

Contrast-induced nephropathy after primary angioplasty for acute myocardial infarction

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Submitted on: 05/13/2015.

Approved on: 08/03/2015.

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DOI: 10.5935/0101-2800.20150070

ABSTRACT

Introduction: The prevention of contrast-induced nephropathy (CIN) is difficult in emergency situations, making it essential to study CIN in patients submitted to urgent angioplasty. **Objective:** To determine the incidence and associated factors to CIN in patients with myocardial infarction (MI) submitted to primary angioplasty in the first 12 hours after onset of symptoms. **Methods:** We studied 201 consecutive cases of MI with ST-segment elevation with less than 12 hours of evolution. All patients were submitted to the same angioplasty protocol. CIN was defined as an absolute increase of creatinine of at least 0.5 mg/dL and/or a relative increase of creatinine of 25% in relation to baseline in a period between 48 and 72 hours after contrast administration. The variables that differed between patients with and without CIN in univariate analysis were analyzed by logistic regression. **Results:** The sample was formed by 135 (67.2%) men and 66 (32.8%) women, with mean age of 66.6 ± 11.7 years. The incidence of CIN was 23.8%. In univariate analysis the patients with CIN were older and had higher frequency of left ventricular ejection fraction $\leq 40\%$ and Killip classification ≥ 2 . In multivariate analysis, we did not find independent predictors of CIN. **Conclusion:** CIN occurred in $\frac{1}{4}$ of the patients with MI submitted to angioplasty without predictor variables. This finding highlights the need for CIN preventive measures after contrast use in emergency angioplasty.

Keywords: acute kidney injury; angioplasty, balloon, coronary; contrast media; myocardial infarction.

INTRODUCTION

Acute myocardial infarction (AMI) is a common disease associated with high morbidity/mortality and high treatment costs.¹ In recent decades there has been a significant reduction in mortality in patients with AMI with ST-segment elevation (STEMI) due to several factors, especially early diagnosis and treatment, advances in relation to the management of complications, such as recurrent ischemia and heart failure, and increased availability of pharmacological and mechanical reperfusion therapies.^{2,3} Despite this, AMI still represents a major cause of death in developed countries.¹

Primary percutaneous coronary intervention (PPCI) is a safe and effective strategy in the treatment of STEMI, able to significantly reduce mortality compared to treatment by thrombolysis.^{3,4} However, the contrast media used during PPCI may cause allergic reactions and acute deterioration of kidney function.⁵

The incidence of contrast-induced nephropathy (CIN) varies widely depending on sample-related-factors, such as age, diabetes, renal function prior to contrast infusion, type and volume of contrast used. For this reason, we need evidence generated in multiple care settings for better understanding CIN. This study meets this need.

CIN after primary PCI is a complication that negatively affects both morbidity and mortality during hospitalization in the long run.⁶ The main prevention measure against CIN is hydration with saline prior to contrast use and preferably for a period of time, and such action is impossible to be performed in emergency situations such as AMI. The difficult prophylaxis, combined with the clinical severity of AMI, makes CIN quite prevalent and a subject of great interest in patients undergoing primary angioplasty for acute myocardial infarction. The study aimed to establish the incidence and possible factors associated with CIN in patients with acute myocardial infarction undergoing reperfusion therapy with primary angioplasty within 12 hours after symptoms onset.

METHOD

SAMPLE

We studied consecutive STEMI patients with less than 12 hours of evolution and treated with PPCI at the Heart Hospital of the Santa Casa de Misericórdia de Sobral from March 2013 to June 2014. The hospital is a reference center in heart care for the entire Northwest region of the state of Ceará, made up of 47 municipalities and with a population estimated at 1,300,000 inhabitants. Exclusion criteria were age below 18 years, exposure to contrast media in the 30 days prior to enrollment in the study, death before the 48 hours following the contrast administration, chronic kidney disease (data accessed through records and medical reports of the patients or examination showing glomerular filtration rate < 60 mL/min/1.73m² for more than three months), AMI in saphenous vein bypass grafts, “culprit” vessel for the AMI with a diameter < 2.5 mm, coronary lesions with length > 64 mm, need for emergency coronary artery bypass surgery and previous use of thrombolytic agent. The patients in the sample were prospectively evaluated and are characterized by cases of STEMI patients submitted to PPCI with persistent chest pain for over 30 minutes and associated with ST-segment elevation of at least 0.1 mV in two or

more contiguous electrocardiographic leads, with hospital admission within 12 hours after symptoms onset; and patients with chest pain for more than 30 minutes and/or new left branch block. All patients participating in the study signed an informed consent form and the study was approved by the Ethics Committee of the Federal University of Ceará (protocol under 143,737).

