Determinants and Prognostic Implications of Reperfusion Injury During Primary Percutaneous Coronary Intervention in Chinese Patients with Acute Myocardial Infarction

Address for correspondence:
Yi Luo, MD, PhD
Department of Cardiology
Guangzhou First People's
Hospital Affiliated to
Guangzhou Medical College
1 Panfu Road, Guangzhou 510180
Guangdong, China
yiluo63@yahoo.com.cn

Yi Luo, MD, PhD,* Guang-Lian Li, MD,* Yi-Zhi Pan, MD,*
Shu-Feng Zhou, MD, PhD†

*Department of Cardiology, Guangzhou First People's Hospital Affiliated to Guangzhou Medical College, Guangdong, China; †Division of Chinese Medicine, School of Health Sciences, WHO Collaborating Center for Traditional Medicine, RMIT University, Melbourne, Victoria, Australia

ABSTRACT

Background: The poor clinical outcome in acute myocardial infarction (AMI) patients undergoing primary percutaneous coronary intervention (PCI) has been attributed to myocardial ischemia-reperfusion injury (MIRI).

Objective: This study aimed to identify the predictive factors of MIRI during PCI in Chinese AMI patients with or without ST-segment elevation.

Methods: Clinical and angiographic data of 228 patients in whom the infarct-related artery (IRA) was successfully recanalized by primary PCI were retrospectively analyzed. Multiple logistic regressions were used.

Results: Compared with non-MIRI group ($n = 109$), patients with MIRI ($n = 119$) were characterized by more inferior infarct location, shorter ischemic duration, more frequently right coronary artery as IRA, more lesion vessels, more often thrombolysis in myocardial infarction (TIMI) 0 flow in IRA prior to PCI, less preinfarction angina, and more renal insufficiency. Ischemic time ≤ 6 hours ($p = 0.014$), inferior infarct location ($p = 0.006$), and initial antegrade flow in IRA $\leq$ TIMI grade 1 ($p = 0.028$) were independent risk factors for MIRI. Other risk factors included multivessel lesions ($p = 0.063$) and renal insufficiency ($p = 0.067$). Only preinfarction angina was a protective factor ($p = 0.005$).

Conclusions: The factors promoting MIRI during primary PCI includes short ischemic time from AMI onset to IRA recanalization, inferior infarct location, low IRA antegrade flow prior to PCI, multivessel lesions, and renal insufficiency, whereas preinfarction angina is a protective factor attenuating MIRI.

Key words: myocardial infarction, angioplasty, transluminal, percutaneous coronary, ischemia-reperfusion injury, myocardial

Introduction

Myocardial infarction is the major cause of death worldwide. Rapidly initiating coronary reperfusion therapy has become the most effective and an established standard approach for the management of acute myocardial infarction (AMI). Primary percutaneous coronary intervention (PCI) is a preferred reperfusion therapy for AMI with ST-segment elevations, as many randomized prospective clinical trials have shown that PCI is more effective than intravenous thrombolysis in restoring thrombolysis in myocardial infarction (TIMI)-3 flow, and improving cardiac function and consequently reducing the mortality rate of patients.^{1–6} However, a substantial number of patients receiving PCI fail to obtain complete and sustained myocardial reperfusion and remain at risk of developing large infarcts.⁷ The in-hospital mortality of AMI patients undergoing PCI remains between 4% and 7%.^{8,9} The poor outcome in

these patients has been attributed to myocardial ischemia-reperfusion injury (MIRI).^{10,11} Regardless of the extensive studies on MIRI, the pathological mechanism of MIRI is unknown.^{7,12} MIRI may be clinically manifested by myocardial necrosis, severe cardiac arrhythmia, myocardial stunning, and endothelial- and microvascular dysfunction including the no-reflow phenomenon.¹¹ Animal studies have demonstrated that MIRI is mediated largely by multiple noxious factors such as free radicals generated during ischemia-reperfusion and embolization of the destroyed plaque.^{7,12} To predict the potential of reperfusion injury in patients undergoing PCI, several studies have reported the determining factors for MIRI occurrence. In a study in Belgium, AMI patients undergoing PCI, patients ≥ 55 years of age with systolic pressures ≤ 120 mmHg were at higher risk for development of impaired reperfusion.¹³ Iwakura et al.¹⁴ found that TIMI flow grade 0 of the infarct-related artery (IRA) prior to intervention was an independent

predictor of no-reflow in Japanese patients with an anterior wall AMI who underwent successful PCI. The absence of preinfarction angina appears a determinant of poor ST-segment resolution and no-reflow.^{15,16} We have conducted a retrospective analysis of clinical and angiographic data in Chinese AMI patients in order to identify the risk factors for occurrence of MIRI.

