.[8,9,11] In one study, despite pre-procedure hydration and the use of non-ionic CM, CIN occurred in one-third of 439 consecutive patients who underwent PCI and had baseline serum creatinine $\geqslant 1.8$ mg/dl.[11]

The higher the baseline creatinine value, the greater is the risk of CIN. As shown in one of the studies, if baseline plasma creatinine level is $\leqslant 1.2$ mg/dl, the risk of CIN is only 2%.[12] In patients with values of creatinine in the range of 1.4–1.9 mg/dl, the risk of CIN compared with that in the previous group increases fivefold (10.4%).[12] As for patients with baseline creatinine level $\geqslant 2.0$ mg/dl, more than half of them (62%) subsequently develop CIN.[12]

However, baseline creatinine is not reliable enough for identification of patients at risk for CIN. This is because serum creatinine value varies with age, muscle mass, and gender. Since creatinine production decreases with age, a normal serum creatinine in an elderly patient generally correlates with at least moderate decrease in renal function. To evaluate renal function reliably, assessment of creatinine clearance should be performed. While it is not practical to measure creatinine clearance directly, its estimation based on the Cockcroft–Gault formula or Modification of Diet in Renal Disease equation may be easily performed. Several studies showed that an estimated glomerular filtration rate (eGFR) of 60 ml/min/1.73 m^2 is a reliable cutoff point for identifying patients at high risk for the development of CIN. This makes calculation of eGFR highly recommended before exposure to CM for the CIN risk assessment.[13,14]

Patients with a renal transplant are at increased risk of CIN due to high prevalence of diabetes, renal insufficiency, and the use of nephrotoxic drugs (e.g. cyclosporine and nephrotoxic antibiotics) in this population.[15] In one study, the incidence of CIN in patients with renal transplant was 21.2%, being especially high (42.8%) among those who have not received pre-procedure hydration.[15]

Diabetes mellitus

Diabetic patients represent a significant proportion of those undergoing contrast exposure due to high prevalence of diabetes in the general population and the ability of the disease to cause a broad spectrum of cardiovascular diseases that require radiological procedures using CM. The incidence of CIN in diabetic patients varies from 5.7 to 29.4%.[5,16] Importantly, in diabetics patients with preserved renal function and the absence of other risk factors, the rates of CIN are usually comparable to those of a non-diabetic population,[5] while clinically important CIN usually occurs in a subset of diabetics with underlying renal insufficiency.[16–18] In one study, CIN occurred in 27% of diabetic patients with baseline serum creatinine 2.0–4.0 mg/dl and in 81% of those with serum creatinine >4.0 mg/dl.[19] In another study, CIN post-PCI occurred in 15.1% of patients without chronic kidney disease vs 27.4% in those with chronic kidney disease, and *de-novo* dialysis was instituted in 0.1 vs 3.1%, respectively (both $P<0.0001$).[16]

Age

Several studies provided evidence that older age is an independent predictor of CIN.[6,20,21] The reasons for higher risk to develop CIN in elderly were not studied specifically and probably are multifactorial, including age-related changes in renal function (diminished glomerular filtration rate, tubular secretion, and concentrating ability). The presence of multivessel coronary artery disease, necessitating complex PCI, coupled with more difficult vascular access resulting from tortuosity and calcification of the vessels frequently requires greater amount of CM, and therefore represent additional factors of increased CIN in elderly.

Volume of CM

The volume of CM is a main modifiable risk factor in the development of CIN. The correlation between the amount of CM and the risk of CIN is well documented.[9,21–25] Most of the studies indicate that the higher volume of CM is especially deleterious in the presence of other risk factors. Even relatively low doses of contrast (less than 100 ml) can

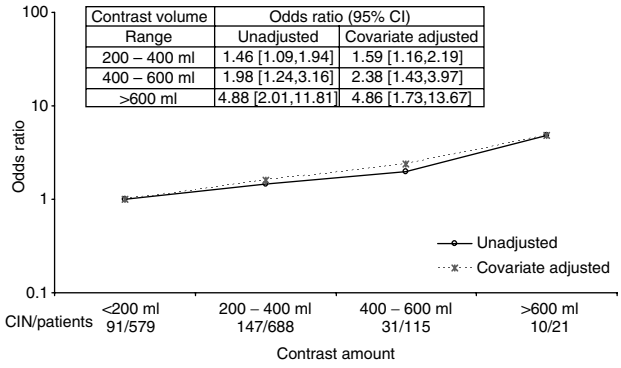

Figure 1 | Unadjusted and covariate adjusted odds ratios of CIN in patients stratified by amount of CM administered. The calculations were performed using the patients who were administered <200 ml of CM as a reference group.
CIN, contrast-induced nephropathy.