PPCI PROTOCOL

PPCI was performed according to the following protocol in all patients: cannulation of the femoral or the radial artery; use of fractionated intravenous heparin (100 IU/kg) after cannulation; introduction of 6F guide-catheter into the coronary artery ostium; and injection of low-osmolar ioxaglate 320 mg/ml (Hexabrix[®]) contrast. The coronary flow of the infarct-related artery before and after PPCI was visually graded according to the TIMI flow classification.⁷ This classification considers four types of degrees: grade 0 - no antegrade flow beyond the occlusion point; grade 1 - the contrast medium reaches place upstream of the obstruction, but without opacification of the distal coronary bed; Grade 2 - passage of the contrast through the obstruction with distal bed opacification, but slowly; Grade 3 - Complete coronary perfusion with antegrade flow in the distal bed, occurring readily as in the proximal coronary bed.

All patients were treated with coronary stents and with the drugs commonly used in PPCI, such as acetylsalicylic acid, clopidogrel or ticagrelor. The use or nonuse of glycoprotein IIb/IIIa inhibitors and manual vacuum were at the discretion of the interventional cardiologist who performed the procedure.

MAIN OUTCOME

CIN was the main study endpoint, defined as an absolute increase in serum creatinine of at least 0.5 mg/dL or a relative serum creatinine increase of 25% compared to baseline (= serum creatinine upon admission) or a combination of both, from 48 to 72 hours after contrast administration.⁸

VARIABLES

The following data was collected: age, gender, body mass index (kg/m²), body surface area (m²), comorbidities (hypertension, diabetes and dyslipidemia), smoking, medication use (specifically statins, converting enzyme inhibitors, diuretics, beta-blockers, oral hypoglycemic agents and insulin), family history of coronary artery disease, previous occurrence of cerebral vascular accident (stroke), myocardial infarction, coronary catheterization and coronary artery bypass surgery, arterial mean pressure, systolic and diastolic blood pressure before contrast use, contrast volume used, daily hemoglobin and serum creatinine values upon admission, 48 and 72 hours after infusion of contrast. Left ventricular ejection fraction was calculated using left ventriculography in diastole and systole, in the right anterior oblique projection. Data collected regarding PPCI was mean time of ischemia (= interval in minutes between the onset of symptoms and the first balloon inflation), time pain-door (= interval in minutes between the onset of symptoms and the first hospital care) and door-to-balloon time (= time in minutes between the first hospital care and the first balloon inflation). The Killip classification was used for staging the degree of heart failure.⁹

The success of primary PCI was defined as angiographic success in the absence of major complications, such as death, myocardial infarction and/or a need for further urgent revascularization. Bleeding complications were defined according to the criteria from the Thrombolysis in Myocardial Infarction¹⁰ as: minimal (any clinical sign of hemorrhage associated with falling hemoglobin < 3 g/dL), lower (clinical signs of bleeding associated with a hemoglobin drop of 3 g/dL to 5 g/dL) and higher (intracranial bleeding, clinically significant sign of bleeding associated with the drop in hemoglobin > 5 g/dL or fatal bleeding). The following adverse events were also considered: cardiac death, reinfarction and stroke. Reinfarction was diagnosed by the appearance of a new Q wave in two or more contiguous leads or elevated

creatine kinase MB fraction greater than three times the upper normal limit. Stroke was defined as loss of neurological function lasting longer than 24 hours or by the presence of a new area of cerebral infarction by imaging techniques, regardless of symptoms duration.