Materials and Methods

Study Patients

A total of 228 consecutive patients with AMI from January 2003 to December 2004 in whom IRA was successfully recanalized by primary PCI were retrospectively enrolled. AMI was diagnosed based on clinical presentation, electrocardiogram, and biochemical markers of myocardial damage.¹⁷ The candidate criteria for primary PCI: (i) ≥ 30 minutes of chest pain; (ii) ST-segment elevation ≥ 0.2 mV in at least two contiguous chest leads or ≥ 0.1 mV in at least two limb leads or ST-segment depression ≥ 0.1 mV; (iii) positive cardiac troponin T test in patients presenting ST-segment depression; and (iv) within 12 hours after the onset of chest pain, or continuing chest pain despite over 12 hours. The location of posterior infarct was judged by ST-segment elevation of leads V₇, V₈, and V₉ with ≥ 1 of R/S ratio of V₁ and V₂, while an ST-segment depression was seen in V₁ and V₂ leads for posterior infarct. Patients were excluded if they had left bundle branch block or poorly interpretable ST segments. All the patients or their families gave written informed consents to the interventional therapies. The ethics permit for this study was obtained from the Ethics Committee of Guangzhou First People's Hospital Affiliated to Guangzhou Medical College, Guangzhou, China.

Angiographic Data

Angiograms were analyzed separately by two experienced cardiologists who were blinded to all other data. The angiography was performed via a transfemoral approach using a 6-French diagnostic catheter (Judkins type) with ULTRAVIST, a nonionic contrast medium. Prior to the angiography, 5000 units of heparin were given from the side arm of artery canula sheath. Multidirectional cineangiograms (Siemens, Munich, Germany) of coronary arteries were recorded. A multivessel lesion was defined as the presence of a lesion with $>50\%$ diameter stenosis in a noninfarct-related coronary artery. The TIMI angiographic scale was used to determine the recanalization status of the IRA and was assessed visually.

Procedure of Percutaneous Coronary Intervention and Medication During Perioperative Period

Upon admission, 300 mg of aspirin and 300 mg of clopidogrel were administered orally for all the patients. The time period between aspirin/clopidogrel administration and

PCI was 30 minutes to 1 hour. Isosorbide dinitrate or nitroglycerin was administered intravenously in patients without hypotension. None of the patients were treated with a glycoprotein IIb/IIIa receptor antagonist due to unavailability. Primary angioplasty of IRA was performed following the diagnostic coronary angiography with an additional injection of 5000 units of heparin. Thereafter, an additional injection of 2500 units of heparin per hour was continued. The devices used during the procedure included a 6- or 7-French Judkins or Amplatz type guiding catheter, an intracoronary guide wire (0.014 inches in diameter), and a 1.5 or 2.0 mm angioplastic balloon. The target vessel lesion was dilated using a balloon inflated to 8–10 bars for 15–30 seconds. After balloon dilatation, repeat coronary angiography was done, and then stent implantation was performed, which was deployed to the lesion at 12–15 bars for 20 seconds. There were 115 and 101 patients in the MIRI and non-MIRI group undergoing balloon dilatation prior to stent implantation, respectively. In the MIRI group, 102 and 17 patients received a bare metal stent and a drug-eluting stent, respectively; 98 patients were implanted with bare metal stent and 11 for drug-eluting stent in the non-MIRI group. Only IRA was managed emergently, and other diseased vessels of a few of the patients with multivessel lesions were treated with selected PCI in convalescence of AMI. The chronic total occlusion due to multivessel lesions was seen only in 8 patients. All the patients were also treated with heparin or low molecular weight heparin for 3–5 days, 75 mg of clopidogrel for at least 4 weeks, 100 mg of aspirin after PCI. There were 103 and 104 patients in the MIRI and non-MIRI groups eventually discharged from the hospital, respectively. In the MIRI group, 92, 103, 90, 100, 103, 28, and 5 patients were treated with β -blockers, statins, angiotensin-converting enzyme inhibitors, aspirin, clopidogrel, oral hypoglycemic medications, or insulin, respectively; these numbers were 95, 104, 92, 98, 104, 30, and 4, respectively, in the non-MIRI group.

