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# Altered serum creatine kinase level and cardiac function in ischemia-reperfusion injury during percutaneous coronary intervention

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A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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## Summary

**Background:** Myocardial ischemia-reperfusion injury (MIRI) resulting from primary percutaneous coronary intervention (PCI) for acute myocardial infarction (AMI) is considered harmful to the patient, but its clinical significance remains unclear. This study explored the relationship of cardiac function examined by echocardiography and serum creatine kinase (CK) and CK-MB levels with MIRI in a cohort of Chinese AMI patients.

**Material/Methods:** We retrospectively analysed the clinical and angiographic data in 228 AMI patients in whom the infarct-related artery (IRA) was successfully recanalized by primary PCI. Cardiac function was evaluated by use of echocardiography before discharge from hospital.

**Results:** The in-hospital mortality rate in the MIRI group was 13.4% (16/119), which was significantly higher than the 4.6% (5/109) mortality rate in the non-MIRI group ($P$=0.021). The median of peak serum CK level was remarkably lower in the suppression-type MIRI group than in the non-MIRI group. There were no significant differences in the peak serum CK or CK-MB levels between the irritation-type MIRI group and the non-MIRI group. The peak CK and CK-MB levels were significantly higher in the no-reflow-type MIRI group than in the non-MIRI group. Left ventricular ejection fraction in the no-reflow-type MIRI group was significantly lower than in the non-MIRI group; left ventricular end-diastolic volume was significantly higher than in the irritation-type MIRI subgroup; and left ventricular end-systolic volume was greater than that in non-MIRI group and suppression-type MIRI group.

**Conclusions:** MIRI (especially the no-reflow type) may lead to acute hemodynamic disorders and increase the mortality rate. However, suppression- and irritation-type MIRI may imply the existence of surviving myocardium.

**key words:** **myocardial infarction • percutaneous coronary angioplasty • myocardial ischemia-reperfusion injury • creatine kinase • cardiac function**

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## Background

Myocardial infarction is the leading cause of death in developed countries. Over the last 2 decades, coronary reperfusion therapy has become an established treatment for acute myocardial infarction (AMI) [1]. Primary percutaneous coronary intervention (PCI) is the preferred therapy for AMI with ST-segment elevation, based on its better clinical prognosis and reduced mortality rate compared to thrombolysis therapy [2–7]. By dilatation of the ischemic lesion and reopening of the infarct-related artery (IRA), PCI rescues ischemic myocardium, limits or reduces infarct size, and preserves cardiac function [2,5]. Accumulating clinical evidence indicates that PCI markedly decreases the incidence of re-infarction, and considerably improves clinical prognosis [2]. PCI is more effective than thrombolysis in restoring thrombolysis in myocardial infarction (TIMI) 3 flow and thus decreases the mortality rate [3,8].

However, after reopening of the IRA, some patients do not benefit from PCI and even die of abrupt hemodynamic disorders. Despite the high technical success rate, the in-hospital mortality of non-selected consecutive AMI patients undergoing primary PCI remains 4% to 7% [9–12]. The poor outcomes are attributed to myocardial ischemia-reperfusion injury (MIRI), which is largely mediated by cytotoxic effects of free radicals generated during ischemia, complement activation, injury of endothelial cells and inflammation [11,13–17]. It is generally considered that MIRI is potentially a poor predictor of prognosis [11]; however, both the precise biochemical mechanisms and the clinical significance of MIRI are not fully understood. This study aimed to explore the relationship of serum creatine kinase (CK) and CK-MB levels and cardiac function with MIRI in AMI patients undergoing primary PCI.