ANALYSIS

The values of continuous variables were presented as mean \pm standard deviation. Categorical variables were presented as absolute values and percentage. Ratio differences were evaluated by Fisher's exact and chi-square tests when indicated. The normal distribution of continuous variables was calculated by the Shapiro-Wilk test. The Student *t*-test (for normal distribution) and Mann-Whitney test (for not normal distribution) were used to compare continuous variables. The variables that differed between patients with and without CIN were analyzed by logistic regression using the stepwise backward method with the Wald statistics as to a possible association with CIN. Odds ratio (OR) and their respective confidence intervals (95% CI) were presented to quantify the effects.

RESULTS

The sample consisted of 201 patients. Four patients had died before the 48 hours after hospital admission and therefore were taken off the sample. No patient underwent dialysis at least within 72 hours after hospital admission. There were 135 (67.2%) men and 66 (32.8%) women with a mean age of 66.6 \pm 11.7 years. The main arteries related to AMI were the anterior descending coronary artery (45.8%) and the right coronary (38.8%), followed by the circumflex artery (13.9%) and left main coronary artery (1.5%). The mean contrast medium volume used in primary PCI was 137.3 \pm 7.5 ml. The incidence of CIN was 23.8%.

There was no difference between the values of baseline serum creatinine on admission among patients with and without CIN, respectively, 0.9 \pm 0.1 mg/dL *versus* 1.0 \pm 0.1 mg/dL (*p* = 0.547). As expected, serum creatinine levels after 48

and 72 hours were higher among patients who developed CIN, respectively 1.3 ± 0.9 mg/dl *versus* 1.0 ± 0.1 mg/dl ($p < 0.001$) and 1.4 ± 1.1 mg/dl *versus* 1.0 ± 0.1 ($p < 0.001$).

When comparing patients with and without CIN, patients with CIN were older (69.6 ± 11.4 *versus* 65.7 ± 11.6 years; $p = 0.040$), had a higher frequency of left ventricular ejection fraction $\leq 40\%$ (16.7% *versus* 4.6% ; $p = 0.010$) and a higher incidence of Killip classification ≥ 2 (18.7% *versus* 7.1% ; $p = 0.019$). The other comparisons of demographic, clinical and angiographic characteristics regarding the procedure between patients with and without CIN did not differ and are presented on Tables 1 and 2. The frequency of death, PPCI clinical success and adverse events did not differ between patients with and without CIN (Table 3).

In the multivariate analysis, considering the variables that differed between patients with and without CIN, there were no independent predictors of risk for the development of CIN (Table 4).

DISCUSSION

Our study showed the incidence of CIN in $\frac{1}{4}$ of the patients who underwent coronary angiography due to AMI. The incidence of CIN following coronary angiography varies greatly depending on the demographic and clinical variables of the sample, as well as the characteristics of the angiography. After cardiac catheterization, the incidence of CIN may be as low as 6% in patients undergoing elective catheterization (diagnosis);¹¹ approaching 16% in samples encompassing both cases of elective and urgent catheterization;¹² and it reaches 25% in samples such as ours, involving urgent catheterization.¹³

In our study it was not possible to identify the variables that traditionally increase the risk of CIN onset. The variables that differed in the comparison of patients with and without CIN were not independent predictors in the multivariate analysis. They were: older age, left ventricle ejection fraction $\leq 40\%$ and Killip ≥ 2 . In traditional risk scores for CIN, such as Mehran¹⁴

and Bartholomew,¹⁵ these three variables generate points in their respective forecast ranges of risk categorized as “age > 75 years” and “degree of heart failure” (in our study the degree of heart failure was estimated by the left ventricle ejection fraction and the Killip classification).

