Clinical Research

hs-CRP is a potential predictor of no-reflow in patients with AMI after emergency PCI

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Objective  The paper aims to determine whether the inflammation, a powerful risk factor that has been demonstrated for the development of coronary artery disease, plays a role in no-reflow phenomenon in patients with acute myocardial infarction (AMI) after percutaneous coronary intervention (PCI).

Methods  We prospectively analyzed 656 patients with AMI after primary PCI. Based on post-PCI angiography data, patients were divided into two groups: the no-reflow group (TIMI=2, n =60) and the reflow group (TIMI=3, n =596).

Results  Our results showed that the inflammatory factors including leukocyte count (×10⁹/L) (10.90±4.04 vs. 9.12±2.98, P=0.002), hs-CRP (5.04±0.71 vs. 4.70±0.75, P=0.001) and other factor platelet count (×10⁹/L) (210.96±33.42 vs. 196.41±46.06, P=0.033) in no-reflow group are significantly higher than those in reflow group, major adverse cardiac events happened in the patients with no-reflow are higher than in reflow patients no matter in hospital or at the end of follow-up. We also found the left ventricular ejection fraction (LVEF) dramatically decreased (58.65±9.34 vs. 51.29±11.38, P<0.001) and left ventricular end-diastolic dimension (LVEDD) significantly increased (49.94±6.75 mm vs. 54.66±6.68mm, P<0.001) in no-reflow patients at the end of follow-up.

Conclusions  Our results suggest that inflammation factors function in no-reflow phenomenon, and no-reflow is a serious complication after primary PCI which predicts poor left ventricular systolic functional recovery and mortality in patients with AMI. (J Geriatr Cardiol 2008; 5:217-222)

Key words  No-reflow; inflammation factors; acute myocardial infarction; percutaneous coronary intervention

Introduction

Percutaneous coronary intervention (PCI) is now already a routine therapy for patients with AMI, and is increasingly used to treat complex coronary lesions with good long-term outcome. However, the annual risk of a major adverse cardiac event, defined as cardiac death, nonfatal myocardial infarction (MI) or a re-intervention procedure (e.g. coronary artery bypass grafting, repeat PCI, or PCI for a new lesion), approached 7% in the multicenter of Lescol Intervention Prevention Study.1 Restoration of normal flow and tissue-level perfusion are key factors in the reduction of cardiac events in AMI. The goal of reperfusion by PCI should restore not only epicardial patency and flow, but also upstream myocardial tissue perfusion.2 Nonetheless the benefits are limited by microvascular hypoperfusion, named “no-flow” phenomenon which happened in some patients after PCI. Mechanisms underlying no-reflow are complex and only partially understood.3 Microvascular obstruction due to neutrophil and platelet plugging, intense vasoconstriction and external microvascular compression are potential causes.4 However, whether inflammation factors play some roles in no-reflow phenomenon remains unknown up to now. Therefore, our study aimed to examine the alteration of inflammation and prognosis of this phenomenon.

Patients and methods

Study population

In the period of January 2003 to January 2007, we consecutively investigated 656 patients who were treated with primary PCI in our Cardiac Center presenting with AMI less than 6h. AMI inclusion criteria: myocardial enzyme concentrations, typical chest pain persisting longer than 30 min or electrocardiographic changes (including ischemic ST-segment depression, ST-segment elevation>2mV in two or more adjacent leads, new or undetermined duration of left bundle branch block on admission). The cut-point of 6h from symptoms onset was chosen to avoid necrosis as a possible determinant of serum high sensitivity C-reaction protein (hs-CRP) levels. Indeed, myocardial necrosis causes an inflammatory reaction which starts raising hs-CRP levels approximately 6h after symptoms onset. We systematically compared the clinical data (see Table 1), from each patient
in the Catheterization Laboratory before PCI. Blood was centrifuged from a brachial vein and serum was stored at -80°C in appropriate cuvettes until assayed. These data include age, gender, target vessel number, diabetes mellitus (diabetes mellitus was diagnosed according to the WHO criteria), total cholesterol, triglyceride, LDL-cholesterol, HDL-cholesterol, total blood platelet count, left ventricular ejection fraction (LVEF), left ventricular end-diastolic dimension (LVEDD), creatine kinase (CK), CK-MB and inflammation factors such as total leukocyte count, total neutrophilic granulocyte count and hs-CRP. We also excluded those patients with various diseases, like severe chronic heart failure, severe valvular heart disease, acute or chronic infections, autoimmune disease, liver disease, neoplasia, immunologic disorder and the use of anti-inflammatory or immunosuppressive therapy and recent (<3 months) surgical procedures or trauma.