## Material and Methods

### Study patients

A total of 228 consecutive patients with AMI 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 [18,19]. Candidate criteria for primary PCI were: (1) ≥30 min of ischemic chest pain symptoms; (2) ST-segment elevation of ≥0.2 mV on the electrocardiogram in at least 2 contiguous chest leads or ≥0.1 mV in at least 2 limb leads or ischemic ST-segment depression of ≥0.1 mV; (3) positive result of cardiac troponin T test in the patients presenting ST-segment depression; and (4) within 12 hrs after the onset of chest pain, or chest pain continuing despite over 12 hrs. AMI patients with ST-segment elevation or suppression were included, as MIRI could occur in both cases while the mechanisms are unknown. Killip class was used to measure the severity of heart failure with AMI, and patients with Killip Class IV (cardiogenic shock) were excluded. Upon admission, the patients who met the candidate criteria were advised to accept primary PCI, and all the patients or their families gave written informed consent to the interventional therapies. The study was approved by the Ethics Committee of Guangzhou First People's Hospital, Guangzhou, China.

### Angiographic data

Angiograms were analyzed separately by 2 experienced cardiologists who were blinded to all other data apart from coronary angiograms. The angiography was performed via a transfemoral approach using a 6-French diagnostic catheter (Judkins type) with 370 mgI ULTRAVIST (iopromide provided by Bayer Healthcare Pharmaceuticals Inc., Wayne, NJ), a non-ionic, iodinated, low-osmolar radiological contrast agent. Multi-directional cineangiograms (SIEMENS ANGIOSTAR, Digital Subtraction Angiography System, Munich, Germany) of coronary arteries were recorded. Multivessel lesion was defined as the presence of a lesion with >50% diameter stenosis in a non-infarct-related coronary artery. The TIMI angiographic scale was used to determine the recanalization status of IRA and was assessed visually.

### Procedure of PCI

Upon admission, 300 mg of aspirin and 300 mg of clopidogrel were administered orally. Isosorbide dinitrate or nitroglycerin was administered intravenously in patients without hypotension. Primary angioplasty of the IRA was performed following the diagnostic coronary angiography with an additional injection of 5,000 units of heparin. 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 to 10 Atm for 15 to 30 seconds. After balloon dilatation, repeat coronary angiography was done, and then stent implantation was performed, which was deployed to the lesion at 12 to 15 Atm for 20 seconds. Only the IRA was managed emergently, and the other diseased vessel of a few of the patients with multivessel lesions was treated with selective PCI in convalescence of AMI. Serial ST-segment analysis on a 12-lead ECG recording before and at the end of the coronary intervention was conducted by 1 observer blinded to clinical data.

### Definitions, criteria and classifications of MIRI

A TIMI 3 flow for primary PCI with a residual luminal stenosis of less than 20% indicates a successful PCI [20]. MIRI was defined as acute cardiac events occurring immediately after IRA reopening, including severe bradycardia with hypotension, or lethal ventricular arrhythmias requiring electrical cardioversion, or myocardial reperfusion ≤ myocardial blush grade 2 without angiographic evidence for abrupt closure due to target vessel thrombus, emboli, dissection or spasm [12]. We designated the above 3 kinds of MIRI phenomena as suppression-type, irritation-type, and no-reflow-type, respectively. The ischemic time was defined as the period from the onset of chest pain symptom to IRA reopening. Infarct region was divided into anterior (anteroseptal, anterior, extensive anterior, anterolateral, and high lateral) and inferior location (inferior, true posterior, inferoposterior, and right ventricular).

### Cardiac functional examination by echocardiography

Left ventricular systolic function was evaluated by use of 2-dimensional echocardiography before discharge from hospital [21]. Left ventricular length, and left ventricular area (both at the end of systolic and diastolic phases) were measured in