Criteria and Definitions of Myocardial Ischemia-Reperfusion Injury

A TIMI-3 flow for primary PCI with a residual luminal stenosis of less than 20% indicates a successful PCI.¹⁸ "IRA reopening" was defined as adequate restoration of coronary patency (TIMI flow grade ≥ 2) and postballoon-dilatation diameter stenosis of the IRA $<50\%$. MIRI was defined as events occurring after IRA reopening, including severe bradycardia with hypotension, or lethal ventricular arrhythmias requiring electrical cardioversion, or myocardial reperfusion $\leq$ myocardial blush grade 2 without angiographic evidence for abrupt closure due to target vessel thrombus, emboli, dissection or spasm.¹² Severe bradycardia with hypotension was defined as bradycardia requiring atropine or pacing with systolic blood pressure <90 mmHg for >30 minutes or requiring pressor therapy. The ischemic

time was defined as the period from the onset of chest pain symptoms to IRA reopening. Some patients undergoing PCI experience severe arrhythmias and disturbed hemodynamics after the IRA achieves reopening. Both severe bradycardia with hypotension and lethal ventricular arrhythmias are closely associated with MIRI and are thus considered as useful indicators of MIRI. The definition of MIRI we adopted in this study is generally accepted by clinical cardiologists.^{13–16}

Statistical Methods

Data were analyzed using the SPSS Version 10 (SPSS Inc., Chicago, IL). For dichotomous variables, a χ^2 test or Fishers's exact test was used for comparisons. Multivariate logistic regression analysis was used to assess the relationship between the patient characteristics and MIRI development. Multiple logistic regression was conducted to identify predictors of MIRI, with stepwise method criteria of an entry *p*-value <0.05 and removal *p*-value <0.10. All tests were two-sided and a *p*-value <0.05 was considered significant.

Results and Discussion

A total of 228 patients with AMI in whom IRA was successfully recanalized by primary PCI. All patients had chest pain. The study population included 213 patients (93.4%) with ST-segment elevation and 15 (6.6%) with non-ST-segment elevation. There were 120 cases of 228 AMI patients with an anterior AMI (52.6%) while 108 patients underwent an inferior AMI (47.4%). The proportion of anterior AMI in our study falls into the ranges reported in the literature.^{19,20} A 43.7 and 68.0% of anterior AMI were found in AMI patients with reflow- and nonreflow AMI patients undergoing PCI, respectively,¹⁹ but a 72%–80% of anterior AMI was reported in another study.²⁰ The ischemic time ranged from 1 to 120 hours (median: 4 h). The ischemic time was 6 hours or less in 64.0% of patients, 12 hours or less in 82.5%, and 24 hours or less in 95.2%. There were 6, 4, and 4 patients with lethal arrhythmias, balloon pump, and cardiogenic shock prior to PCI, respectively.

Among 228 assessable patients, MIRI was observed in 119 patients (52.2%). Among the 119 MIRI patients, 54 cases presented with severe bradycardia with hypotension, 29 developed lethal ventricular arrhythmias requiring electrical cardioversion, and 36 experienced myocardial reperfusion $\leq$ myocardial blush grade without angiographic evidence for abrupt closure due to target vessel thrombus, emboli, dissection or spasm. No patients experienced major bleeding during hospitalization, but minor bleeding without hypotension was seen in 15 patients. MIRI and non-MIRI groups were comparable with regard to sex, age, Q-wave infarction, ST-elevation infarction, Killip class on admission, hypertension, and hyperuricacidemia. However, MIRI group was characterized by more inferior infarct location, shorter ischemic duration, more frequently right

coronary artery as IRA, more lesion vessels, more often TIMI grade 0 of initial antegrade flow in IRA, less preinfarction angina, and more renal insufficiency (*p*<0.05) (Table 1). The in-hospital mortality in MIRI group was 13.4% (16/119), which was significantly higher than 4.6% (5/109) in the non-MIRI group (*p* = 0.021). As shown in Table 2, a multivariate logistic regression analysis identified major independent risk factors of MIRI included ischemic time $\leq$ 6 hours (*p* = 0.014), inferior infarct location (*p* = 0.006), and initial antegrade flow in IRA $\leq$ TIMI grade 1 (*p* = 0.028). In addition, multivessel lesions (*p* = 0.063) and renal insufficiency (*p* = 0.067) were risk factors for MIRI. Notably, pre-infarction angina was an independent protective factor (*p* = 0.005). Hypertension tended to be a "protective" factor for MIRI (*p* = 0.057).

