The clinical and renal consequences of contrast-induced nephropathy

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Abstract
Contrast-induced nephropathy (CIN), an impairment of renal function following intravascular injection of contrast media, is commonly defined as an increase in the baseline serum creatinine concentration of >25% or ≥0.5 mg/dl (44 μmol/l). The incidence of CIN does not appear to have changed appreciably in the last three decades, and it continues to be the third leading cause of hospital-acquired acute renal failure (ARF). In the general population, the incidence of CIN is estimated to be 1–2%. However, the risk for developing CIN may be as high as 50% in some high-risk patient subgroups, such as those with diabetes mellitus and pre-existing renal impairment. Patients who develop CIN after percutaneous coronary intervention sustain an increase in both short- and long-term mortality whether or not chronic kidney disease was present prior to contrast exposure. The diminished long-term survival in patients with CIN has been observed for both, those whose ARF is not severe enough to require dialysis as well as those requiring dialysis. Treatment is limited to supportive measures while awaiting the resolution of the renal impairment. At times, this does not occur. Because of the lack of treatment options and because CIN is associated with serious short- and long-term sequelae, emphasis needs to be directed at preventative measures, identification of high-risk patients and education of all physicians involved in the care of these patients in order to reduce the incidence of CIN.

Keywords: acute renal failure; contrast-induced nephropathy (CIN); serum creatinine

Introduction
Acute impairment of renal function within 3 days of exposure to contrast media (CM) may occur for a variety of reasons. These include atheroemboli, a risk in patients with diffuse vascular disease, acute interstitial nephritis resulting from hypersensitivity to CM and pre-renal causes such as may occur with intravascular volume depletion or other conditions leading to a reduction in renal blood flow. When all other aetiologies have been excluded, the nephropathy is believed to be directly caused by exposure to the CM and is termed contrast-induced nephropathy (CIN) [1].

The most commonly used clinical definition of renal impairment in CIN is a relative rise in serum creatinine (SCr) ≥25% from the baseline value or an absolute increase ≥0.5 mg/dl (44 μmol/l) within 48 h after the administration of CM. As will be discussed, an increase in SCr ≥50% or 1.0 mg/dl (88 μmol/l) above baseline indicates serious renal impairment and has more grave implications.

CIN is the third most common cause of hospital-acquired renal failure [2,3]. Unfortunately, many physicians who refer patients for contrast procedures are not fully informed about the risk for CIN. For example, in a survey of 203 physicians who commonly refer patients for computed tomography (CT) scans, more than half were not aware of the potential risks associated with CM and less than half considered type 2 diabetes mellitus to be a risk factor for complications [4]. With the number of procedures that involve the use of CM increasing at a rapid rate, the consultant nephrologist can play a vital role in reducing the incidence of CIN by helping referring physicians to understand the short- and long-term consequences in patients who develop CIN.

Relevance of a modest serum creatinine rise after contrast procedures
The clinical importance of an increase in baseline SCr of 25% or 0.5 mg/dl (44 μmol/l) has been questioned in the past. Because of the curvilinear relationship
between SCr and the glomerular filtration rate (GFR), patients at any level of renal function at baseline would have to exhibit doubling of SCr in order to have a corresponding 50% decrease in GFR (i.e. 1.0–2.0; 2.0–4.0; 4.0–8.0 mg/dl) (Figure 1). However, at each step, the absolute change in GFR is progressively less. This is best illustrated by expressing the changes in terms of the reciprocal of the SCr (1/SCr). Here, the increases in the SCr represent step-wise decreases in the GFR of 50, 25 and 12.5%, respectively. The converse is that in patients with chronic kidney disease (CKD) and an already elevated SCr, small changes in the GFR produce dramatic changes in the SCr. It might be inferred that a relatively small change in the SCr that occurs in a patient with CKD following CM exposure is a result of a clinically unimportant reduction in GFR.