**Table 1.** Baseline characteristics of AMI patients undergoing primary PCI with and without MIRI.

| Parameter | non-MIRI (n=109) | MIRI (n=119) | P |
|---|---|---|---|
| Gender (%) | | | |
| Male | 79 (72.5) | 88 (73.9) | 0.802 |
| Female | 30 (27.5) | 31 (26.1) | 0.881 |
| Age (yr) | 65.5 (38–87) | 65.0 (43–86) | 0.773 |
| Ischemic time (hr) | 6.0 (1–120) | 3 (2–96) | 0.007 |
| ≤6 hr (%) | 59 (54.1) | 87 (73.1) | 0.003 |
| ≤12 hr (%) | 86 (78.9) | 102 (85.7) | 0.177 |
| ≤24 hr (%) | 102 (93.6) | 115 (96.6) | 0.281 |
| AMI (%) | | | |
| Inferior location | 36 (33.0) | 72 (60.5) | 0.000 |
| Q-wave | 95 (87.2) | 102 (85.7) | 0.751 |
| ST-elevation | 101 (92.7) | 112 (94.1) | 0.658 |
| 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 |
| RCA | 35 (32.1) | 64 (53.8) | 0.001 |
| Multivessel lesions (%) | 32 (29.4) | 54 (45.4) | 0.013 |
| Blood flow in IRA (%) | | | |
| TIMI grade 0 | 57 (52.3) | 85 (71.4) | 0.003 |
| TIMI grade 1 | 5 (4.6) | 7 (5.9) | 0.662 |
| TIMI grade 2 | 22 (20.2) | 8 (6.7) | 0.003 |
| TIMI grade 3 | 25 (22.9) | 19 (16.0) | 0.183 |
| Coronary heart disease history (%) | 14 (12.8) | 24 (20.2) | 0.138 |

LAD – left anterior descending artery; LCX – left circumflex artery; RCA – right coronary artery. A $P$ value <0.05 was considered significant.

the 4-chamber apical views. Left ventricular ejection fraction (LVEF), left ventricular end-systolic volume (LVESV) and left ventricular end-diastolic volume (LVEDV), were calculated by using Simpson's 2 cross-section formula.

### Determination of serum CK and CK-MB

Serum CK and CK-MB were measured by electrochemiluminescence using an Elecsys (Roche Diagnostics) as described [22]. The assay coefficient of variance (CV) was <6.0%, with a detection limit of 1 IU/L.

### Statistical methods

Data were analyzed using the Statistics Package for Social Science (SPSS Version 10). Data were expressed as the mean value ±SD for continuous variables following a normal distribution, and T test or 1-way ANOVA was used for comparison between groups. Data were shown as median (minimum – maximum) for continuous variables following a skewed distribution, and Mann-Whitney or Kruskal-Wallis test was used to test differences among groups. Data were expressed as percentage of patients in groups for qualitative variables, and $\chi^2$ test was used for comparison. In this study, $P$ values less than 0.05 were considered to be statistically significant.

## Results

### General clinical data

In the same period, a total of 436 patients with AMI were admitted to hospital and 261 of the 436 patients were accepted as primary PCI. In 33 of the 261 patients undergoing primary PCI, their IRAs were not successfully reopened by PCI, or they did not meet the candidate criteria or were excluded owing to Killip Class IV (cardiogenic shock). Finally, a total of 228

**Table 2.** Myocardial enzyme peak values and echocardiographic cardiac function in AMI patients undergoing primary PCI.

| Parameter | Non-MIRI (n=109) | MIRI (n=119) | | |
|---|---|---|---|---|
| | | Suppression (n=54) | Irritation (n=29) | No-reflow (n=36) |
| Peak CK (IU/L) | 2521 (361–6855) | 2010 (331–8310)[a] | 2317 (579–7760) | 4573 (1620–9400)[a,b,c] |
| Peak CK-MB (IU/L) | 142 (39–744) | 98 (35–535) | 134 (54–480) | 338 (135–805)[a,b,c] |
| LVEF (%) | 51.2±8.1 | 54.0±8.9 | 51.8±7.9 | 38.7±8.3[a,b,c] |
| LVEDV (ml) | 119±28 | 118±21 | 105±19 | 135±32[c] |
| LVESV (ml) | 54±24 | 56±19 | 55±22 | 82±33[a,b] |