The present data showed that the short ischemic time, namely $\leq$ 6 hours from the onset of chest pain symptom to IRA reopening, was an independent risk for MIRI. The incidence of reperfusion-related arrhythmias is greater in patients with short ischemia compared to those with a long duration of ischemia.²¹ The median time period from chest pain to IRA reopening was 4 hours, with 146 patients (64.0%) having an ischemic time of $\leq$ 6 hours, 188 patients (82.5%) $\leq$ 12 hour, and 217 patients (95.2%) $\leq$ 24 hours. Thus, the percentage of patients with a time interval of 6–24 hours was 31.2%, which was approximately 50% of patients within 6 hours. In the 146 patients with ischemic time of $\leq$ 6 hours, 59 patients (54.1%) were in non-MIRI group, whereas 87 patients (73.1%) underwent MIRI (*p* = 0.003). However, when the time interval was extended to 12 or 24 hours, there were no significant differences in the percentages of non-MIRI and MIRI patients.

Inferior infarct location was another independent risk for MIRI. This might be associated with the feature of innervation in the inferior wall of heart. Bradycardia and hypotension usually arose immediately after IRA reopening in patients with inferior AMI. The hemodynamic disturbance could not be corrected by temporary external pacing and pressor agents, whereas atropine was often dramatically effective, suggesting the involvement of aberrant vagal reflex due to disrupted blood supply to the neurons and abnormal catecholamine levels in local tissue and in blood.

A low level of initial TIMI flow grade of IRA was an independent risk factor for the development of MIRI, which is in agreement with the result reported by Iwakura et al.¹⁴ In the present study, the other two risk factors for MIRI were multivessel lesions and renal insufficiency. In general, there is more extensive and more severe ischemia at the baseline in the myocardium with multivessel disease, compared with single-vessel lesions. With respect to renal insufficiency as a risk factor for MIRI, multiple factors may be involved, including impaired blood vessel tone, abnormal electrolytes, and accumulation of toxins.

The presence of preinfarction angina has been shown to exert a favorable effect on left ventricular function in

TABLE 1: Clinical characteristics of AMI patients at baseline

Factor	NonMIRI (n = 109)	MIRI (n = 119)	p
Male sex (%)	79 (72.5)	88 (73.9)	0.802
Age (y)	65.5 (38–87)	65.0 (43–86)	0.773
Inferior AMI (%)	36 (33.0)	72 (60.5)	0.000
Q-wave AMI (%)	95 (87.2)	102 (85.7)	0.751
ST-elevation AMI (%)	101 (92.7)	112 (94.1)	0.658
Ischemic time (h, %)	6.0 (1–120)	3 (2–96)	0.007
≤6	59 (54.1)	87 (73.1)	0.003
≤12	86 (78.9)	102 (85.7)	0.177
≤24	102 (93.6)	115 (96.6)	0.281
Killip class	1 (1–4)	1 (1–4)	0.126
IRA (%)			
LAD	65 (59.6)	46 (38.7)	0.002
LCX	9 (8.3)	9 (7.6)	0.846
RAD	35 (32.1)	64 (53.8)	0.001
Multivessel lesions (%)	32 (29.4)	54 (45.4)	0.013
Collaterals (%)	18 (16.5)	24 (20.2)	0.477
Blood flow in IRA (TIMI grade, %)			
0	57 (52.3)	85 (71.4)	0.003
1	5 (4.6)	7 (5.9)	0.662
2	22 (20.2)	8 (6.7)	0.003
3	25 (22.9)	19 (16.0)	0.183
Preinfarction angina ^a (%)	38 (34.9)	20 (16.8)	0.002
Coronary heart disease history (%)	14 (12.8)	24 (20.2)	0.138
History of hypertension (%)	55 (50.5)	46 (38.7)	0.559
History of diabetes (%)	20 (18.3)	15 (12.6)	0.229
Smoker (%)	33 (30.3)	40 (33.6)	0.589
Hyperlipidemia ^b (%)	29 (26.6)	38 (31.9)	0.378
Renal insufficiency ^c (%)	5 (4.2)	14 (11.5)	0.050
Hyperuricacidemia ^d (%)	24 (22.0)	26 (21.8)	0.975