Patients underwent coronary angiography with culprit artery completely occluded were treated with PCI. They were divided into two groups based on angiography data: the no-reflow group (n = 60) and the reflow group (n = 596). The oral medicines treated for each patient are similar including nitrates, ACEI or ARB, β receptor blocker, aspirin plus clopidogrel and statins (see Table 1).

### In-hospital major adverse cardiac events and follow-up

Mortality and the major adverse cardiac events including heart failure, angina, nonfatal arrhythmia and non-fatal acute myocardial infarction were statistically filed after the patients were treated with PCI during the hospital stay and follow-up. All patients were periodically followed up at out-patient clinic intervention for 1 year after they were discharged. Each patient received echocardiogram detection in hospital and at the end of follow-up. Echo technicians didn’t know the patient outcome of the PCI and the echocardiogram. LVEF measure was used by Simpson’s rule, LVEDD measure by two-dimensional echocardiography in parasternal left ventricular long-axial plane.

#### Angiographic definition of no-reflow

Coronary angiograms were carefully reviewed at our Catheterization Laboratory. The no-reflow phenomenon was determined based on Thrombolysis in Myocardial Infarction (TIMI) trial grades 0, 1 or 2, because recently, numerous trials have demonstrated that the clinical outcomes for patients with TIMI 2 flow are much closer to those with TIMI 0 or 1 flow than to those with TIMI 3 flow. Exclusion criteria were coronary thrombosis, embolism, spasm, absence of coronary stenosis ≥50% and hypotension. The grade 3 of TIMI trail flow was considered as successful reflow in angiography. Treatment of no-reflow, including intracoronary infusion of vasodilators, was at the physician’s discretion.

### Table 1    Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>No-reflow group n =60</th>
<th>reflow group n =596</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>63.57±9.83</td>
<td>61.49±11.11</td>
<td>0.130</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>48(79.4%)</td>
<td>447(75.0%)</td>
<td>0.435</td>
</tr>
<tr>
<td>Stent length (mm)</td>
<td>19.43±4.25</td>
<td>18.78±6.08</td>
<td>0.480</td>
</tr>
<tr>
<td>Angiography degree of CAD, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-vessel disease</td>
<td>26(43.4%)</td>
<td>263(44.1%)</td>
<td>0.308</td>
</tr>
<tr>
<td>2-vessel disease</td>
<td>23(38.3%)</td>
<td>189(31.7%)</td>
<td>0.892</td>
</tr>
<tr>
<td>3-vessel disease</td>
<td>11(18.3%)</td>
<td>144(24.2%)</td>
<td>0.344</td>
</tr>
<tr>
<td>Total triglycerides (mmol/L)</td>
<td>1.45±0.81</td>
<td>1.65±0.65</td>
<td>0.104</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.80±1.15</td>
<td>5.16±1.18</td>
<td>0.113</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L)</td>
<td>3.05±1.12</td>
<td>3.37±1.05</td>
<td>0.142</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>1.14±0.35</td>
<td>1.13±0.30</td>
<td>0.944</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>60(100%)</td>
<td>596(100%)</td>
<td>-</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>60(100%)</td>
<td>596(100%)</td>
<td>-</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>49</td>
<td>477</td>
<td>0.866</td>
</tr>
<tr>
<td>β receptor blocker</td>
<td>43</td>
<td>481</td>
<td>0.126</td>
</tr>
<tr>
<td>Statins</td>
<td>51</td>
<td>527</td>
<td>0.406</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>56.96±7.29</td>
<td>58.06±10.31</td>
<td>0.461</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>51.87±5.32</td>
<td>50.70±5.90</td>
<td>0.169</td>
</tr>
<tr>
<td>CK-MB (ng/ml)</td>
<td>69.80±8.36</td>
<td>68.65±11.52</td>
<td>0.457</td>
</tr>
<tr>
<td>CK (ng/ml)</td>
<td>647.10±93.72</td>
<td>663.63±98.51</td>
<td>0.220</td>
</tr>
</tbody>
</table>
Final TIMI flow grade was assessed on the final shot of the emergent coronary angiography.