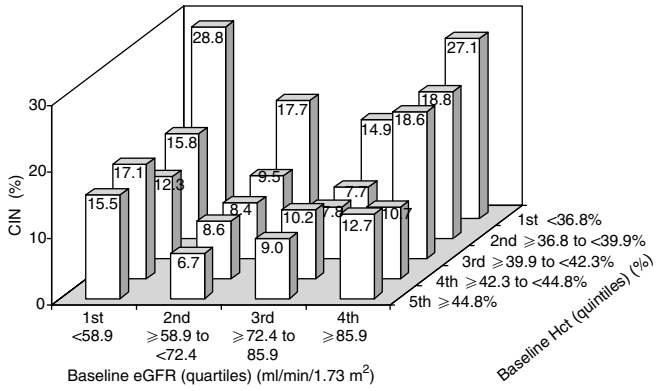

Figure 2 | Risk of CIN in relation to baseline hematocrit and eGFR.

induce permanent renal failure and the need for dialysis in patients with chronic kidney disease.[26,27] In the study on a diabetic population, CIN developed in approximately every fifth, fourth, and second patient who received 200–400, 400–600, and >600 ml of CM, respectively.[16] In the same study, each 100 ml increment in contrast volume resulted in a 30% increase in the odds of CIN (odds ratio 1.30, 95% confidence interval 1.16–1.46), and there was a significant ($P<0.0001$) trend towards increased covariate adjusted odds of CIN across increased amounts of CM (Figure 1).[16]

Anemia and procedure-related blood loss

Anemia might be one of the factors contributing to renal ischemia. In a study based on interventional cardiology database analysis, rates of CIN steadily increased as pre-procedure hematocrit quintile decreased (from 10.3% in the highest quintile (hematocrit value ⩾44.8%) to 23.3% in the lowest quintile (hematocrit value <36.8%); χ^2 for trend $P<0.0001$).[28] Stratification by baseline eGFR and baseline hematocrit showed that the rates of CIN were the highest (28.8%) in patients who had the lowest level for both baseline eGFR and pre-procedure hematocrit. Patients with the lowest eGFR but relatively high baseline hematocrit values had remarkably lower rates of CIN (15.8, 12.3, 17.1, and 15.4% in the second, third, fourth, and fifth quintiles of baseline hematocrit, respectively; $P<0.0001$) (Figure 2). The rates of CIN increased also with increment in change in hematocrit compared to the baseline value. Patients in the lowest quintile of baseline hematocrit with an absolute hematocrit drop >5.9% had almost twice the incidence of CIN compared with patients with hematocrit change <3.4% (38.1 vs 18.8%, respectively; $P<0.0001$).[28] By multivariate analysis, lower baseline hematocrit was identified as an independent predictor of CIN regardless of the presence or absence of chronic kidney disease: 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). When introduced into the multivariate model instead of baseline hematocrit, change in hematocrit also showed a significant association with CIN.[28]

Other risk factors

Advanced congestive heart failure, compromised left ventricle systolic performance, dehydration, hypotension, the use of IABP and several drugs (angiotensin-converting enzyme inhibitors, diuretics, and non-steroidal anti-inflammatory drugs) were also recognized as prognostic factors of CIN.[2,29–31]

Periprocedural hypotension and the use of IABP have a negative impact on the development of CIN.[28,32] The detrimental influence of prolonged hypotension on kidney function is well known. However, even relatively short periods of hypotension may be hazardous.[28] IABP insertion may be linked with CIN through mechanisms that may either provoke or potentate renal impairment via[1] atheroemboli to the renal circulation during IABP insertion, contrapulsation or removal;[2] as a partial occlusion of the renal blood flow if it is positioned too low (i.e. in the abdominal instead of the descending thoracic aorta) and[3] as a marker of increased vascular complications and post-PCI hypotension. Peri-PCI hypotension and use of IABP were shown to be powerful independent predictors of CIN.[28,32]

The role of angiotensin-converting enzyme inhibitors has been controversial. In one study, patients receiving angiotensin-converting enzyme inhibitors had a significant increase in serum creatinine after the procedure compared with patients without such therapy.[21] However, prior use of angiotensin-converting enzyme inhibitors predicted the occurrence of CIN only on univariate, but not on multivariate, analysis.[21]

Type of contrast agents

Controversy exists whether the use of different contrast agents is of any benefit in diminishing the risk of CIN. In studies by Katholi *et al.*[33] and by Harris *et al.*,[34] the decrease in creatinine clearance was more pronounced and lasted longer in the group that received high-osmolality CM compared to the arm exposed to low-osmolality CM. On the contrary, Schwab *et al.*[35] did not show any significant differences in nephrotoxic effect between several studied CM.

