Contrast-Induced Nephropathy in Patients Undergoing Primary Angioplasty for Acute Myocardial Infarction

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OBJECTIVES
The aim of this research was to assess the incidence, clinical predictors, and outcome of contrast-induced nephropathy (CIN) after primary percutaneous coronary intervention (PCI) for acute myocardial infarction (AMI).

BACKGROUND
Contrast-induced nephropathy is associated with significant morbidity and mortality after PCI. Patients undergoing primary PCI may be at higher risk of CIN because of hemodynamic instability and unfeasibility of adequate prophylaxis.

METHODS
In 208 consecutive AMI patients undergoing primary PCI, we measured serum creatinine concentration (Cr) at baseline and each day for the following three days. Contrast-induced nephropathy was defined as a rise in Cr >0.5 mg/dl.

RESULTS
Overall, CIN occurred in 40 (19%) patients. Of the 160 patients with baseline Cr clearance ≥60 ml/min, only 21 (13%) developed CIN, whereas it occurred in 19 (40%) of those with Cr clearance <60 ml/min (p < 0.0001). In multivariate analysis, age >75 years (odds ratio [OR] 5.28, 95% confidence interval [CI] 1.98 to 14.05; p = 0.0009), anterior infarction (OR 2.17, 95% CI 0.88 to 5.34; p = 0.09), time-to-reperfusion >6 h (OR 2.51, 95% CI 1.01 to 6.16; p = 0.04), contrast agent volume >300 ml (OR 2.80, 95% CI 1.17 to 6.68; p = 0.02) and use of intraaortic balloon (OR 15.51, 95% CI 4.65 to 51.64; p < 0.0001) were independent correlates of CIN. Patients developing CIN had longer hospital stay (13 ± 7 days vs. 8 ± 3 days; p < 0.001), more complicated clinical course, and significantly higher mortality rate (31% vs. 0.6%; p < 0.001).

CONCLUSIONS
Contrast-induced nephropathy frequently complicates primary PCI, even in patients with normal renal function. It is associated with higher in-hospital complication rate and mortality. Thus, preventive strategies are needed, particularly in high-risk patients. (J Am Coll Cardiol 2004;44:1780–5) © 2004 by the American College of Cardiology Foundation

Contrast-induced nephropathy (CIN) is a possible complication of coronary diagnostic and interventional procedures. Its development has been associated with increased in-hospital and long-term morbidity and mortality, prolonged hospitalization, and long-term renal impairment (1–7). Several risk factors for CIN have been identified. Chronic renal insufficiency, diabetes mellitus, congestive heart failure, intravascular volume depletion, and the use of a large amount of contrast agent are considered important predisposing factors (5,7,8).

Increasing evidence exists that primary percutaneous coronary intervention (PCI) obtains rapid restoration of coronary artery patency and increases threatened myocardium salvage, thus preserving ventricular function and improving survival of patients with acute myocardial infarction (AMI) (9,10). However, patients treated with primary PCI may represent a population at higher risk for CIN than those undergoing elective PCI. Several conditions may contribute to renal injury in this setting. Among them, hypotension or even shock, a large volume of contrast media, and the impossibility of starting a renal prophylactic therapy are the factors most likely involved. The impact of these factors on renal function, and the clinical relevance of CIN in the setting of primary PCI remain unknown, but are thought to be considerable. Only recently have studies demonstrated that renal insufficiency and AMI represent a high-risk combination (11). Moreover, other clinical observations have shown that renal dysfunction is an independent risk factor for death in AMI patients (12–14).

The purpose of this prospective study was to determine the incidence, the clinical predictors, and the clinical consequences of CIN development in an unselected population of consecutive patients undergoing primary PCI for AMI.

METHODS

Study population. Between January 1, 2001, and June 30, 2003, we enrolled all consecutive patients admitted to our coronary care unit (CCU) for ST-segment elevation AMI who were treated with primary PCI. According to our institute protocol, patients were included if they presented...
within 12 h (18 h for AMI complicated by cardiogenic shock) from the onset of symptoms (characteristic chest pain lasting for at least 30 min, not responsive to nitrates, with electrocardiographic ST-segment elevation of at least 0.2 mV in two or more contiguous leads, or left bundle-branch block). Patients were excluded if the coronary anatomy was not suitable for PCI or if emergency bypass grafting was required. Patients in chronic peritoneal or hemodialytic treatment were also excluded. The study was approved by the ethics committee of our institution, and informed consent was obtained from all patients.