Despite the high incidence of CIN, as we have in this type of sample (urgent catheterization due to AMI), we could find “protective” characteristics concerning the occurrence of CIN, such as average age below 75 years; Low infused contrast volume (in our study the average infused volume was 137.3 ml, well below the cut off points of risk listed in the literature: for some > 200 ML¹⁶ and others > 300 ML¹²); low average serum creatinine on admission with only four patients with serum creatinine greater than 2 mg/dL, which prevented comparisons of statistical value among patients with creatinine equal to or lower *versus* higher than 2 mg/dL (creatinine limit is usually used as a risk criteria for CIN); few patients with previous PPCI and mean ischemia time of less than 6 hours. Prior PPCI and ischemia time greater than six hours were risk factors in previously published studies.^{12,13}

But even with the “protective” characteristics seen in the sample, CIN incidence was quite high, indicating the need for preventive measures. The first point is to consider all patients with acute myocardial infarction undergoing primary PCI as having high risk for developing CIN. The most effective preventive measure, which is hydration prior to use of contrast, is difficult to perform due to the emergency nature of AMI. Thus, drugs that could be used immediately before contrast infusion would be the ideal preventative measure. With regards to N-acetylcysteine, despite being studied for a long time, data is still conflicting as to its power to prevent CIN after coronary angiography studies.¹⁷ Pentoxifylline was not protective for the occurrence of CIN in low-risk samples (elective coronary angiography),^{18,19} we are still missing data on patients undergoing

TABLE 1 COMPARISON OF PATIENTS WITH AND WITHOUT CONTRAST-INDUCED NEPHROPATHY (CIN)

Variables	Without CIN	With CIN	<i>p</i>
Age (years)	65.7 ± 11.6	69.6 ± 11.4	0.040
Men	74 (54,8)	61 (45,2)	0.135
Body Mass Index (kg/m ²)	26.8 ± 3.4	26.4 ± 2.8	0.498
Body Surface (m ²)	1.7 ± 0.1	1.7 ± 0.1	0.496
Risk factors for coronary disease			
Arterial Hypertension	54 (35,2)	20 (41,6)	0.424
Dyslipidemia	59 (38,5)	16 (33,3)	0.513
Diabetes	22 (14,3)	10 (20,8)	0.286
Smoking	79 (51,6)	18 (37,5)	0.087
Family history of coronary disease	21 (13,7)	4 (8,3)	0.453
History of stroke	6 (3,9)	1 (2,0)	0.470
Prior myocardial infarction	7 (4,5)	1 (2,0)	0.391
Prior coronary intervention	5 (3,2)	1 (2,0)	1.000
Prior surgical revascularization	11 (7,1)	2 (4,1)	0.360
Baseline creatinine (mg/dL)	1.0 ± 0.1	0.9 ± 0.1	0.547
Creatinine after 48 hours (mg/dL)	1.0 ± 0.1	1.3 ± 0.9	< 0.001
Creatinine after 72 hours (mg/dL)	1.0 ± 0.1	1.4 ± 1.1	< 0.001
Mean time of ischemia (min)*	378.4 ± 192.2	348.1 ± 149.7	0.449
Pain-door time (min)**	311.2 ± 154.6	297.8 ± 150.5	0.597
Door-balloon time (min)***	76.2 ± 142.3	50.3 ± 18.8	0.136
Door-balloon time > 90 min	10 (6,5)	3 (6,3)	0.622
Left ventricle ejection ≤ 40%	7 (4,6)	8 (16,7)	0.010
Killip ≥ 2	11 (7,1)	9 (18,7)	0.019
Measurement in use			
Statin	18 (11,7)	7 (14,5)	0.605
Angiotensin Converting Enzyme inhibitor	51 (33,3)	17 (35,4)	0.790
Diuretic	4 (2,6)	2 (4,2)	0.440
Beta-blockers	2 (1,3)	1 (2,1)	0.561
Oral hypoglycemic agent	17 (11,1)	8 (16,7)	0.308
Insulin	6 (3,9)	2 (4,2)	0.608

Results in mean ± standard deviation and percentages between parenthesis. *Interval between symptoms onset and the first balloon inflation **Interval between symptoms onset and the first hospital care ***Interval between the first hospital care and the first balloon inflation.

emergency coronary angiography. In a recent meta-analysis, intravenous fenoldopam was not superior to saline or N-acetylcysteine.²⁰ Rosuvastatin and atorvastatin are promising drugs that have proven effective in preventing CIN in a meta-analysis based on randomized clinical trials.²¹

In our study, CIN was not associated with mortality or adverse events in the short term (72 hours). It is known, however, that CIN increases by 14.4% the death rate within 30 days and 17.4% after three years.¹⁷

In our opinion, the importance of this study is to fill the information gap about CIN after urgent AMI coronary angiography in cardiology services in Brazil. Still waiting for multicenter studies, it is essential to have anecdotal reports from various services that can demonstrate the incidence and factors associated with CIN, as a first step towards the organization of a body of evidence that enables the proposal of strategies to prevent the alarming incidence of ¼ CIN after PPCI in AMI cases.