However, this is not the case. Patients with severe CKD are in fact at a greater risk for developing clinically significant CIN than are those with a less severe disease or normal function (Figure 2) [5–7]. Specifically, patients who exhibit these seemingly modest increases in SCr after contrast procedures have a higher in-hospital mortality rate, as shown in a retrospective analysis by Weisbord et al. [8]. This analysis used a dataset for >9700 patients without end-stage renal disease (ESRD) who underwent diagnostic or therapeutic coronary angiograms and for whom there were complete data on both the SCr within 72 h of the procedure and the in-hospital mortality. A rise in SCr of ≥25% occurred in 7.5% of these patients at 24 h and in 14.2% at 48 h. The in-hospital mortality rates were 13.6 and 13.9%, for patients showing this increase at 24 and 48 h, respectively. The corresponding odds ratios (OR) for in-hospital mortality (adjusted for the presence of diabetes and baseline GFR) associated with a ≥25% rise in SCr at 24 and 48 h, were 3.9 and 3.3, respectively ($P < 0.0001$). The significantly increased OR for in-hospital mortality observed in this analysis indicates that a ≥25% rise in SCr within 48 h of a contrast procedure is indeed clinically important.
It should be noted that in addition to the GFR, the SCr concentration is influenced by age, sex and body weight because these factors are related to total muscle mass and consequently, to creatinine production. For elderly patients with low muscle mass, the age or disease-related decline in renal function may be matched by a proportionate decrease in muscle mass, leaving the SCr unchanged. There are several formulas that estimate the GFR from combinations of age, race [9], body weight and gender of patients and include the values of SCr, blood urea nitrogen (BUN) and serum albumin. These are much better indicators of renal function than the standard laboratory reference ranges of the SCr and provide greater accuracy for diagnosing renal impairment after contrast procedures [10]. Estimation of the GFR can be done using the Cockcroft–Gault equation, which takes into account age, body mass and sex [11]. Alternatively, it may be possible to more accurately estimate GFR from demographic and laboratory test values using the equation developed and validated using data obtained from patients in the Modification of Diet in Renal Disease Study [9]. These are readily available for use on hand-held electronic devices and if not routinely given as a part of the laboratory report should be used in all patients when considering the administration of CM.

Incidence of contrast-induced nephropathy and risk factors

In 1983, Hou et al. [2] published a prospective study that assessed the causes of hospital-acquired renal insufficiency (HARI) in consecutive medical and surgical patients admitted to the Tufts-New England Medical Center between September 1978 and February 1979. Of the 2216 patients included in the analysis [those admitted because of acute renal failure (ARF) and those receiving long-term renal dialysis were excluded], 109 patients (4.9%) developed HARI. Exposure to CM was the third most frequent cause of acquired renal failure in this setting, after decreased renal perfusion and major surgery. ARF due to CM accounted for 16 out of 129 episodes (12.4%) of acute renal insufficiency [2].

Nash et al. [3] conducted a similar prospective study at Rush Presbyterian-St Luke’s Medical Center, obtaining data from 4622 consecutive medical and surgical patients (excluding those admitted due to renal failure, those receiving long-term dialysis and renal transplantation recipients) admitted between 29 February 1996 and 30 June 1996. A total of 322 patients (7.0%) experienced an episode of HARI; 380 episodes in total were recorded. The third most common cause of HARI in this study was the administration of CM, after decreased renal perfusion and the use of nephrotoxic medications. CM was implicated in 43 out of the 380 cases of HARI (11.3%) [3].

Table 1 lists the incidence of CIN from various types of studies, including retrospective analyses of institutional databases and prospective studies of consecutive patients undergoing contrast procedures [12–24]. The incidence of CIN in these studies ranges from 3.1 to 31%. These findings, along with those of Hou et al. [2] and Nash et al. [3], indicate that despite greater knowledge about the risk factors for CIN and the development of low-osmolar CM and iso-osmolar CM, the incidence of CIN has not changed during this time period.

The risk factors for CIN are discussed in more detail in the manuscript by Lameire [25] in this supplement. Perhaps the most significant risk factor is pre-existing renal impairment [26–31]. Diabetes mellitus also increases the risk for CIN [26–31], and patients with concomitant diabetes mellitus and impaired renal function have a particularly high risk for this complication [27,32,33], with an incidence of CIN as high as 50% [34]. Referring physicians may not be sufficiently educated as to which patients are most likely to develop CIN. For example, a survey published in 2002 that studied 203 physicians from three university hospitals revealed a relatively high correct response rate for questions about patients who might develop anaphylactoid reactions, with 81.3, 77.8 and 61.6% identifying patients with asthma, food allergy and hay fever being at risk. However, only 38.9% considered diabetes mellitus as risk factor for complications after CM administration [4].