**Study protocol.** After contrast exposure, physiologic (0.9%) saline was given intravenously at a rate of 1 ml/kg/h for 12 h. In patients with left ventricular dysfunction (ejection fraction <40%) or overt heart failure, the hydration rate was reduced to 0.5 ml/kg/h. The use of beta- adrenergic blocking agents, angiotensin-converting enzyme inhibitors, platelet glycoprotein IIb/IIIa receptor inhibitors (abciximab), diuretics, or the indication to intraaortic balloon pump or inotropic drugs support, was left to the discretion of the interventional and CCU cardiologists, according to our institute’s clinical protocols and international experience guidelines (15). An echocardiographic evaluation was performed in all patients within 12 h from hospital admission. Serum creatinine concentration (Cr) was measured at the time of admission (just before primary PCI), every day for the following three days, and at discharge from the CCU. Creatinine clearance was calculated by applying the Cockcroft-Gault formula to the Cr (16). During hospitalization the following adverse clinical events were considered: major bleeding requiring ≥2 U of blood, acute pulmonary edema, acute renal failure requiring emergency renal replacement therapy (hemofiltration or hemodialysis), cardiogenic shock, tachyarrhythmias and bradyarrhythmias, and death.

**Primary PCI.** Primary PCI was performed by a 24-h on-call interventional team, according to standard clinical practice, using the femoral approach and 7-F guiding catheters. Type of contrast agent and contrast dose, angio-plasty technique, and supportive pharmacologic therapies were left to the discretion of the interventional cardiologist. Patients received a bolus of 5,000 U heparin in the CCU, followed by an additional bolus during the procedure, if deemed necessary.

**Definitions.** Contrast-induced nephropathy was defined as an absolute increase in Cr >0.5 mg/dl after PCI (17).

According to our clinical protocol, emergency renal-replacement therapy (hemofiltration or hemodialysis) was performed if there was oligoanuria for more than 48 h, despite the administration of more than 1 g of intravenous furosemide per 24 h. Emergency renal-replacement therapy was performed earlier in the event of concomitant overt heart failure (18). Blood transfusion was initiated in case of hemoglobin reduction below 8.0 g/L. Time-to-reperfusion was measured as the time from symptom onset to coronary reperfusion obtained with balloon inflation. Cardiogenic shock was defined as prolonged hypotension (systolic blood pressure <85 mm Hg) with evidence of decreased organ perfusion caused by severe left ventricular dysfunction, right ventricular infarction, or mechanical complications of infarction and not due to hypovolemia, bradyarrhythmias, or tachyarrhythmias.

**Statistical analysis.** Continuous data are reported as the mean value ± SD, unless otherwise specified. Categorical data are presented as absolute values and percentages. Comparison of continuous variables was performed by means of Student t test. Chi-square and Fisher exact tests were used for comparison of categorical variables as appropriate. The trend of CIN incidence and in-hospital mortality according to ordinal variables was assessed by the Mantel-Haenszel chi-square for trend. A multivariable logistic regression model was applied including all the potential confounding variables (i.e., age ≥75 years, anterior AMI, time-to-reperfusion ≥6 h, contrast agent volume ≥300 ml, and use of intraaortic balloon pump). A p value <0.05 was considered statistically significant. Analyses were conducted using SAS statistical software (Version 8.02, SAS Institute Inc., Cary, North Carolina).

**RESULTS**

Incidence of CIN and clinical characteristics. Of a total of 218 AMI patients, 10 were excluded (7 because there was no indication for PCI, 2 who were treated with coronary bypass surgery because of coronary anatomy not suitable for PCI, and 1 because of chronic dialysis). Hence, a total of 208 patients (165 men, 43 women; mean age 62 ± 11 years) were included in this study. Of them, 40 (19%) developed CIN. The incidence of this complication was 17% when patients with baseline increased Cr (>1.5 mg/dl) were excluded. **Table 1** shows the baseline clinical and procedural characteristics of patients who developed CIN and of those who did not present this complication after primary PCI. Patients developing CIN were older and more frequently had anterior AMI, higher baseline Cr value, longer time-to-reperfusion, higher enzymatic peak, and lower left ventricular ejection fraction. In addition, they received a higher volume of the contrast agent during PCI than patients without CIN. Of note, contrast volume was higher in anterior AMI (335 ± 158 ml) compared with inferior AMI (270 ± 128 ml; p = 0.001). In 11 (5%) of the 208 patients, abnormal Cr (>1.5 mg/dl) was present at hospital admis-
sion. Seven of these patients had no history of pre-existing renal insufficiency; this suggests that the increased Cr value was likely due to changes in renal hemodynamics associated with impaired systemic perfusion during the acute cardiac event. When creatinine clearance was estimated (16), 48 (23%) of the 208 patients had a moderately impaired renal function (<60 ml/min). Of them, 19 (40%) developed CIN.