Statistical analysis

Numerical data were expressed as mean±SD. Chi-square analysis was used to assess the difference among categorical variations. Student’s t-test was used to evaluate differences in numerical data. A multiple regression analysis was performed after stepwise regression analysis including all clinical variables. In this study, P<0.05 was considered to be significant. Odds ratios (OR) and 95% confidence intervals (CI) of in-hospital and follow-up adverse events were calculated using logistic regression analysis. All analyses have been performed by statistical software SPSS 11.1.

Results

Patient characteristics

The baseline clinical characteristics of the patients assigned to the reflow and no-reflow groups are listed in Table 1. No significant differences were observed between the two groups in age, gender, target vessel, hyperlipidemia, LVEF, LVEDD, CK, CK-MB and medications. In addition, similar proportions of patients with no-reflow and with reflow were on aspirin, β blockers, angiotensin-converting enzyme inhibitors, statins, and clopidogrel at the time of the procedure.

Independent predictors of no-reflow

Patients with diabetes mellitus (21.7% vs. 7.6% P=0.001) and serum insulin, hs-CRP, total leukocyte, neutrophilic leukocyte and platelet counts had more significant differences in no-reflow group than those in reflow group (see Figure 1). Stepwise regression analysis indicated hs-CRP is a more sensitive predictor to no-reflow phenomenon (OR=0.498, P<0.001) in those observation factors.

Prognosis in hospital and follow-up

During the hospital stay and/or one-year follow-up after PCI treatment, the mortality and major adverse cardiac events in patients of no-reflow group occurred significantly higher than in reflow group (see Table 2). At the end of follow-up, the LVEF in no-reflow group was significantly lower than that in reflow group, but LVEDD was larger than that in reflow group. We also found LVEF decreased (P=0.010), and LVEDD increased (P=0.033) in no-reflow group. However, we didn’t see statistical difference in reflow group (see Figure 2).

Relation between hs-CRP with cardiac event in hospital and out hospital

hs-CRP Concentration was also independently related to major adverse cardiac event in hospital and out hospital (r=0.147 P=0.012 and r=0.253 P=0.026).

Discussion

The aim of emergence PCI treatment is to quickly restore myocardial flow in AMI patients. And PCI has become a key therapy for AMI patients nowadays. But patients in some cases can’t obtain sufficient perfusion in the myocardial tissue even after they were successfully treated with PCI, which has recently attracted clinical investigators to pay much more attention to this phenomenon called no-reflow. Several studies have reported that no-reflow incidence occurs from 0.6% to 14%. We prospectively analyzed 656 patients who accepted PCI therapy in our Cardiac Center. No-reflow phenomenon occurred in 60 patients, 9.15 percent of the total, during their angiograms after stent were successfully placed in them. Mechanisms underlying no-reflow are complicated. Impaired microvasculature is primarily caused by two mechanisms: (1) microvascular obstruction, due to platelet microembolism, thrombosis, and neutrophil plugging; (2) reperfusion injury, due to neutrophil aggregation and free-radical release as well as endothelial dysfunction and microvascular constriction.

Our studies found patients with no-reflow had a significant higher level of inflammation factors, such as leukocyte, neutrophils and hs-CRP. The mechanism by which leukocyte and neutrophil cause this phenomenon is unclear. Kloner RA et al have documented that leukocyte and neu-
Neutrophils activation and accumulation effect on no-reflow shortly after IRA recanalization. After neutrophil activation, cellular deformability is further attenuated, leukocytes adhere to endothelium and platelets when an ischemic bed is reperfused. The distribution of leukocytes in capillaries correlates well with the distribution of no-reflow in animal studies. So adhesion of leukocytes to the ischemic-reperfused coronary endothelium is believed to be a prerequisite for neutrophil-mediated reperfusion injury.