Abbreviations: LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery. ^aRepeated typical angina pectoris that lasts 15 min or less within 48 h prior to AMI. ^bPlasma level of total cholesterol >6.2 mM and/or triglyceride >1.7 mM. ^cSerum creatinine >177 μM. ^dBlood uric acid >420 μM (350 μM for female subjects). A p-value <0.05 was considered significant.

TABLE 2: Various factors in AMI patients during PCI

Variable	Wald χ^2 value	p	Odds ratio (95% CI)
Gender	0.053	0.817	0.896(0.351–2.285)
Age	0.470	0.493	0.985(0.945–1.028)
Ischemic time ≤ 6 h	5.538	0.019	2.891(1.194–6.998)
Inferior AMI	1.101	0.294	2.227(0.500–9.901)
Killip class	1.781	0.182	1.416(0.850–2.361)
Q-wave AMI	0.276	0.599	0.710(0.197–2.551)
IRA	0.189	0.664	1.188(0.547–2.577)
Multivessel lesion	2.564	0.109	2.083(0.848–5.117)
Collateral	0.182	0.670	0.785(0.259–2.383)
Flow $\leq$ TIMI grade 1	4.462	0.035	2.625(1.072–6.410)
Preinfarction angina	8.118	0.004	0.247(0.095–0.647)
History of coronary heart disease	1.492	0.222	1.975(0.663–5.889)
History of hypertension	2.704	0.100	0.489(0.208–1.147)
History of diabetes	0.007	0.935	0.953(0.296–3.065)
Hyperlipidemia	1.444	0.229	1.751(0.702–4.369)
Smoker	0.038	0.846	1.090(0.458–2.591)
Renal insufficiency	2.963	0.085	4.846(0.804–29.223)
Hyperuricacidemia	0.693	0.405	0.623(0.204–1.900)
Variables finally entered			
Ischemic time ≤ 6 h	5.992	0.014	2.733(1.222–6.115)
Inferior AMI	7.479	0.006	2.907(1.353–6.250)
Flow $\leq$ TIMI grade 1	4.854	0.028	2.481(1.105–5.556)
Multivessel lesions	3.462	0.063	2.152(0.960–4.822)
Preinfarction angina	7.996	0.005	0.268(0.108–0.668)
History of hypertension	3.632	0.057	0.463(0.209–1.022)
Renal insufficiency	3.349	0.067	4.083(0.905–18.424)

Chinese AMI patients. Our finding is consistent with those reported in the literature.^{14–16} The preventive effect of preinfarction angina on MIRI may be explained, at least in part, by the beneficial effects of ischemic preconditioning on myocardium.

Hypertension seemed to be a “protective” factor for MIRI. The reason for this is unknown. Little is known about the effect of hypertension on MIRI development. Theoretically, the pathophysiological changes (e.g. endothelial injury and

increased blood vessel tone) brought about by hypertension should precipitate MIRI.

Our study has several limitations. The study was a retrospective analysis and prospective studies are certainly needed to affirm our results. The sample size also limited our further stratification analysis. More factors associated with the patients, disease and treatment should be taken into account. Additionally, no patients in our study received glycoprotein IIb/IIIa inhibitor therapy before or periprocedural. Early administration of glycoprotein IIb/IIIa

inhibitors in ST-segment elevation myocardial infarction has been shown to decrease the incidence of no-reflow and mortality.²²

In conclusion, the factors promoting the development of MIRI during primary PCI includes short ischemic time from the onset of AMI to IRA recanalization, inferior infarct location, low antegrade flow in IRA before recanalization, multivessel lesions, and renal insufficiency, whereas preinfarction angina is a protective factor attenuating MIRI. More studies are warranted to explore the clinical relevance of these factors in predicting the prognosis of AMI patients.

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