In contrast, of the 160 patients with a baseline Cr clearance value >60 ml/min, only 21 (13%) developed CIN after primary PCI (p < 0.0001).

Figure 1 shows the Cr values in the two groups during the CCU stay. When the maximal Cr increase versus baseline was considered, regardless of the time point of occurrence, a mean value of 106±93% was found in patients with CIN and of 8±13% in patients without CIN.

The relation of CIN with in-hospital outcome. Patients with CIN experienced a more complicated in-hospital clinical course (Table 2). All of the major adverse clinical events occurred more frequently in this group. Furthermore, the average length of hospital stay in patients with CIN was approximately 1.5 × longer than that in patients without CIN (13 ± 7 days vs. 8 ± 3 days; p < 0.001). Nine patients (one with CIN and eight without CIN) underwent elective coronary bypass after successful primary PCI to complete coronary revascularization; the length of their in-hospital period was not considered.

The overall in-hospital mortality in the entire population was 6.2% (n = 13). However, the mortality rate was significantly higher in patients developing CIN. Indeed, 12 (31%) patients died in the CIN group (5 for cardiogenic shock, 3 for multiorgan failure, 2 for refractory heart failure, 1 for sudden death, and 1 for ischemic stroke), whereas only 1 death (0.6%; p < 0.0001) occurred in the group without CIN, due to left ventricular free-wall rupture with cardiac tamponade.

Table 1. Baseline Clinical and Procedural Characteristics of the Study Patients

<table>
<thead>
<tr>
<th></th>
<th>CIN (n = 40)</th>
<th>No CIN (n = 168)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>67 ± 12</td>
<td>61 ± 11</td>
<td>0.002</td>
</tr>
<tr>
<td>Age &gt;75 yrs</td>
<td>14 (36%)</td>
<td>17 (10%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Men</td>
<td>36 (90%)</td>
<td>129 (77%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Smokers</td>
<td>17 (42%)</td>
<td>93 (55%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3 (7%)</td>
<td>20 (12%)</td>
<td>0.58*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>21 (52%)</td>
<td>68 (42%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>7 (17%)</td>
<td>54 (32%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>10 (25%)</td>
<td>22 (13%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>3 (7%)</td>
<td>4 (2%)</td>
<td>0.0015*</td>
</tr>
<tr>
<td>Anterior infarction</td>
<td>29 (72%)</td>
<td>77 (46%)</td>
<td>0.0015*</td>
</tr>
<tr>
<td>Time-to-reperfusion (h)</td>
<td>5.6 ± 2.7</td>
<td>3.8 ± 2.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean LVEF (%)</td>
<td>41 ± 11</td>
<td>51 ± 9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVEF &lt;40%</td>
<td>20 (50%)</td>
<td>18 (11%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)†</td>
<td>1.2 (1.1–1.36)</td>
<td>1.0 (0.9–1.15)</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>Serum creatinine &gt;1.5 mg/dl</td>
<td>7 (17%)</td>
<td>4 (2%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>61 ± 19</td>
<td>80 ± 24</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Highest total creatine kinase (IU/l)</td>
<td>3,445 ± 2,448</td>
<td>1,897 ± 1,786</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Culprit lesion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>30 (77%)</td>
<td>72 (43%)</td>
<td></td>
</tr>
<tr>
<td>Left circumflex</td>
<td>2 (5%)</td>
<td>29 (17%)</td>
<td></td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>8 (20%)</td>
<td>64 (38%)</td>
<td></td>
</tr>
<tr>
<td>Bypass graft</td>
<td>0 (0%)</td>
<td>3 (2%)</td>
<td></td>
</tr>
<tr>
<td>Coronary stenting</td>
<td>39 (97%)</td>
<td>165 (98%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Abciximab</td>
<td>19 (48%)</td>
<td>86 (51%)</td>
<td>0.67</td>
</tr>
<tr>
<td>Contrast volume (ml)</td>
<td>378 ± 200</td>
<td>286 ± 125</td>
<td>0.008</td>
</tr>
<tr>
<td>Contrast volume &gt;300 ml</td>
<td>26 (65%)</td>
<td>65 (39%)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*By Fisher exact test; †median and interquartile ranges; ‡by nonparametric Wilcoxon rank test.