Data are the mean ±SD except for CK and CK-MB which are expressed as the median (minimum-maximum) as the data are of a skewed distribution.
[a] $P<0.05$, either type of MIRI *vs.* non-MIRI; [b] $P<0.05$, no-reflow *vs.* suppression-type MIRI; [c] $P<0.05$, non-reflow *vs.* irritation-type MIRI.
AMI – acute myocardial infarction; PCI – percutaneous coronary intervention; MIRI – myocardial ischemia-reperfusion injury; CK – creatine kinase; CK-MB – MB isoenzyme of creatine kinase; LVEF – left ventricular ejection fraction; LVEDV – left ventricular end-diastolic volume; and LVESV – left ventricular end-systolic volume.

patients with AMI in whom IRA was successfully recanalized by primary PCI were enrolled for this study; 120 of 228 AMI patients had an anterior AMI and 108 patients had an inferior AMI (Table 1). The ischemic time ranged from 1 to 120 hrs (median 4 hours). 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%. Among 228 patients, MIRI was observed in 119 patients (52.2%), including 54 suppression-type, 29 irritation-type and 36 no-reflow-type. MIRI and non-MIRI groups were comparable with regard to sex, age, Q wave infarction, ST-segment elevation infarction, Killip class on admission, and history of coronary heart disease (Table 1). The in-hospital mortality rate in the MIRI group was 13.4% (16/119), which was significantly higher than the 4.6% (5/109) rate in the non-MIRI group ($P$=0.021). For more details on the study patients, please refer to our previous study [8].

### Changes in CK and CK-MB levels

The median of peak serum CK level was remarkably lower in the suppression-type MIRI group than in the non-MIRI group (2,010 *vs.* 2,521 IU/L, $P$=0.039). The peak serum CK median was significantly higher in the no-reflow-type MIRI group (4,573 IU/L) than in the non-MIRI group ($P$<0.0001) (Table 2). However, there were no significant differences in the peak serum CK median between the irritation-type MIRI group (2,317 IU/L) and the non-MIRI group ($P$=0.627). On the other hand, the peak serum CK-MB median in the suppression-type group tended to be lower compared with the non-MIRI group (98 *vs.* 142 IU/L, $P$=0.091). The peak serum CK-MB median was significantly higher in the no-reflow-type MIRI group (338 IU/L) than in the non-MIRI group ($P$<0.0001) (Table 2). However, there were no differences in the peak serum CK-MB median between the irritation-type MIRI group (134 IU/L) and the non-MIRI group ($P$=0.500). In MIRI, the no-reflow subgroup had the highest peak median of serum CK and CK-MB contents.

### Changes in cardiac function

Echocardiography was performed in 210 patients at a median of 16 (range, 10–36) days after PCI, including 104 cases of non-MIRI, 50 cases of suppression-type MIRI, 22 patients with irritation-type MIRI and 34 patients with no-reflow-type MIRI. There were no significant differences in the incidence of pump failure and Killip class prior to PCI between the non-MIRI group and any subgroups of MIRI. The present study showed a favorable trend in LVEF for the suppression-type MIRI subgroup compared with the non-MIRI group (54.0±8.9% *vs.* 51.2±8.1%, $P$=0.312), but this did not achieve statistical significance. LVEF in the irritation-type subgroup (51.8±7.9%) did not significantly differ from that in the non-MIRI group ($P$=1.000). LVEF in the no-reflow-type subgroup (38.7±8.3%) was significantly lower than that in the non-MIRI group ($P$<0.0001) (Table 2).

LVEDV in the no-reflow-type subgroup was significantly greater than that in the irritation-type MIRI subgroup (135±32 *vs.* 105±19 ml, $P$=0.029). However, there was no statistical significance in differences between any other groups or subgroups ($P$=0.328–1.000) (Table 2). Notably, LVESV in the no-reflow-type MIRI subgroup was significantly greater than that in the non-MIRI group (82±33 *vs.* 54±24 ml, $P$=0.008) and in the suppression-type MIRI subgroup (56±19 ml, $P$=0.025). However, there was no statistical significance in differences between any other groups or subgroups ($P$=0.102–1.000) (Table 2).