In the meta-analysis of 45 trials, the greater increase in serum creatinine after administration of high- compared with low-osmolality CM was seen only in patients with pre-existing renal failure.[36] Within the variety of currently available CM with low osmolality, there are certain differences in nephrotoxic effect that seem to be more evident with ionic than non-ionic agents. A randomized, double-blind, prospective, multicenter Nephrotoxicity in High-Risk Patients Study of Iso-Osmolar and Low-Osmolar Non-Ionic Contrast Media study showed that CIN may be less likely to develop in high-risk patients (baseline serum creatinine 1.5–3.5 mg/dl) when iso-osmolality, non-ionic iodixanol is used rather than a low-osmolality, non-ionic iohexol.[37] The issue of the nephrotoxic effects of various CM is addressed more fully in a subsequent paper in this symposia.

Despite the still existing uncertainty regarding the degree of nephrotoxicity produced by various contrast agents, in current practice non-ionic low-osmolar CM is a preferred agent in patients with renal impairment. Further study is warranted to clarify the issue of minimizing the renal damage, while using the different contrast material.

Combination of multiple risk factors: CIN risk score

Apart from the known unfavorable combination of diabetes and renal insufficiency, the presence of two or more other risk factors for CIN also has an additive influence on the rates of CIN.[9] In one study, for example, CIN occurred in 1.2% of the patients without risk factors, 11.2% with one risk factor (contrast volume greater than 200 ml, serum albumin level <35 g/l, diabetes mellitus, serum sodium level <135 mmol/l, and serum creatinine level >133 mmol/l), and in $>20\%$ of the patients with two or more risk factors.[7]

To assess the cumulative risk of several variables on renal function, a simple CIN risk score that could be readily applied was developed.[38] Based on the odds ratio derived from multivariate logistic regression model, eight variables (hypotension, intraaortic balloon pump, congestive heart failure, chronic kidney disease, diabetes, age >75 years, anemia, and volume of contrast) were assigned a weighted integer; the sum of the integers was a total risk score for each patient (Figure 3). The occurrence of CIN was found to be 7.5–57.3% for a low ($\leqslant 5$) and high ($\geqslant 16$) risk score, respectively. The simplicity of assessment of the risk for CIN post-PCI using readily available information encourages the more widespread use of this risk score for both clinical and investigational purposes.[38]

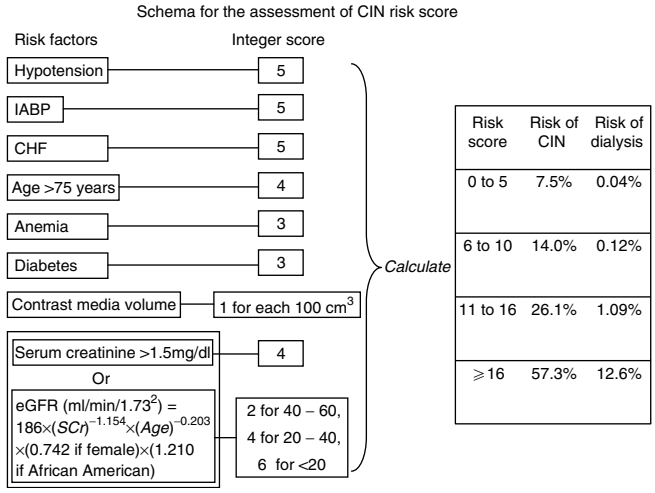

Figure 3 | Scheme to define CIN risk score. CHF denotes congestive heart failure class III–IV by the New York Heart Association classification and/or history of pulmonary edema. eGFR denotes estimated glomerular filtration rate by Modification of Diet in Renal Disease formula. Anemia: baseline hematocrit value $<39\%$ for men and $<36\%$ for women. Hypotension: systolic blood pressure <80 mm Hg for at least 1 h requiring inotropic support with medications or IABP within 24 h periprocedurally.

CONCLUSIONS

CIN is an iatrogenic disorder, resulting from the administration of CM. Although rare in the general population, CIN occurs frequently in patients with underlying renal dysfunction, diabetes, anemia, and the elderly. These risk factors are synergistic in their ability to predispose to the development of CIN. A careful risk–benefit analysis must always be performed prior to the administration of CM to patients at risk for CIN. Given the volume of CM is one of the strongest predictor of CIN, an attempt should be made to reduce the amount of CM. Individual patient risk for CIN after PCI can be globally assessed with the calculation of a simple risk score based on readily available information.

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