Consequences of contrast-induced nephropathy

Short-term mortality

Patients who develop CIN have been shown to have a higher rate of in-hospital mortality when compared with those who do not. This fact by itself validates the definition of CIN previously discussed. For example, a study of 1826 consecutive patients undergoing coronary interventions reported by McCullough et al. [20] found that the in-hospital mortality rate for the 264 patients (14.4%) who developed CIN (SCr increase >25% within 5 days) but who did not require dialysis was significantly greater than that of the patients who did not develop CIN (7.1 vs 1.1%, P < 0.000001; Figure 3). The corresponding OR for in-hospital mortality associated with CIN was 6.56 (95% CI 3.34–12.92; P < 0.00001) [20].

A retrospective analysis of data from the Mayo Clinic PCI Registry also demonstrated significantly greater short-term mortality with CIN. Of the 7586 patients undergoing percutaneous coronary intervention (PCI) included in the analysis, 254 patients (3.3%) experienced CIN (SCr increase >0.5 mg/dl), and the in-hospital mortality rate for these patients was 22% compared with a rate of 1.4% for the patients who did not develop CIN ($P < 0.0001$) [22].
Table 1. Incidence of CIN in representative studies during the past 30 years

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of study</th>
<th>Patients, n</th>
<th>Contrast procedure</th>
<th>Study definition of CIN</th>
<th>Incidence of CIN (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older et al. [12]</td>
<td>Prospective, randomly chosen patients</td>
<td>90</td>
<td>Angiography</td>
<td>SCr increase within 4 days (\geq 20%) (\geq 0.3,\text{mg/100,ml})</td>
<td>18.8</td>
</tr>
<tr>
<td>Swartz et al. [13]</td>
<td>Retrospective, consecutive patients</td>
<td>109</td>
<td>Angiography</td>
<td>BUN increase within 48 h (\geq 50%) (\geq 20,\text{mg/dl}) or SCr increase within 48 h (\geq 50%) (\geq 1,\text{mg/dl})</td>
<td>12</td>
</tr>
<tr>
<td>Teruel et al. [14]</td>
<td>Prospective, randomly chosen patients</td>
<td>124</td>
<td>IV urography</td>
<td>SCr increase within 48 h (\geq 25%) (\geq 1,\text{mg/dl})</td>
<td>21.8</td>
</tr>
<tr>
<td>Martin-Paredero et al. [15]</td>
<td>Retrospective</td>
<td>400</td>
<td>Major aortography</td>
<td>BUN increase within 48 h (\geq 50%) (\geq 20,\text{mg/dl}) or SCr increase within 48 h (\geq 50%) (\geq 1,\text{mg/dl}) within 48 h</td>
<td>11.3</td>
</tr>
<tr>
<td>Gomes et al. [16]</td>
<td>Retrospective</td>
<td>364</td>
<td>Abdominal aortography (\text{Aortic arch studies}) (\text{Aortic arch plus selective carotid angiography})</td>
<td>SCr increase within 48 h (\geq 50%) (\geq 1,\text{mg/dl})</td>
<td>7.1</td>
</tr>
<tr>
<td>Mason et al. [17]</td>
<td>Prospective</td>
<td>*</td>
<td>Angiography</td>
<td>CrCl decrease (\geq 25%)</td>
<td>31</td>
</tr>
<tr>
<td>Taliercio et al. [18]</td>
<td>Retrospective</td>
<td>139\footnote{\text{y}}</td>
<td>Cardiac angiography</td>
<td>SCr increase (\geq 1.0,\text{mg/dl}) between days 1 and 5</td>
<td>23</td>
</tr>
<tr>
<td>Rich et al. [19]</td>
<td>Prospective</td>
<td>183\footnote{\text{z}}</td>
<td>Cardiac catheterization</td>
<td>SCr increase (\geq 44,\mu\text{mol}) within 48 h</td>
<td>11.5</td>
</tr>
<tr>
<td>McCullough et al. [20]</td>
<td>Prospective, consecutive patients</td>
<td>1826</td>
<td>Coronary interventions</td>
<td>SCr increase (\geq 25%) within 5 days</td>
<td>14.5</td>
</tr>
<tr>
<td>Schillinger et al. [21]</td>
<td>Retrospective, consecutive patients</td>
<td>213</td>
<td>I-arterial digital subtraction angiography followed by percutaneous balloon angioplasty</td>
<td>CrCl increase (\geq 20%) within 24 h</td>
<td>12.0</td>
</tr>
<tr>
<td>Rihal et al. [22]</td>
<td>Retrospective</td>
<td>7586</td>
<td>Coronary interventions</td>
<td>SCr increase (\geq 0.5,\text{mg/dl}) within 48 h</td>
<td>3.3</td>
</tr>
<tr>
<td>Iakovou et al. [23]</td>
<td>Retrospective</td>
<td>8628</td>
<td>PCI</td>
<td>SCr increase (\geq 25%) within 48 h</td>
<td>16.5</td>
</tr>
<tr>
<td>Nikolsky et al. [24]</td>
<td>Retrospective</td>
<td>6773</td>
<td>PCI</td>
<td>SCr increase within 48 h (\geq 25%) (\geq 0.5,\text{mg/dl})</td>
<td>13.9</td>
</tr>
</tbody>
</table>