CABG = coronary artery bypass graft surgery; CIN = contrast-induced nephropathy; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention.
Independent correlates of CIN. In multivariate analysis, the following variables remained significant independent correlates of CIN: age ≥75 years (odds ratio [OR] 5.28, 95% confidence interval [CI] 1.98 to 14.05; p = 0.0009), anterior AMI (OR 2.17, 95% CI 0.88 to 5.34; p = 0.09), time-to-reperfusion ≥6 h (OR 2.51, 95% CI 1.01 to 6.16; p = 0.04), contrast agent volume ≥300 ml (OR 2.80, 95% CI 1.17 to 6.68; p = 0.02), and use of intra-aortic balloon pump (OR 15.51, 95% CI 4.65 to 51.64; p < 0.0001).

Using these variables as risk indicators for CIN, we developed a risk scoring system. A value of 1 was assigned when a factor was present, and 0 when it was absent. For each patient, the score was calculated as the sum of the number of independent variables (range 0 to 5) recorded in the initial hours of hospital stay (at admission and at the end of primary PCI). The incidence of CIN (Fig. 2), as well as the in-hospital mortality rate (Fig. 3), revealed a significant gradation as the risk score increased in the study population.

Table 2. In-Hospital Clinical Complications

<table>
<thead>
<tr>
<th></th>
<th>CIN (n = 40)</th>
<th>No CIN (n = 168)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPR, VT, or VF</td>
<td>3 (8%)</td>
<td>7 (4%)</td>
<td>0.41*</td>
</tr>
<tr>
<td>High-rate atrial fibrillation</td>
<td>6 (15%)</td>
<td>6 (4%)</td>
<td>0.01*</td>
</tr>
<tr>
<td>High-degree conduction disturbances requiring permanent pacemaker</td>
<td>2 (5%)</td>
<td>0 (0%)</td>
<td>0.04*</td>
</tr>
<tr>
<td>Acute pulmonary edema</td>
<td>5 (13%)</td>
<td>3 (2%)</td>
<td>0.008*</td>
</tr>
<tr>
<td>Respiratory failure requiring mechanical ventilation</td>
<td>8 (20%)</td>
<td>2 (1%)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Cardiogenic shock requiring intra-aortic balloon counterpulsation</td>
<td>13 (33%)</td>
<td>7 (4%)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Major bleeding requiring blood transfusion</td>
<td>4 (10%)</td>
<td>5 (3%)</td>
<td>0.07*</td>
</tr>
<tr>
<td>Acute renal failure requiring renal replacement therapy</td>
<td>6 (15%)</td>
<td>0 (0%)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Patients with two or more clinical complications</td>
<td>14 (35%)</td>
<td>4 (3%)</td>
<td>&lt;0.0001*</td>
</tr>
</tbody>
</table>

*By Fisher exact test.
CIN = contrast-induced nephropathy; CPR = cardiopulmonary resuscitation; VF = ventricular fibrillation; VT = ventricular tachycardia.

DISCUSSION

This study demonstrates that CIN is a frequent complication after primary PCI in AMI, even in patients with normal baseline renal function, and is associated with increased in-hospital morbidity, mortality, and prolonged hospitalization.

Growing evidence indicates that primary PCI is the most effective treatment of AMI, and many studies have demonstrated both that ventricular function is preserved and that survival improved when AMI patients with acute ST-segment elevation undergo this therapeutic approach (9,10). The aim of reperfusion therapy in AMI is to reduce mortality and morbidity, and this goal is best achieved when patency of the infarct-related coronary artery is obtained as early as possible. In our study population, the in-hospital mortality rate was 6.2%, a value comparable with those reported in larger clinical trials (10). In this prospective analysis, we have focused our evaluation on the development of CIN during AMI as a possible complication of primary PCI.
PCI. Acute renal deterioration occurred in 19% of all patients undergoing primary PCI, and was a strong predictor of in-hospital morbidity and mortality. Patients with CIN had a more prolonged and complicated clinical course and a strikingly higher in-hospital mortality (31%). It is noteworthy that the in-hospital mortality of patients who did not develop CIN after primary PCI was only 0.6%.