TABLE 2 COMPARISON OF THE ANGIOPLASTY-RELATED FACTORS AMONG PATIENTS WITH AND WITHOUT CONTRAST INDUCED NEPHROPATHY (CIN)

Variables	Without CIN	With CIN	<i>p</i>
Artery related to the infarction			
Left coronary trunk	3 (2.0)	0 (0)	0.438
Anterior descending	69 (45.1)	23 (47.9)	0.732
Circumflex	20 (13.1)	8 (16.7%)	0.530
Right coronary	61 (39.9)	17 (35.4%)	0.580
Contrast volume (ml)	1372 ± 7.8	1371 ± 7.3	0.956
MAP upon angioplasty onset (mmHg)	94.6 ± 17.6	91.2 ± 14.3	0.227
SBP upon angioplasty onset (mmHg)	130.8 ± 25.3	125.0 ± 21.9	0.151
DBP upon angioplasty onset (mmHg)	76.5 ± 15.7	74.3 ± 11.6	0.373
IIb/IIIa glycoprotein inhibitor	8 (5.2)	3 (6.3)	0.512

Results in mean ± standard deviation and percentages within parenthesis. MAP: Mean Arterial Pressure; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure.

TABLE 3 COMPARISON OF THE CLINICAL SUCCESS FREQUENCY OF ANGIOPLASTY, ADVERSE EVENTS AND DEATH AMONG PATIENTS WITH AND WITHOUT CONTRAST-INDUCED NEPHROPATHY (CIN)

Variables	Without CIN	With CIN	<i>p</i>
Angioplasty clinical success	136 (88.8)	44 (91.6)	0.583
Reinfarction	8 (5.2)	0	0.107
Cerebral vascular accident (stroke)	3 (2.0)	0	0.438
Larger bleeding	6 (3.9)	1 (2.0)	0.470
Death	13 (8.5)	4 (8.3)	0.614

Percentage within parenthesis.

TABLE 4 LOGISTIC REGRESSION CONCERNING CONTRAST-INDUCED NEPHROPATHY

Variables	Univariate analysis			Multivariate analysis		
	O R	IC 95%	<i>p</i>	O R	IC 95%	<i>p</i>
Age	1.03	1.00-1.06	0.047	1.02	0.98-1.05	0.211
LVEF ≤ 40%	4.17	1.42-12.19	0.009	3.09	0.63-15.07	0.162
Killip ≥ 2	2.29	1.08-4.89	0.031	1.22	0.39-3.77	0.728

LVEF: left-ventricle ejection fraction.

LIMITATIONS

First, the lack of factors traditionally associated and predictors of CIN in our study may be due to the small sample size. Second, the short follow-up precluded the finding of adverse outcomes, either death or complications in the medium and long terms. Third, there was an exclusion of patients recently submitted to any kind of contrast media. Previous use of contrast is a recognized risk for CIN. Thus, the inclusion of these patients could have been interesting, considering that currently this group of patients undergoing repeated contrast studies

corresponds to a considerable portion. Fourth, there are creatinine limitations in the context of acute renal injury. Currently, studies using biomarkers point to the role of NGAL in both the risk of detecting (by the dosage prior to the use of contrast) as in the early diagnosis (by measuring it one day after the use of contrast) CIN. Despite the limitations, our study confirms the high incidence of CIN in patients with acute myocardial infarction undergoing primary PCI and highlights the need for randomized clinical trials concerning prophylactic measures in urgent angiograms.

CONCLUSION

CIN affects ¼ of patients with acute myocardial infarction undergoing primary PCI, without a variable that can predict its occurrence and with no association with death and/or adverse events in the short term. The high incidence points to the need for studies on preventive measures for CIN after contrast use in emergency angiography.

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