AMI, acute myocardial infarction; BUN, blood urea nitrogen; CIN, contrast-induced nephropathy; PCI, percutaneous coronary interventions; SCr, serum creatinine; CrCl, creatinine clearance. \footnote{\text{y}}The analysis included 120 procedures, but the number of patients was not specified; \footnote{\text{z}}patients with SCr \(\geq 2.0\,\text{mg/dl}\); \footnote{\text{z}}\text{aged} \(\geq 70\) years.
The severity of CIN associated with CM exposure has been associated with the in-hospital mortality rate. The study by McCullough et al. [20] also assessed the in-hospital mortality rates for patients who developed CIN requiring dialysis, of which there were 14. The in-hospital mortality rate for these patients was 35.7%, with a corresponding OR of 13.54 (95% CI 3.92–46.8; \( P < 0.00001 \)) [20].

The effect of CIN on short-term mortality in patients with CKD and/or diabetes mellitus was assessed by Nikolsky and Mehran [35]. Outcomes for patients with CIN from 7445 consecutive patients undergoing PCI were stratified according to the presence or absence of CKD and diabetes mellitus. In-hospital mortality rates were relatively low for patients without CKD and diabetes, and for diabetic patients without CKD (0.7 and 1.0%, respectively); these rates were greatly increased for both non-diabetic and diabetic patients with CKD (2.3 and 3.7%, respectively) [35].

Thirty-day mortality was also increased in those with CIN, as shown by Sadeghi et al. [36] in a prospective, multicentre trial of the prognostic implications of CIN in 2082 patients undergoing PCI after acute myocardial infarction (MI) without shock. For patients developing CIN (defined as a 0.5 mg/dl increase in SCR during the index hospitalization), the 30-day mortality rate was 16.2%, compared with 1.2% for patients who did not develop CIN (\( P < 0.0001; \) Figure 4). These data correspond to a relative risk for 30-day mortality associated with CIN of 13.8 (95% CI 7.3–26.2) [36].

**Long-term mortality**

Patients who develop CIN also have a diminished long-term survival. The trial reported by Sadeghi et al. [36] found that patients with CIN had a significantly greater 1-year mortality rate (23.3%) compared with those who did not develop CIN (3.2%; \( P < 0.0001; \) Figure 4), and the relative risk of 1-year mortality after CIN was 7.4 (95% CI 4.7, 11.7). The retrospective analysis of data from the Mayo Clinic PCI Registry shows significantly higher 6-month, 1 and 5-year mortality rates for patients with CIN compared with those who did not develop CIN (\( P < 0.0001; \) Figure 5) [22].