Inflammation is a widely-known major factor in atherosclerosis. There are accumulating evidences that C-reactive protein (CRP), a critical inflammation factor, is one of the most powerful predictors for atherosclerosis and cardiovascular death. C-reactive protein is not only a marker of the amount and activity of circulating proinflammatory cytokines; in fact, this protein may also contribute to inflammation in ischemic myocardium by activating complement. It could be stained in the macrophages and atherothrombotic tissue aspirated from the infarct-related coronary artery, so it may cause endothelial dysfunction in microvasculature, which leads to no-flow phenomenon.

In our studies, we found that the levels of hs-CRP of AMI patients in no-reflow group higher than those in reflow group. And by using stepwise regression analysis we found hs-CRP is a predictor more sensitive to no-reflow phenomenon (OR=0.498, \(P<0.001\)). So we concluded that enhanced inflammation response is a possible reason of no-flow phenomenon. Tomoda and Aoki demonstrated that patients with elevated CRP levels had more vulnerable coronary artery lesions and worse clinical outcomes. Our findings also suggested that AMI patients in no-reflow plaque might be more vulnerable than those in reflow group. This conclusion was further supported by a recent autopsy study which demonstrated an increased serum level of hs-CRP was strongly related to atherothrombi and plaque burden in patients with severe coronary artery disease who died suddenly. In conclusion, increased inflammation factors in the blood at the site of the plaque rupture are one of the pathogenetic mechanisms for myocardial “no-reflow” phenomenon in AMI.

Our study also showed patients with on-reflow had a higher incidence of diabetes, significantly higher levels of...
serum insulin and platelet. As we all know, much of the burden of diabetes is attributable to microvascular and macrovascular complication. Several mechanisms might explain the relation between hyperglycemia and the no-reflow phenomenon. Firstly, hyperglycaemia increases intercellular adhesion molecule-1 levels or P-selectin, which would augment plugging of leukocytes in the capillaries. Leukocytes trapped in the coronary capillaries and venules early after coronary reperfusion are observed much more frequently in the diabetic rat heart than in the non-diabetic heart. Plugging of enhanced leukocytes in the microcirculation might further contribute to the no-reflow phenomenon. Secondly, Hyperglycemia may also boost thrombus formation. Shechter M et al.20 found hyperglycemia is an independent predictor of platelet-dependent thrombosis. In company with thrombus formation in AMI, fibrinolysis system was also activated, which leads to increased levels of free thrombin, a potent platelet agonist. Platelet products may exacerbate microcirculatory spasm, leading to further microvascular congestion, thrombosis and sluggish coronary flow. Animal studies provide supportive evidence for the role of platelet-dependent microembolization.22

Early reperfusion of the related artery results in greater myocardial salvage and better left ventricular function.23 But our study showed that the angiographic appearance of no-reflow phenomenon after successful reopening of the infarct-related artery in patients undergoing primary PCI for AMI is associated with worse in-hospital and 1-year outcomes. Our data also showed that LVEF decreased but LVEDD increased in no-reflow group at the destination of follow-up. We analyzed the correlation between no-reflow phenomenon and prognosis in no-reflow group, finding no-flow phenomenon is an important factor of left ventricular dysfunction in patients with AMI who under primary PCI.

Limitations

This was not a randomized study, but comprised consecutive patients enrolled in long-term echocardiography and clinical evaluation program. We could neither successfully analyze the effects of drugs that patients received after hospital, nor further find out why hs-CRP increased faster in no-reflow than reflow group.

Conclusions

Taken together, our findings suggest that inflammation factors, especially hs-CRP play important roles in the prediction of no-reflow phenomenon in AMI patients. “No-reflow” is a serious complication of percutaneous coronary intervention (PCI) in AMI patients, which is associated with worse prognosis. It is also an independent factor about left ventricular remodeling and dysfunction.

References