Most of our patients had a normal renal function before they experienced the acute coronary event. Nevertheless, the in-hospital mortality rate of those who developed CIN approached, or was even greater than, that observed in chronic renal failure patients undergoing elective PCI (6,19), and in patients with chronic renal failure admitted with AMI to a CCU (11–13,20). On the other hand, patients with normal renal function undergoing elective PCI have a significantly lower incidence of CIN (1.2% to 1.6%) than our study population (17%) who had normal Cr at hospital presentation (1,8). Patients with baseline chronic renal failure were only a minority of our population. Thus, no final conclusion can be drawn from their outcome. There are few doubts that poorer clinical outcome can be expected in such patients. Recent results from a clinical study and data from the New York State angioplasty registry showed that baseline Cr and end-stage renal disease are independent risk factors for death after primary PCI (14,21). When creatinine clearance was calculated in our population, a greater number of patients showed reduced baseline renal function (creatine clearance <60 ml/min). The incidence of CIN was higher in these patients as compared with those with preserved renal function (40% vs. 13%).

An increased CIN risk has been reported in patients with chronic renal failure subjected to an early invasive approach for acute coronary syndromes without ST-segment elevation (22,23). In such a population, prophylaxis for CIN is possible, and hemodynamic stability is usually obtained before PCI. In contrast, there is no possibility to perform adequate hydration in AMI patients undergoing primary PCI.

Our data strengthen the crucial link between cardiac and renal dysfunction, and extend the observation of the negative impact on survival deriving from the association between cardiac and renal disease to patients with AMI undergoing primary PCI. Renal function is a major determinant of cardiovascular outcome in a variety of settings, including hypertension (24), chronic heart failure (25,26), acute coronary syndromes (12,23,27,28), AMI (11–14,29), elective PCI (1–7,19), surgical coronary revascularization (30,31), and, more generally, in patients referred to a CCU for any reason (32). This study demonstrates that patients undergoing primary PCI for AMI represent a population at higher risk for CIN, despite the fact that most of them have no history or evidence of pre-existing renal insufficiency.

One strength of this study is that we identified several independent variables for CIN development after primary PCI. In particular, old age (≥75 years), anterior AMI, large (≥300 ml) contrast volume exposure (33), use of intravascular balloon pump, and a longer (≥6 h) time-to-reperfusion were associated with an increased risk of CIN occurrence and a higher mortality rate. Interestingly, the contrast volume needed to perform PCI was higher in anterior compared with inferior AMI. Differences between left and right coronary anatomy and procedural aspects may explain this finding.

Innovative preventive strategies aimed at protecting the kidneys from contrast toxicity and ischemic burden during the acute phase of infarction need to be developed and tested, even in patients with normal renal function. Prophylactic measures will be particularly relevant in patients with an elevated CIN risk score. Although this simple risk score should be tested in an independent and not in a "learning population," it may have wide applicability, and can be easily calculated in the initial hours of hospital presentation in order to predict the risk of CIN and the associated higher adverse event rate in AMI patients undergoing primary PCI. Moreover, it may help to better identify those patients most likely to benefit from a renal-protective intervention. In this regard, saline hydration infusion, performed soon after PCI and prolonged for 12 h, had no major impact on CIN prevention in our patients. Newer pharmacologic (34) or nonpharmacologic (35,36) strategies that showed a benefit in terms of CIN prevention among patients undergoing elective PCI should be evaluated also in high-risk AMI patients treated with primary PCI.

**Study limitations.** Our study has some limitations. First, our study included a small population, admitted to a single center. Our findings should be confirmed and the application of the risk score validated in a large multicenter trial. Second, the definition of CIN is based on the absolute or relative increase in Cr level, compared with baseline value, after a patient has been exposed to a contrast agent, when alternative explanations for renal impairment have been excluded (37). Although all our patients effectively underwent contrast media exposure, and 19% developed acute renal failure within 48 h to 72 h after it, we cannot exclude the possibility that other factors, such as hemodynamic instability, might have contributed, at least in part, to renal impairment, and influenced the clinical outcome of our patients. Indeed, in addition to contrast agent volume, other factors reflecting cardiocirculatory impairment, such as anterior AMI, long time-to-reperfusion, and need for intraaortic balloon pump, were independently related to the development of renal dysfunction. This suggests that kidney hypoperfusion, resulting in ischemic renal injury, might play a major role. However, despite the fact that no firm conclusions can be drawn at this stage, our data suggest that the potential exists for further reduction of mortality after primary PCI. This could probably be obtained on one hand through newer therapies, aimed at preventing acute renal dysfunction, and on the other by shortening time-to-reperfusion and minimizing contrast volume.

**Conclusions.** In the era of primary PCI for AMI, CIN is a frequent complication, even in patients with normal renal
function, and is associated with a more complicated in-hospital course and very high mortality rate. Thus, newer preventive strategies of renal protection during primary PCI are warranted, particularly in high-risk patients.

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