## Discussion

The ischemic or hypoxic damages to the myocardium occur not only during ischemia, but also at reperfusion, which brings about so-called MIRI, often indicating poor prognosis [11]. Severe MIRI will cause acute hemodynamic disorders, which is the acute adverse effect of MIRI. The present data demonstrated that the in-hospital mortality rate of patients with MIRI was remarkably greater than in those without MIRI (13.4% *vs.* 4.6%), and the patients with serious MIRI usually died of acute hemodynamic disorders during or within the 3 days after the PCI procedure.

Data are scant on the influences of MIRI on convalescent cardiac function of AMI patients. In this study, the CK and CK-MB peak value medians were higher in the no-reflow-type

MIRI subgroup than in the non-MIRI group, with less preserved left ventricular systolic function in the former subgroup than the later group, suggesting that no-reflow exacerbates myocardial injury and cardiac function impairment. Iwakura et al [13] evaluated the no-reflow phenomena using myocardial contrast echocardiography in 199 patients with an anterior wall AMI who underwent successful coronary reperfusion with primary coronary angioplasty. The results revealed that the patients with the no-reflow had poor left ventricular function and wall motion. Eeckhout and Kern [10] reported that patients with no-reflow often developed congestive heart failure early and left ventricle enlarged progressively in AMI convalescence compared with patients with a good blood flow.

Additionally, the present study showed a significantly lower CK level, a lower trend for CK-MB and a higher trend for LVEF in the suppression-type MIRI subgroup compared with the non-MIRI group. These findings suggest that suppression-type MIRI did not aggravate myocardial injury and did not increase infarct size, and that early primary PCI salvaged the surviving myocardium in the infarct zone. The lack of a statistical significance for serum CK-MB level and LVEF might be due to the small number of cases in our study. Compared with the non-MIRI group, there were no significant differences in serum levels of CK and CK-MB, and left ventricular systolic function between the irritation-type MIRI subgroup and the non-MIRI group, suggesting that severe ventricular arrhythmias did not exacerbate myocardial damage and did not increase infarct size. However, repeated cardiac electroversions might cause additional damage to myocardium, which could weaken, at least in part, the protective effects of IRA reopening by PCI on myocardium and cardiac function.

The present study showed that MIRI was more frequent in the patients with a short ischemic time, namely ⩽6 hrs from the onset of chest pain symptom to IRA reopening. The strong tendency to MIRI after a short ischemic time might reflect more surviving myocardium in the infarct zone, since it is considered that MIRI does not occur in the severely necrotic myocardium after a long period of ischemia. However, the incidence of reperfusion-related arrhythmias is greater in patients with short ischemia time compared to those with a long duration of ischemia [13], which is harmful to the heart. Since MIRI is caused by multiple factors related to endothelial apoptosis, disrupted microcirculation, cytotoxicity of free radicals and radical oxidative species that also initiate a series of molecular events, and inflammation due to generation of multiple pro-inflammatory cytokines and signaling molecules, it is assumed that MIRI may also trigger some "protective" pathways such as generation of anti-inflammatory cytokines and anti-apoptotic molecules.

Our study has several limitations. The study was a retrospective analysis. The sample size of the 3 MIRI subgroups was small. 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 peri-procedure.

## Conclusions

In conclusion, MIRI may lead to acute hemodynamic disorders and increase mortality rate; in particular, the no-reflow type may induce permanent impairment of cardiac function. However, other types of MIRI, especially suppression- and irritation-type MIRI, may imply the existence of surviving myocardium. Further studies are needed to explore the theoretical and clinical significance of MIRI in AMI.

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**Disclosure statement**

No conflict of interest declared.

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