CIN has a particularly negative impact on long-term survival in patients with pre-existing CKD. For example, a study by Gruberg et al. [37], which enrolled 439 consecutive patients with pre-existing CKD undergoing coronary interventions, saw a 37.7% 1-year mortality rate for 161 patients who developed CIN (defined as a \( \geq 25\% \) increase in SCR or requirement for dialysis) that was significantly higher than the increase for the patients who did not have pre-existing CKD (19.4%; \( P = 0.001 \)). In addition, an analysis of prospectively collected data from the Cardiovascular Research Foundation (CRF) for 1980 patients with CKD [estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m²] who underwent a first PCI showed that CIN was one of the strongest predictors of 1-year mortality (OR 2.37, 95% CI 1.63–3.44) [38]. Whether or not diabetes mellitus increases the long-term mortality rate in patients with pre-existing CKD is not settled. In the study by Gruberg et al. [37], 1-year Kaplan–Meier survival curves were not significantly different for diabetic and non-diabetic patients with CIN. However, in the study of patients developing CIN after PCI reported by Nikolsky and Mehran [35], the 1-year mortality rate was approximately five times higher in non-diabetic patients with CKD (17.5%) and about eight times greater in diabetic patients with CKD (25.9%) than it was in patients without pre-existing CKD and diabetes (3.4%).
Regardless of kidney function at baseline (1-year incidence of major cardiac adverse events those with CKD). The development of CIN was 14.8% (13.1% of those without CKD and 19.2% of undergoing a first PCI, the incidence of CIN was comes from a total of 7230 consecutive patients prospectively collected data from the CRF on out-utilization associated with CIN. In the analysis of other studies that assessed outcomes and resource (GI) bleeding (Figure 6B).

These findings were consistent with the results of other studies that assessed outcomes and resource utilization associated with CIN. In the analysis of prospectively collected data from the CRF on outcomes from a total of 7230 consecutive patients undergoing a first PCI, the incidence of CIN was 14.8% (13.1% of those without CKD and 19.2% of those with CKD). The development of CIN was associated with a significantly greater cumulative 1-year incidence of major cardiac adverse events regardless of kidney function at baseline ($P < 0.0001$ for patients with and without CKD) [38].

This association of non-renal complications with CIN raises some important questions. Is it the development of CIN that increases the risk for these complications, or do these patients have underlying non-renal conditions (e.g. vascular pathology) that pre-dispose them to CIN? Does medical management of renal failure (e.g. haemodialysis) in patients who develop CIN reduce the mortality rate? Do these patients die from renal failure or from non-renal complications?

A study by Levy et al. [39] attempted to address some of these questions. This retrospective study used a matched-pairs cohort design to compare the cause of death during hospitalization in patients who developed CIN [SCr increase $\geq 25\%$ to at least 2 mg/dl (177 $\mu$mol/l) within 2 days] with patients having stable renal function following a contrast procedure. A total of 183 index patients with confirmed CIN and 174 paired subjects matched for age (within 5 years), with baseline SCr tertile ($\leq 133 \mu$mol/l, 134–221 $\mu$mol/l and $> 221$ $\mu$mol/l), and type of contrast study (CT of the head, CT of the body, cardiac angiography and peripheral angiography) were identified from a database containing 16248 patients who underwent contrast procedures. Matched subjects could not be found for nine index patients with baseline SCr $> 221$ mmol/l, so the analysis was performed on data from the 174 paired subjects and the corresponding 174 index patients [39].

The in-hospital mortality rate was significantly higher for the index patients (i.e. those who had developed CIN) compared with that of the paired subjects (34 vs 7%: $P < 0.001$). Of the 174 index patients included in the analysis, 12% underwent renal replacement therapy (haemodialysis, peritoneal dialysis or continuous arteriovenous haemofiltration). More than half (62%) of the patients who underwent renal replacement therapy died, as did about one-third (31%) of the index patients who did not receive renal replacement therapy.

An analysis according to pre-existing comorbidity showed that among the index patients with certain comorbidities, the in-hospital mortality rate was higher for the index patients than for the paired subjects. For example, 25% of patients with diabetes mellitus who developed CIN died during hospitalization compared with 9% of diabetic patients who did not develop CIN. Other pre-existing comorbidities linked to higher in-hospital mortality rates in patients exhibiting CIN included hypertension, acute congestive heart failure, acute MI, unstable angina, liver disease, GI tract bleeding, non-GI tract bleeding, metastatic cancer, acute leukaemia or lymphoma, sepsis, acute infection and acute mental status changes. The only comorbidities not showing this pattern were stroke and human immunodeficiency virus infection. Consistent with these findings were the results of comparisons of baseline physiological severity scores. These scores were strongly associated with in-hospital mortality, and within a given score category, the in-hospital mortality rates were not significantly different for index patients and matched subjects.

Logistic regression was used to determine the OR for death associated with CIN with adjustment for differences in pre-existing comorbidities. The OR for death associated with CIN was 5.50. The only
comorbidities that significantly influenced this ratio were liver disease, age >60 years, and the physiological severity score.

In-hospital death from untreated renal failure after CIN was rare, occurring in only two patients. Among the 58 other patients with CIN who died, four non-renal conditions predominated: sepsis (57%), respiratory failure (86%), mental status changes (81%) and bleeding (38%). Most of these patients (80%) had at least two causes. For many of these patients, the conditions developed after the onset of CIN. The new-onset rates were 62% for sepsis, 58% for respiratory failure and 61% for bleeding.

These data illustrate a complicated relationship between CIN, comorbidity and mortality. Most patients who developed CIN did not die from renal failure. Rather, the development of CIN was linked to a greater chance of death owing to pre-existing non-renal conditions and perhaps is an indicator of the seriousness of these non-renal conditions. Furthermore, CIN was associated with a greater likelihood of developing other complications that could lead to death.

**Medical resource utilization**

CIN following PCI has been associated with an increased medical resource utilization. An analysis of data from the CRF for 1980 patients undergoing a first PCI found significant differences between patients with and without CIN for the length of hospital stay. The mean post-procedural length of stay for patients with CKD who developed CIN was 6.8±7.1 vs 2.3±2.5 days (P < 0.0001) [38]. An earlier analysis of data from the CRF showed that patients requiring dialysis after PCI had a mean post-PCI hospital stay of 15.4±10.3 days (vs 2.5±3.8 days for patients not needing dialysis; P < 0.0001) and a mean intensive care unit stay of 7.3±7.6 days (vs 0.5±1.9 days for those not needing dialysis; P < 0.0001) [40].

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**Fig. 6.** Development of procedural complications in 7586 patients in the Mayo Clinic PCI Registry according to the development of CIN; (A) cardiac complications (B) vascular and systemic complications [22].
Further economic analysis of the data from 52 patients in the CRF database showed a cost of $128,000 per quality-adjusted life year for patients requiring post-discharge haemodialysis after PCI and a cost of $51,000 per year for haemodialysis [41].

The role of the nephrology consultant

Physicians who refer patients for contrast procedures and those who perform these procedures need to understand the serious prognostic implications of CIN and how to manage their patients to reduce the risk for CIN. Consultant nephrologists can play a pivotal role by educating their colleagues on the best practices for identifying and managing patients at high risk for CIN.

The first step in the prevention of CIN is to identify patients at risk. Patients at a very high risk for CIN should receive a consultation with a nephrologist prior to any contrast procedures, but referring physicians need to know which patient to refer. These high-risk patients include those who might predictably need dialysis after the procedure, those with stage 4 or stage 5 CKD (eGFR 15–30 and <15 ml/min/1.73 m², respectively), those with active renal failure, those with rare established causes of CKD (e.g. membranous nephropathy, IgA nephropathy and polycystic kidney disease), those with known renal artery stenosis, and complicated patients receiving transplantation-related medications (e.g. ciclosporin).

Conclusions

Nephropathy due to exposure to CM is the third leading cause of hospital-acquired ARF. CIN is associated with significant increases in short- and long-term mortality. However, mortality in patients who develop CIN is rarely due to renal failure. Patients who develop CIN have a greater risk for a number of non-renal complications including cardiac, vascular and systemic problems. For patients who develop CIN, treatment is limited to supportive measures until renal impairment resolves. CIN should not be viewed as a treatable and acceptable complication of contrast procedures. Because of the lack of treatment options and because CIN is associated with serious short- and long-term sequelae, nephrologists must educate their colleagues regarding the prognostic implications of CIN.

Conflict of interest statement. None declared.

References


